Shree H. N. Shukla Institute of Pharmaceutical Education and Research, Rajkot

B. Pharm
Semester-III

Subject Name: Physical pharmaceutics-I
Subject Code: BP302TP

CHAPTER-1- STATES OF MATTER

SYLLABUS:

States of Matter and properties of matter: State of matter, changes in the state of matter, latent heats, vapour pressure, sublimation critical point, eutectic mixtures, gases, aerosols– inhalers, relative humidity, liquid complexes, liquid crystals, glassy states, solid-crystalline, amorphous & polymorphism. Physicochemical properties of drug molecules: Refractive index, optical rotation, dielectric constant, dipole moment, dissociation constant, determinations and applications

- The course deals with the various physical and physicochemical properties, and principles involved in dosage forms/formulations.
- Theory and practical components of the subject help the student to get a better insight into various areas of formulation research and development, and stability studies of pharmaceutical dosage forms.

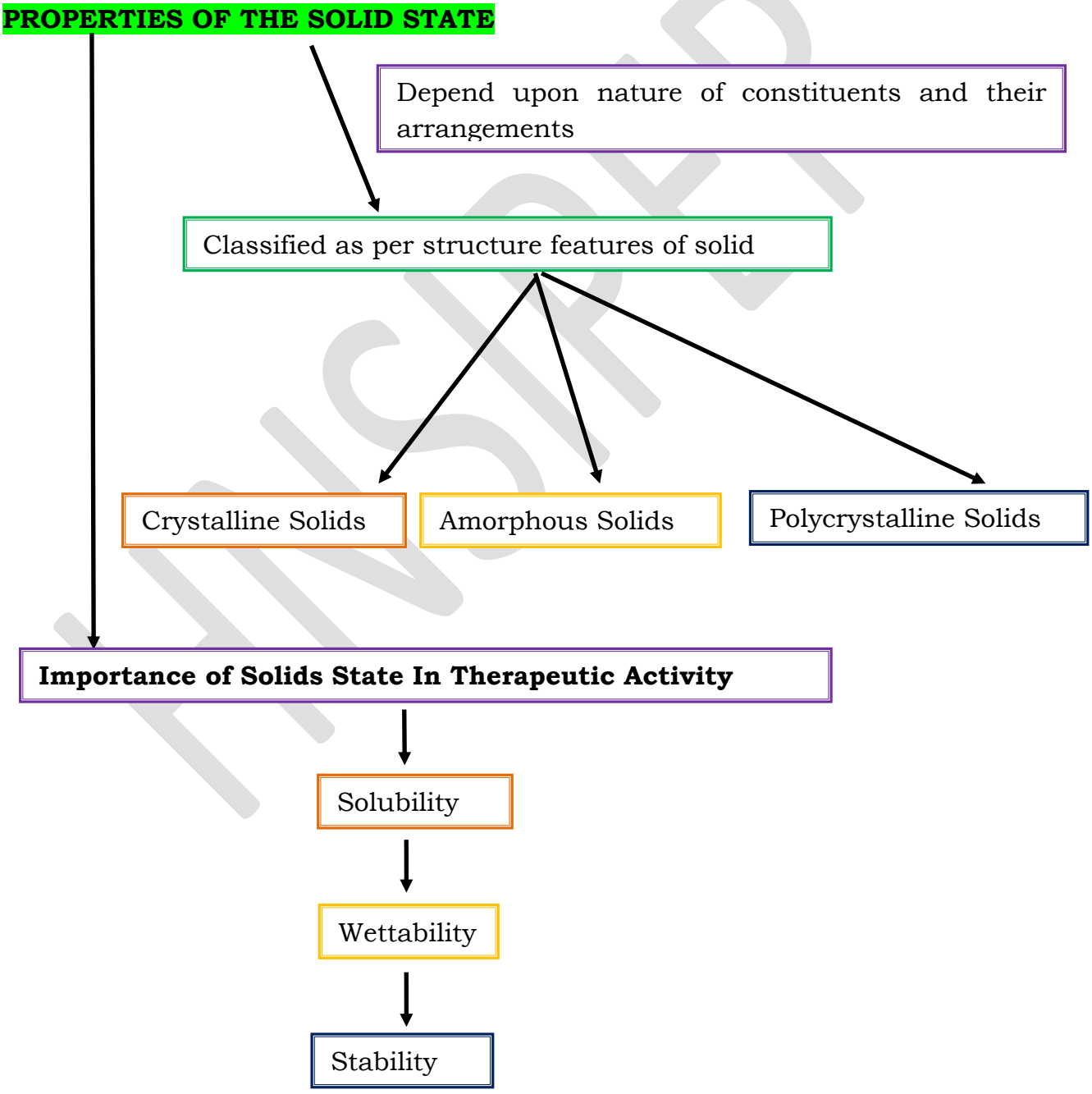
Learning objectives

- Understand the nature of the intra and intermolecular forces that are involved in stabilizing molecular and physical structure.
- Understand the differences in these forces and their relevance to different types of molecules.
- Appreciate the differences in the strengths of the intermolecular forces that are responsible for the stability structures in the different states of matter.
- Understands properties of gaseous states.

STATES OF MATTER

TOPIC: What is Solid State? Explain Classification of Solids as per Structural Features

Ans:



Detailing:

Classified as per structure features of solid

THE SOLID STATE

Properties of the solids not only depend upon the nature of the constituents, but also on their arrangements.

Classified based on structural features of solid.

1) Crystalline solids

2) Amorphous solids

3) Polycrystalline solids

Crystalline Solid.

- The substances whose constituents are arranged in definite orderly arrangements are called crystalline solids.
- Many naturally occurring solid substances occur in the crystalline form.
- eg. Sodium chloride, sulphur, diamond, sugar etc.
- They possess characteristic geometric shapes. The particles in crystals are held by strong inter atomic, inter ionic, or intermolecular forces.
- Crystalline solids have sharp melting points, indicating the presence of a long-range order arrangement in them.
- The long-range order is due to the regular arrangement of the molecules throughout three-dimensional networks of crystals.
- Eg. Crystal of sodium chloride the constituents NA+ and CL- ions are present at alternate sites.

Amorphous Solids.

- Substances whose constituents are not arranged in an orderly manner are called amorphous solids. Eg. Glass, rubber, plastic etc.

Characteristics:

- They do not occur in characteristic geometric shapes. They possess properties incompressibility and rigidity to some extent.
- Their mechanical, electrical and optical properties do not depend upon the direction along which they measured.

Polycrystalline Solids

- These are crystalline solids, constituted of very fine crystals which can not seen by naked eye.
- These solids appear amorphous but are not so because the fine crystals are randomly oriented.
- Each individual crystal is anisotropic but whole appears to be isotropic.

Importance of Solids State In Therapeutic Activity

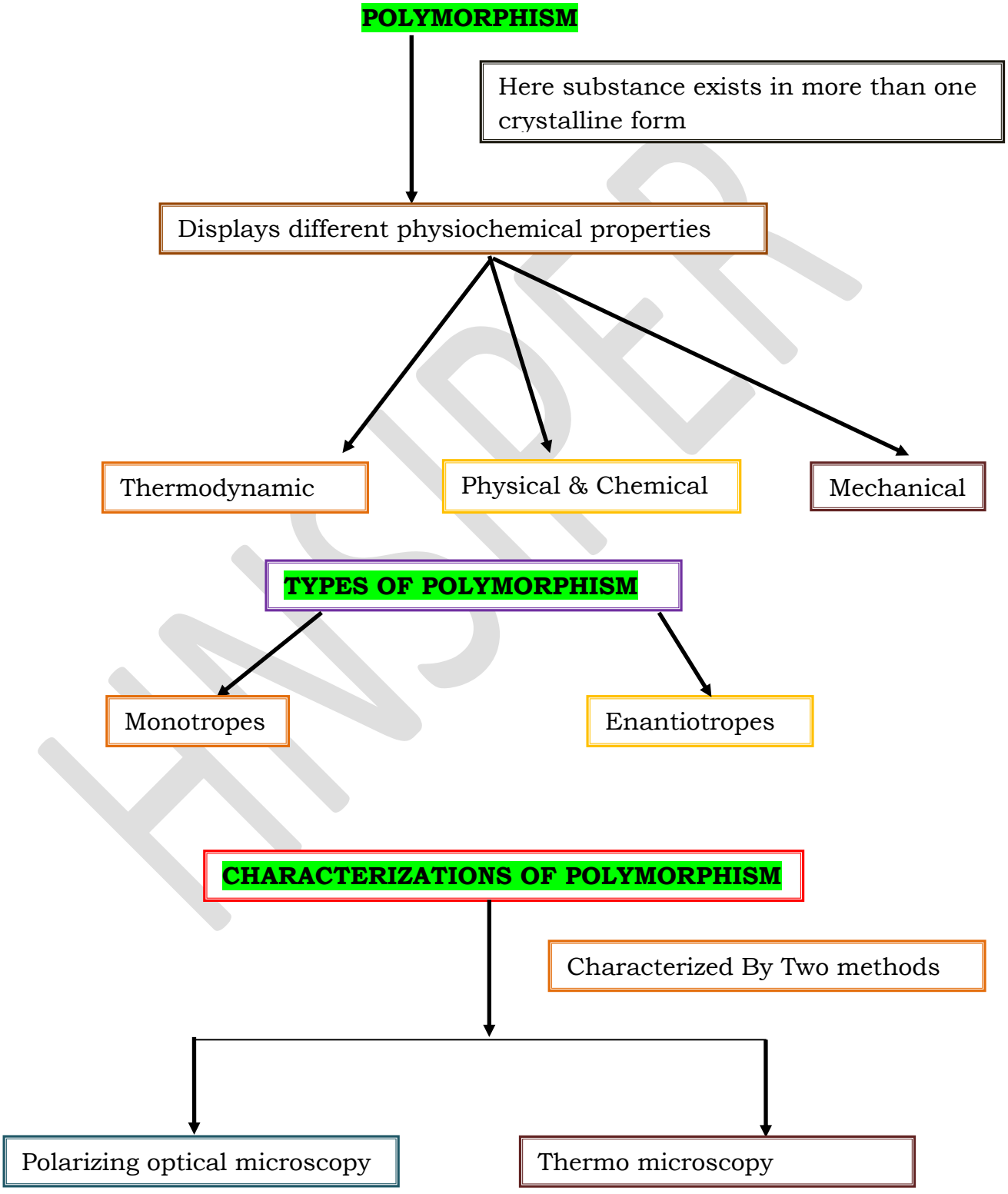
- Solubility: the amorphous state is thermodynamically the form with the highest solubility.
- Amorphous forms will exhibit grater solubility in a solvent then any crystalline.
- Wettability: For a drug dissolve, its surface has first to be wetted by the surrounding fluid.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Natural solid crystalline substance form example?	Sodium chloride
2	Definite ordered arrangements are found in?	Crystalline solid
3	Sharp melting point is observed in?	Crystalline solid
4	The particles in crystals are held by which bond?	Inter atomic bond
5	Constituents are arranged in random manner in?	Amorphous solid
6	Example of amorphous solids?	Glass
7	Isotropic structure is available in which solid?	Polycrystalline
8	Which state has greater water solubility?	Amorphous
9	Reason of Amorphous shows better dissolved.	Wettability
10	Which form has greater stability?	Amorphous

TOPIC: What is Polymorphism?

Ans



Detailing:

POLYMORPHISM

- Polymorphism (polus = many) and (morph = shape) it is the phenomenon in which substance exists in more than one crystalline forms.
- It is happened due to different temperature and pressure.
- And those different crystalline forms are called polymorphic. E.g. Blood group.
- polymorphous substance have similar chemical properties but different physical properties.
- Same molecules exist in different ways.
- Amorphous forms possess a chemically randomized surface, which express equal amount of hydrophobic and hydrophilic interaction which can lead to improved Wettability expressed by a lower contact angle of drug particle surface with a liquid.
- Crystalline forms of drugs may be used because of greater stability than the corresponding amorphous form. E.g. penicillin, Novobiocin , insulin
- Due to selective control of the physical parameter of a drug is very important by which biological response may be optimized.
- If this difference because of packing it is termed as packing polymorphism and if it is due to difference is conformation, it is called conformational polymorphism.
- Because of polymorphism, molecules have different arrangements in the unit cell of its crystal and thus display different physical properties.

- Thermodynamic properties: solubility, free energy, melting point, etc.
- Spectroscopic properties, kinetic properties such as dissolution rate, stability.
- Mechanical properties: hardness, compatibility, tensile strength, etc.

TYPE OF POLYMORPHISMS:

Categorized into two types depending upon stability and range of temperature and pressure.

1) MONOTROPES: Polymorphs, which are stable at all temperatures below melting point, is known as Monotropes

2) ENANTIOTROPES: When one of the polymorphs is stable over certain temperature range and pressure, while other polymorph is stable over a different temperature and pressure then the two polymorphs are said to be enantiotropes.

CHARACTERIZATION OF POLYMORPHS

- Many methods have been employed for characterizing polymorphs in pharmaceutical solids.
- Two methods:

  1. Polarizing optical microscopy

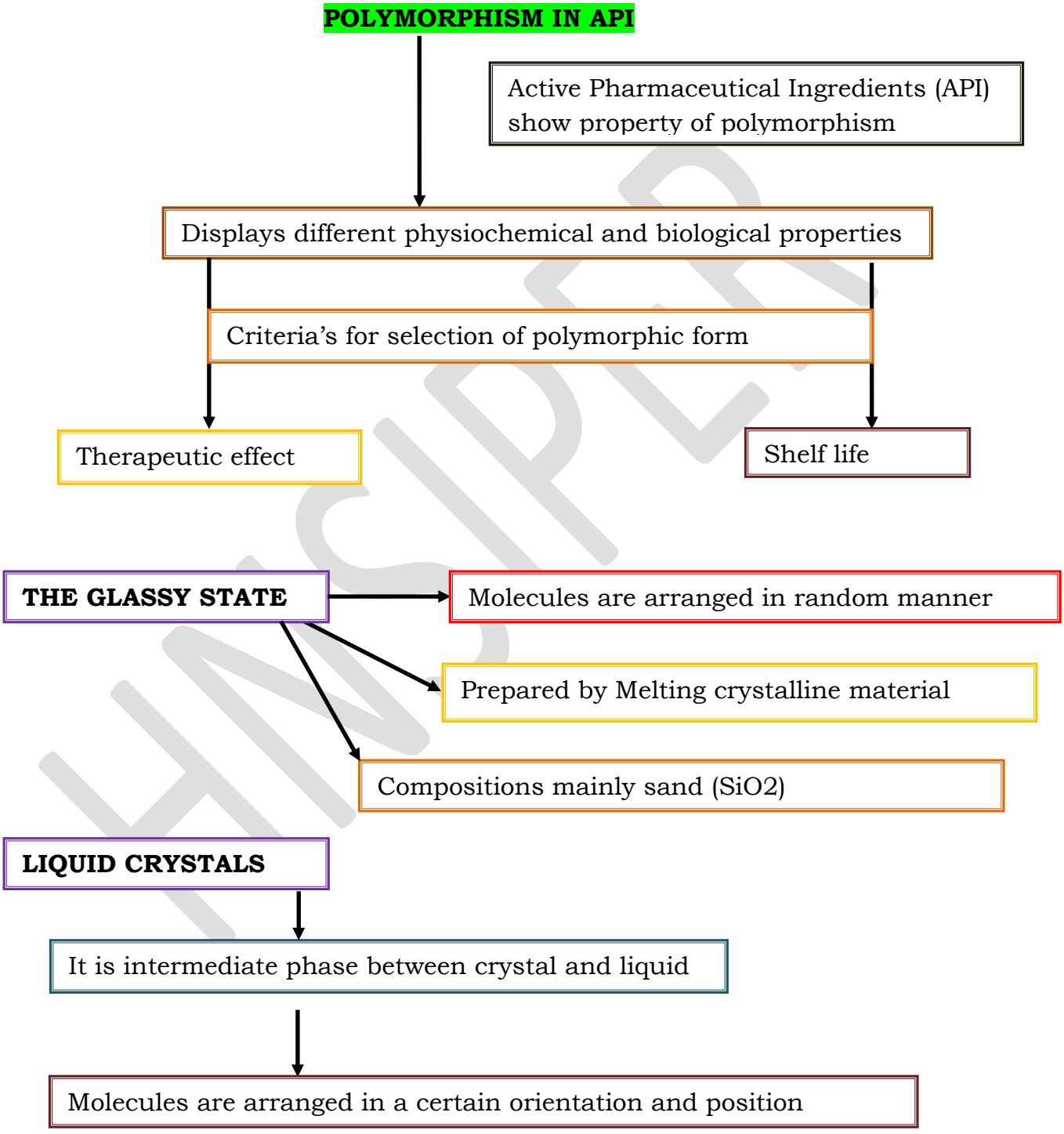
  2. Thermo microscopy
- Thermal analysis procedures such as differential scanning calorimetric (DSC) and thermo gravimetric analysis (TGA), can be used to obtain additional information.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Substance exist more than one crystalline form is?	Polymorphism
2	Different experimental conditions can generate.	Polymorphism
3	How many methods used for characterization?	Two
4	Differential scanning ccalorimetry is one type of?	Thermal analysis
5	Polymorphs are stable at all temperature.	Monotropes
6	Polymorphs are stable in various experimental condition	Enantiotropes

TOPIC: What Is Polymorphism In Pharmaceutical Compounds?

Ans



Detailing:

POLYMORPHISM IN PHARMACEUTICAL COMPOUNDS:

- The property of self- organization of drug molecules in a several ways in solids with nearly same lattice energies and the conformational flexibility of the molecules is the cause for the existence of crystal polymorphism in APIs.
- This study can be helpful in the drug development programmed and can avoid future problems in manufacturing and also in the final performance of the drug delivery systems.
- Many pharmaceutical molecules show the property of polymorphism.
- Which is essentially be studied at large about the changes in the physical and biological properties.
- Thus, it is very important to select the proper polymorphic form of the API for getting desired effect and stability throughout its shelf life.
- Usually the form that is most stable is preferred in market formulation as the metastable form may transform to other stable forms.

THE GLASSY STATE

- Glasses combine some properties of crystals and some of liquids but are distinctly different from both.
- Glass have mechanical rigidity of crystals, but the random disordered arrangement of molecules that characterizes liquids.
- Glass are usually formed by melting crystalline materials at very high temperature.

- It is composed mainly of sand (silicates, SiO_2) and an alkali.
- Depending in the final use and application, the composition of the glass and cooling rate will vary to achieve the adequate properties for the specific application.

  1) Sand (silica) in its pure form.

  2) Soda ash (sodium carbonate).
- Normally SiO_2 soften up to 2000℃ where it starts to degrade. Adding soda will lower the melting point to 1000℃ making it more manageable.

3) Limestone (calcium carbonate or caco3) or dolomite ($MgCO_3$).

LIQUID CRYSTALS

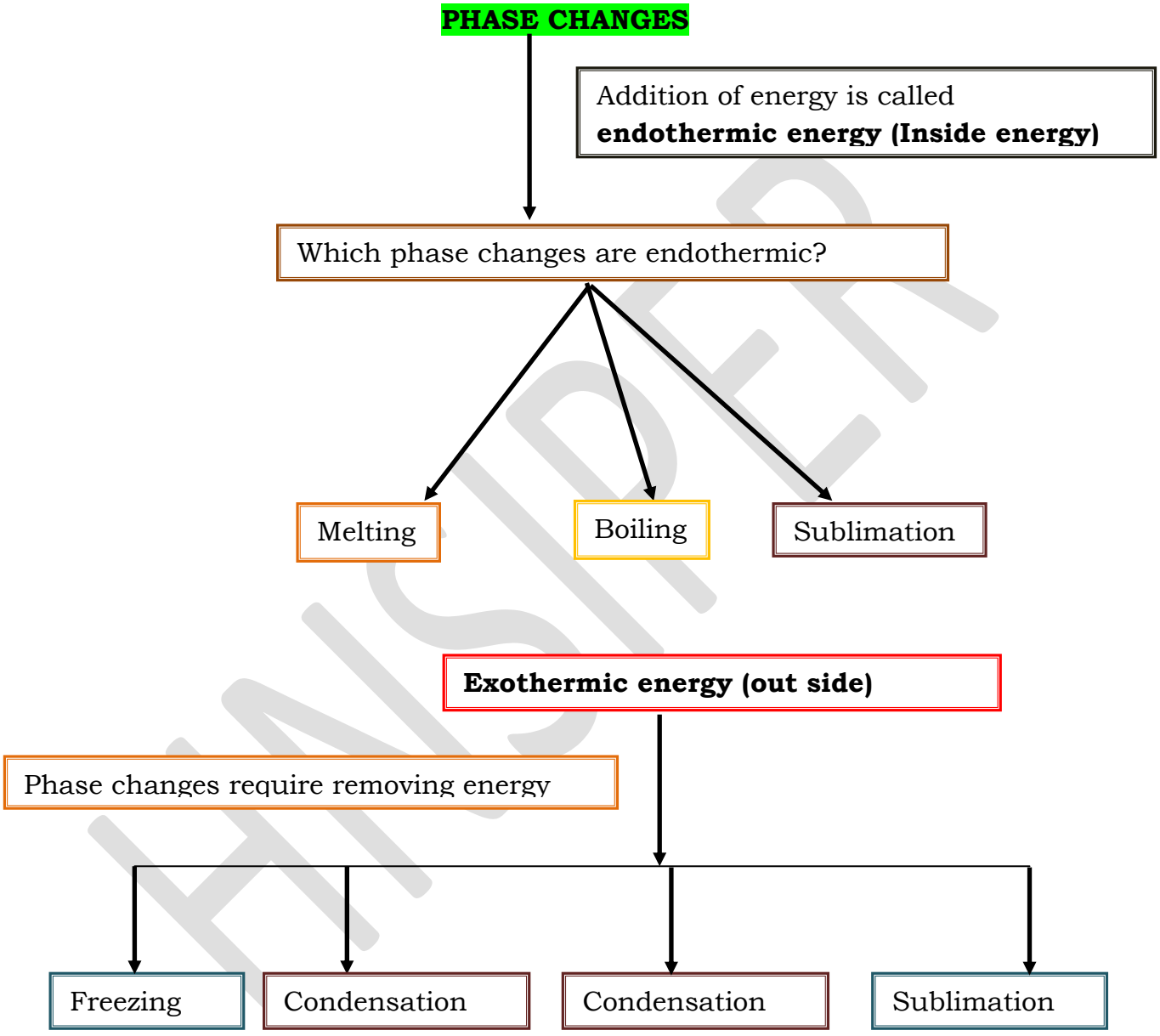
- Liquid crystal if fourth state of matter in which a special condition is arises.
- The molecules in solids exhibit both positional and orientation resulting them in certain direction and position.
- Liquid crystals are a phase of matter whose order is intermediate between a liquid and that of a crystal.
- Molecules in liquid crystal do not exhibit any positional order, but they do possess a certain degree of orientation order.

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Which study is helpful in drug development?	Polymorphism
2	Which is more suitable form in dosage development	Metastable
3	Which substance has combine crystal properties?	Glass
4	Glass composed of sand and	Alkali substance
5	What is chemical name of Limestone.	Calcium carbonate
6	An amorphous solid does not possess a well-defined arrangement and long-range molecular order.	**AMORPHOUS SOLID**
7	The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.	**BIOAVAILABILITY**

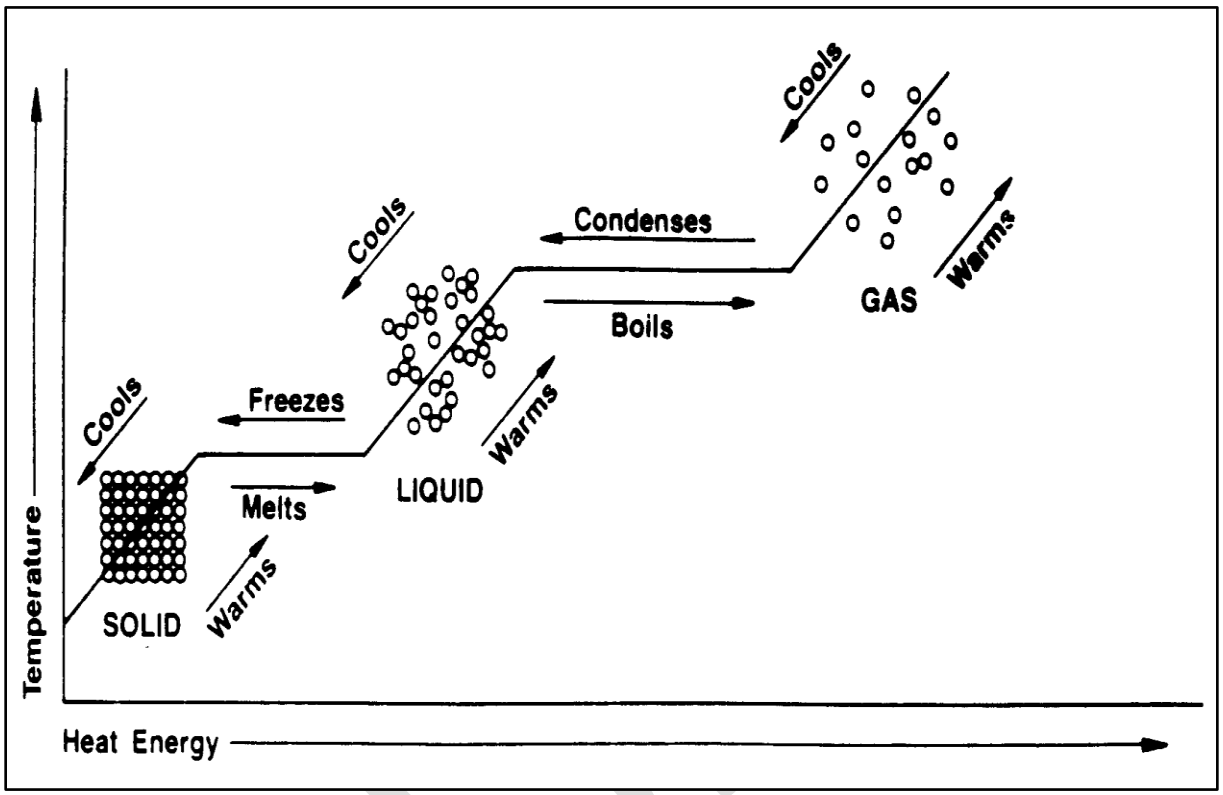
TOPIC: Changes in State of Matter?

Ans:



Detailing:

CHANGES IN THE STATE OF MATTER



Adding Energy:

Phase changes that require the addition of energy are called *endothermic* changes. (*endo* = inside, *therm* = heat)

Which phase changes are endothermic?

- Melting (solid → liquid)
- Boiling (liquid → gas)
- Sublimation (solid → gas)

Removing Energy

- Phase changes that require the removing of energy are called *exothermic* changes.

- (*exo* = outside, *therm* = heat)

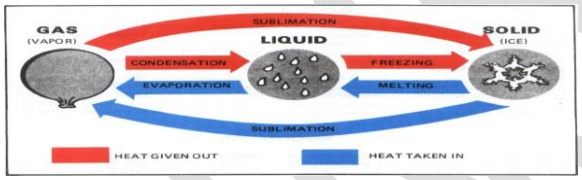
Which phase changes are exothermic?

- Freezing (liquid → solid)
- Condensation (gas → liquid)
- Deposition (reverse sublimation) (gas → solid)

Sublimation – Solid to Liquid

- Solid to gas phase change occurs when the surface particles of a solid change directly into a gas.
- You may notice this in the cold winter with snow. The snow does not melt, but slowly disappears.
- Dry ice goes directly from solid carbon dioxide to gas.

Energy in Phase Change



- The eutectic point is the point at which the liquid and solid phases have the same composition (*the eutectic composition*). The solid phase is an intimate mixture of fine crystals of the two compounds.

Application of eutectic mixture

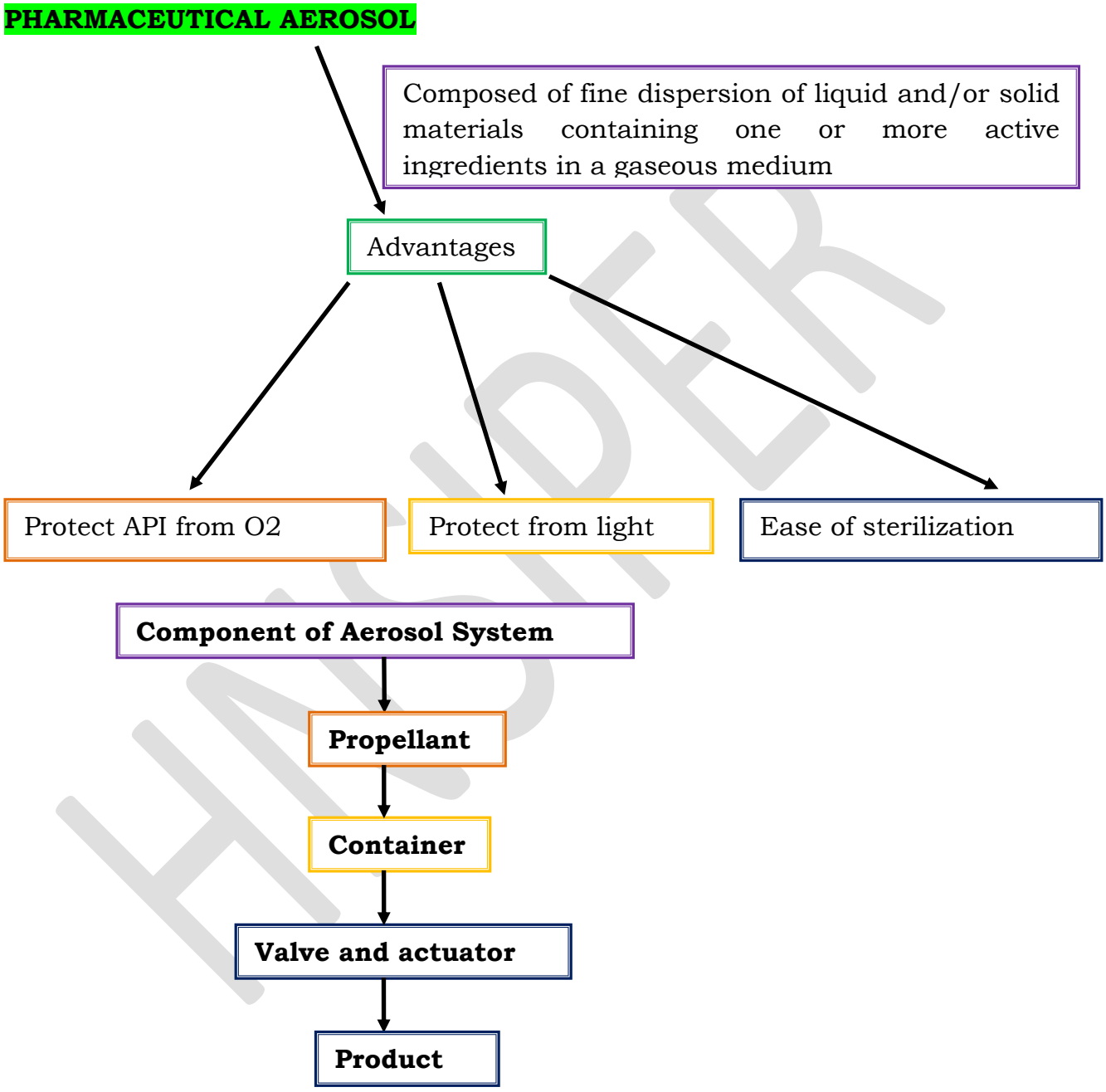
- Lidocaine and prilocaine, two local anesthetic agents, form a 1:1 mixture having a eutectic temperature of 18°C.
- The mixture is liquid at room temperature and forms a mixed local anesthetic that may be used for topical application.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Eutectic Ratio of lidocaine and prilocane is?	1:1
2	Eutectic point of salos-thymol system is?	13°C
3	Dry ice goes directly from solid CO2 to gas is?	Sublimation
4	Freezing and condensation is included in?	Exothermic energy
5	Addition of energy require in boiling is called?	Endothermic energy
6	At which point three phases coexist?	Eutectic point

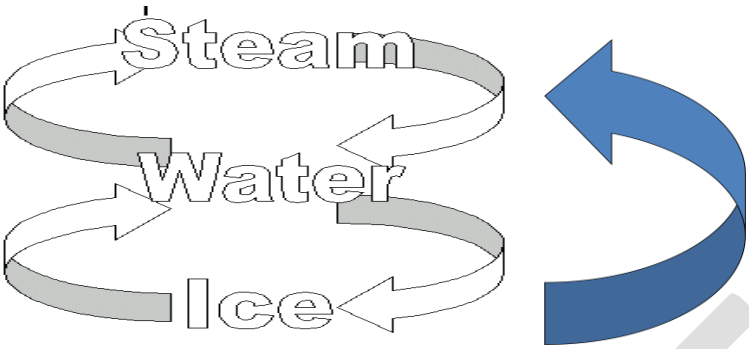
TOPIC: What is Aerosol?

Ans:



Detailing:

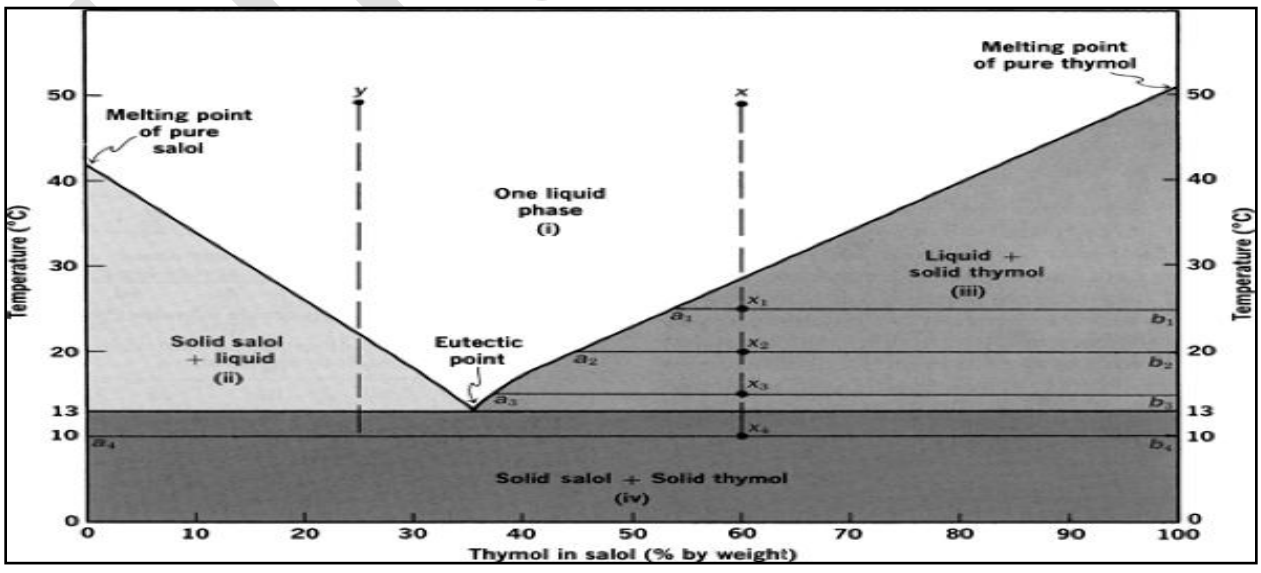
Add the correct terms to the diagram...



Eutectic Mixtures

- solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids.
- Examples of such systems are:
- salol–thymol,
- salol–camphor,
- acetaminophen–propyphenazone.

Phase diagram for the thymol–salol system showing the eutectic point.



There are four regions:

(i) a single liquid phase.

(ii) a region containing solid salol and a conjugate liquid phase.

(iii) a region in which solid thymol is in equilibrium with a conjugate liquid phase.

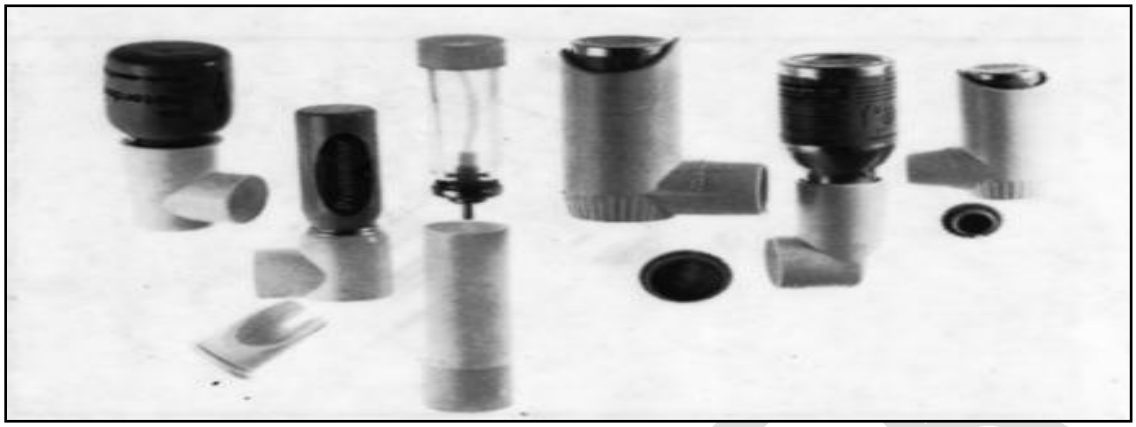
(iv) a region in which both components are present as pure solid phases.

- Those regions containing two phases (ii, iii, and iv) are comparable to the two-phase region of the phenol–water system.
- Thus it is possible to calculate both the composition and relative amount of each phase from knowledge of the tie lines and the phase boundaries.
- As system *x* is progressively cooled, more and more of the thymol separates as solid.
- As system *y* is cooled, the solid phase that separates at 22°C is pure salol.
- The lowest temperature at which a liquid phase can exist in the salol–thymol system is 13°C, and this occurs in a mixture containing 34% thymol in salol.
- This point on the phase diagram is known as the *eutectic point*.
- At the eutectic point, three phases (liquid, solid salol, and solid thymol) coexist.
- The eutectic point denotes an invariant system because, in a condensed system,
- F = 2 - 3 + 1 = 0.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which matters are compressible fluids. Their molecules are widely separated.	**Gas**
2	Which matters are relatively incompressible fluids. Their molecules are more tightly packed.	**Liquids**
3	Which matters are nearly incompressible and rigid. Their molecules or ions are in close contact and do not move.	**Solid**
4	The temperature above which the gas cannot be made to liquefy, OR is the temperature above which the liquid cannot longer exist	**critical temperature (T_c)**
5	In a crystalline solid, atoms, molecules or ions occupy (predictable) positions.	**Crystalline solids**
6	The simplest definition of a cocrystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either an atom, ion, or molecule.	**Cocrystal**

AEROSOLS

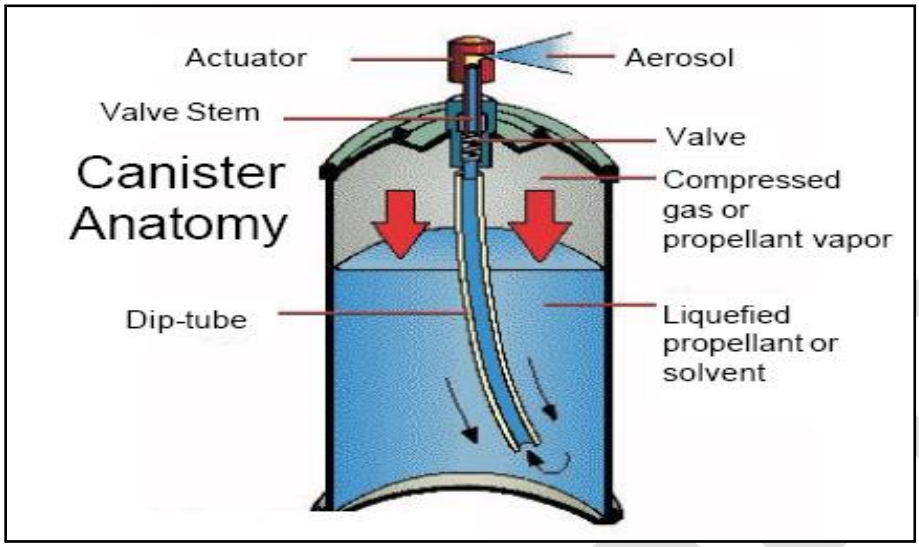


- Pharmaceutical aerosols are pressurized dosage forms that upon actuation emit a fine dispersion of liquid and/or solid materials containing one or more active ingredients in a gaseous medium.
- They differ from most other dosage forms in their dependence upon the function of the container, its valve assembly, and an added component—the propellant—for the physical delivery of the medication in proper form.

Advantages Of The Aerosol Dosage Form

- A portion of medication may be easily withdrawn from the package without contamination or exposure to the remaining material.
- By virtue of its hermetic character, the aerosol container protects medicinal agents adversely affected by atmospheric oxygen and moisture.
- Being opaque, the usual aerosol container also protects drugs adversely affected by light.
- This protection persists during the use and the shelf life of the product. If the product is packaged under aseptic conditions, sterility may also be maintained during the shelf life of the product.

COMPONENTS OF AEROSOL PACKAGE



(1) Propellant.

(2) Container.

(3) Valve and actuator.

(4) Product

Propellants

- Propellants Is a liquefied gas with a vapor pressure greater than atmospheric pressure at a temperature of 105˚ F (40.5 ˚C)
- Physicochemical properties of propellants:
- The propellant is one of the most important components of the aerosol package (It is said to be the heart of the aerosol).
- It provides the necessary force to expel the contents; it causes the product to be dispensed as foam or a spray, depending on the formulation.
- It serves as a solvent for certain active ingredient.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	Which Is a liquefied gas in Aerosol	Propallent
2	The liquefied propellant and vapor composed form?	Two phase system
3	How much time breathing time in aerosol?	10 seconds
4	Actuator, Stem, are parts of?	Valve
5	The relationships between temperature and the compositions and the quantities of phases present **at equilibrium** are represented.	Phase rule
6	As two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are **closer together** than the **similar charges** and forces, causing the molecules to **attract one another.**	Repulsive and attractive force

The propellant used for aerosols include:

1) Liquefied gases.

A. Fluorinated hydrocarbons (halocarbons) (Chlorofluorocarbons [CFCs]).

trichloromonofluoromethane (propellant 11)

dichlorodifluoromethane (propellant 12)

dichlorotetrafluoroethane (propellant 114)

B. Hydrocarbons.

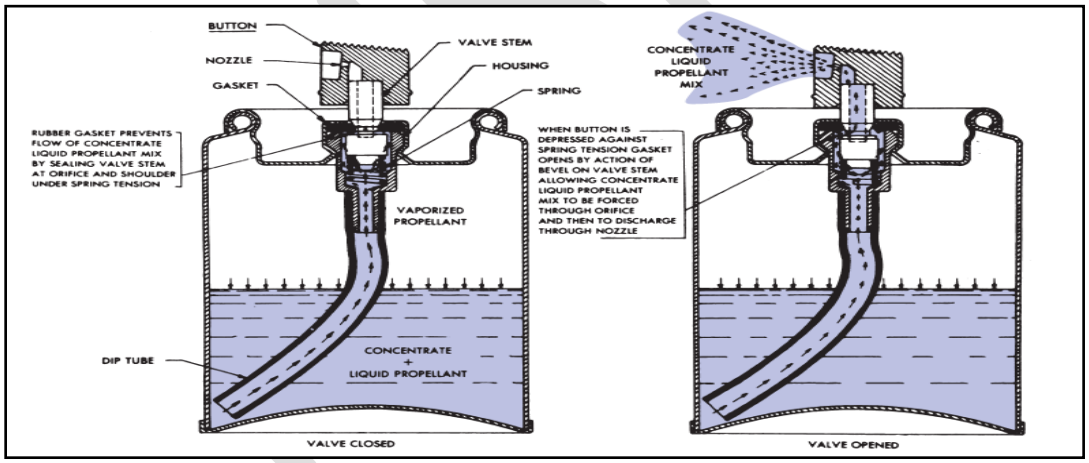
(propane, butane, and isobutane)

2) Compressed gases.

Nitrogen.

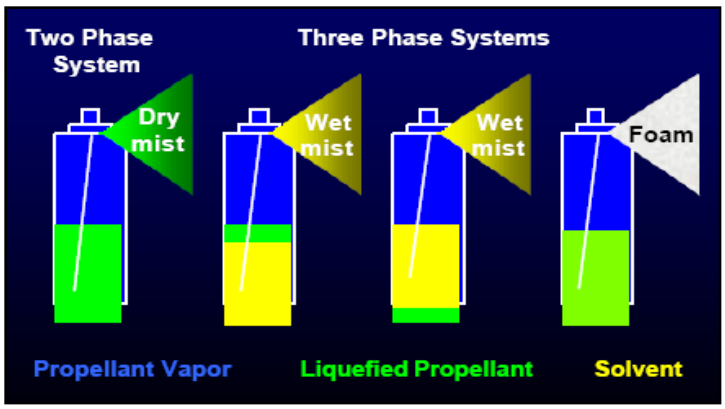
Nitrous oxide.

Carbon dioxide.



1. Two-Phase Systems

- The two-phase aerosol system consists of the liquid phase, containing the liquefied propellant and product concentrate, and the vapor phase.



2. Three-Phase Systems

- The three-phase system consists of a layer of water-immiscible liquid propellant, a layer of highly aqueous product concentrate, and the vapor phase.
- Because the liquefied propellant usually has a greater density than the aqueous layer, it generally resides at the bottom of the container with the aqueous phase floating above it.
- To avoid expulsion of the reservoir of liquefied propellant, the dip tube must extend only within the aqueous phase (product concentrate) and not down into the layer of liquefied propellant. The aqueous product is broken up into a spray by the mechanical action of the valve.
- If the container is shaken immediately prior to use, some liquefied propellant may be mixed with the aqueous phase and be expelled through the valve to facilitate the dispersion of the exited product or the production of foam.
- The vapor phase within the container is replenished from the liquid propellant phase.

- **One Word Question Answer**

SR NO.	QUESTION	ANSWER
1	The minimum pressure required to liquefy a gas at its critical temperature.	**critical pressure (P_c)**
2	Phase changes from solid to liquid is called	**Melting**
3	Phase changes from gas to liquid is called	**Deposition**
4	Phase changes from liquid to gas is called	**Freezing**
5	Phase changes from gas to liquid is called	**Condensation**
6	Phase changes from solid to gas is called	**Sublimation**
7	Phase changes from liquid to gas is called	**Evaporation**

AEROSOL CONTAINER AND VALVE ASSEMBLY

- The formulation must not chemically interact with the container or valve components to interfere with the stability of the formulation or with the integrity and operation of the container and valve assembly.
- The container and valve must be capable of withstanding the pressure required by the product, it must resist corrosion, and the valve must contribute to the form of the product to be emitted.

Containers

- Various materials have been used in the manufacture of aerosol containers, including

(a) glass, uncoated or plastic coated;

(b) metal, including tin-plated steel, aluminum, and stainless steel;

(c) plastics.

- The selection of the container is based on its adaptability to production methods, compatibility with formulation components, ability to sustain the pressure intended for the product, the interest in design and aesthetic appeal on the part of the manufacturer, and cost.
- Tin-plated steel containers are the most widely used metal containers for aerosols.
- When required, special protective coatings are employed within the container to prevent corrosion and interaction between the container and formulation.

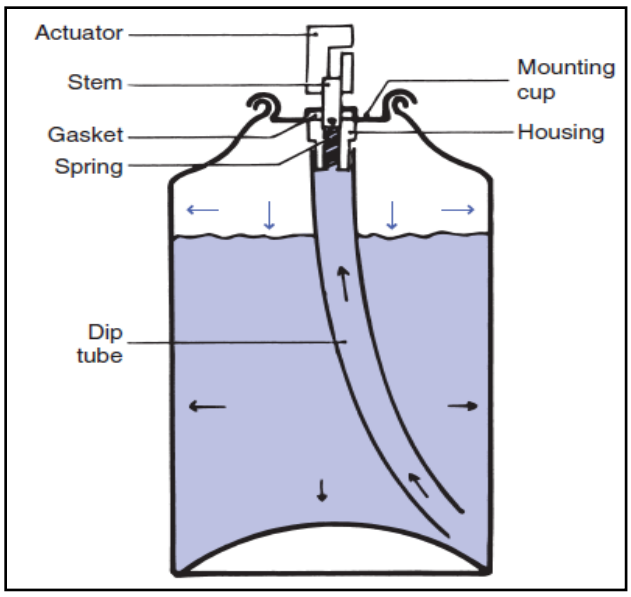
Valve Assembly

- The function of the valve assembly is to permit expulsion of the contents of the can in the desired form, at the desired rate, and in the case of metered valves, in the proper amount or dose.
- The materials used in the manufacture of valves must be inert to the formulations and must be approved by the FDA. Among the materials used in the manufacture of the various valve parts are plastic, rubber, aluminum, and stainless steel.
- The usual aerosol valve assembly is composed of the following parts:

1. ***Actuator***
2. ***Stem***
3. ***Gasket***
4. ***Spring***
5. ***Mounting cup***
6. ***Housing***
7. ***Dip tube***

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	A Properties that can be observed and measured **without changing** the material's composition. Eg. Color, Hardness.	**PHYSICAL PROPERTIES**
2	A property that can only be observed by changing the composition of the material. Eg. Ability to burn and ability to react etc.	**CHEMICAL PROPETIES**
3	Physical change will change the visible appearance, without changing the composition of the material. Can be reversible or irreversible :- BOIL , MELT, CRACK.	**PHYSICAL CHANGE**
4	Chemical change – a change where a new form of matter is made. RUST, BURN, DECOMPOSE.	**CHEMICAL CHANGE**
5	The substances whose constituents are arranged in definite orderly arrangements are called crystalline solids.	**CRYSTALLINE SOLID**



Method of use therapeutic inhalation aerosols

- The cap should be removed and inhaler shaken to dispense the drug.
- The patient should breathe out normally, but not fully. The inhaler mouthpiece is then put in the mouth and the lips closed round it.

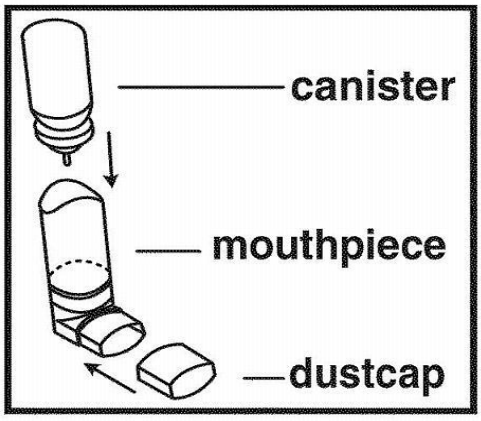


Figure 1

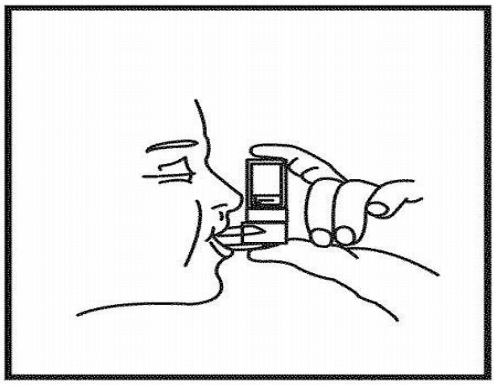


Figure 2

- The patient then breathes in slowly and at the same time activates the aerosol by pressing down on the canister.
- The breath should be held for 10 seconds or as long as the patient can comfortably manage.

- The patient then slowly exhales.
- If another dose has to be taken at least 1 minute should elapse before repeating the exercise.

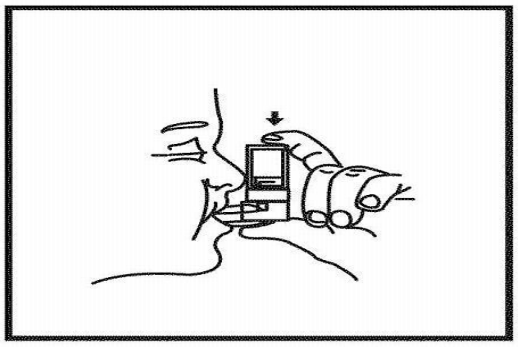


Figure 3

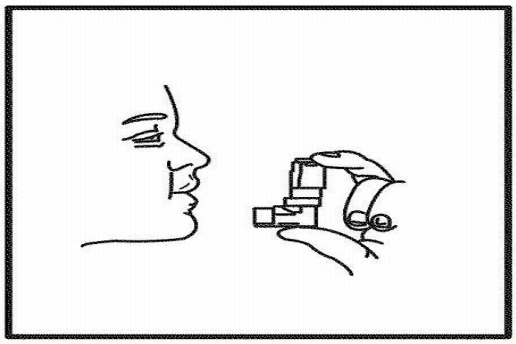


Figure 4

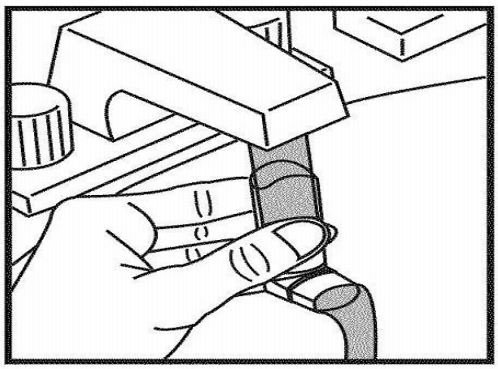


Figure 5

Storage of aerosols

- Store in cool place.
- Protect from heat, sun.
- Not freeze.

Advice to patient

- ***(Not exceed the recommended dose).***

One Word Question Answer

SR NO.	QUESTION	ANSWER
1	Substances whose constituents are not arranged in an orderly manner are called amorphous solids. Ex. Glass, rubber, plastic etc.	**AMORPHOUS SOLIDS**
2	Polymorphism (polus = many) and (morph = shape) it is the phenomenon in which substance exists in more than one crystalline forms.	**POLYMORPHISM**
3	Liquid crystals are a phase of matter whose order is intermediate between a liquid and that of a crystal.	**LIQUID CRYSTALS**
4	Pharmaceutical aerosols are pressurized dosage forms that upon actuation emit a fine dispersion of liquid and/or solid materials containing one or more active ingredients in a gaseous medium.	**AEROSOLS**
5	Propellants Is a liquefied gas with a vapor pressure greater than atmospheric pressure at a temperature of 105˚ F (40.5 ˚C).	**PROPELLANTS**