PREFORMULATION STUDIES

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- Particle size, shape and surface area
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- Preformulation stability studies
- A consideration of physico-chemical characteristics of new drug molecules with respect to different dosage forms

Preformulation

- Preformulation is branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance.
- Prior to the development of any dosage form new drug , it is essential that certain fundamental physical & chemical properties of drug powder are determined .
- This information may dictate many of subsequent event & approaches in formulation development.
- This first learning phase is called as preformulation.

INTRODUCTION

DEFINITION:-

Investigation of physico-chemical properties of the new drug compound that could affect drug performance and development of an efficacious dosage form".

Preformulation commences when a newly synthesized drug shows a sufficient pharmacologic promise in animal model to warrant evaluation in man.

INTRODUCTION

- The preformulation is the first step in the rational development of a dosage form of a drug substance alone and when combined with excipients.

- Objective :

  To generate useful information to the formulator to design an optimum drug delivery system.

GOALS OF PREFORMULATION

- To establish the necessary physicochemical parameters of new drug substances.
- To determine kinetic rate profile.
- To establish physical characteristics.
- To establish compatibility with common excipients.

PRELIMINARY EVALUATION

a) Compound identity.

b) Formula and molecular weight.

c) Structure.

d) Therapeutic indications:

- Probable human dose.
- Desired dosage form(s)
- Bioavailability model
- Competitive products

PRELIMINARY EVALUATION

e) Potential hazards

f) Initial bulk lots:

- Lot number
- Crystallization solvent(s)
- Particle size range
- Melting point
- % volatiles

g) Analytical methods:

- HPLC assay
- TLC assay
- UV/ Visible spectroscopy

ORGANOLEPTIC PROPERTIES

COLOR	ODOUR	TASTE
OFF-WHITE	PUNGENT	ACIDIC
CREAM-YELLOW	SULFUROUS	BITTER
SHINY	FRUITY	SWEET
	AROMATIC	TASTELESS
	ODOURLESS	TASTELESS

COLOR

- Color is generally a function of a drug's inherent chemical structure relating to a certain level of unsaturation.
- Color intensity relates to the extent of conjugated unsaturation as well as the presence of chromophores.
- Some compound may appear to have color although structurally saturated.

PURITY

- Designed to estimate the levels of all known & significant impurities & contaminates in the drug substance under evaluation.
- Study performed in an analytical research & development group.
- It is another parameter which allows for comparison with subsequent batches.
- Occasionally, an impurity can affect stability.

  e.g.

  - Metal contamination
  - Appearance

PURITY

- The techniques used for characterizing the purity of a drug are the same as those used for other purpose in a preformulation study.
- Thin layer chromatography is a wide ranging applicability & is an excellent tool for characterizing the purity.
- HPLC, paper chromatography & gas chromatography are also useful.
- More quantitative information can be obtained by using quantitative differential scanning colorimetry.

PARTICLE SIZE

- Particle size is characterized using these terms :

i. Very coarse (#8)
ii. Coarse (#20)
iii. Moderately coarse (#40)
iv. Fine (#60)
v. Very fine (#80)

PARTICLE SIZE

- Particle size can influence variety of important factors :
  - Dissolution rate
  - Suspendability
  - Uniform distribution
  - Penetrability
  - Lack of grittiness

Methods to Determine Particle Size

- Sieving
- Microscopy
- Sedimentation rate method
- Light energy diffraction
- Laser holography
- Cascade impaction

Methods to Determine Particle Size

1. **Sieving method :**

- Range : 50 – 150 µm
- Simple, inexpensive
- If powder is not dry, the apertures get clogged.

2. **Microscopy :**

- Range : 0.2 – 100 µm
- Particle size can be determined by the use of calibrated grid background.
- Most direct method.
- Slow & tedious method.

Methods to Determine Particle Size

3. Sedimentation method :

- Range : 1 - 200 µm
- Andreasen pipette is used.
- Particle size is calculated by stoke's law :

$$d_{st} = \sqrt{\frac{18\,\eta_0 h}{(\rho_s - \rho_0)\,g t}}$$

Where,

h = distance of fall in time, t

n_o = viscosity of the medium

ρ_s = density of the particles

ρ_0 = density of the dispersion medium

Methods to Determine Particle Size

4. Light energy diffraction :

- Range : 0.5 – 500 µm
- Particle size is determined by the reduction in light reaching the sensor as the particle, dispersed in a liquid
- or gas, passes through the sensing zone.

  Quick & fast.

5. Laser holography :

- Range : 1.4 – 100 µm
- A pulsed laser is fired through an aerosolized particle spray & photographed in three dimensional with holographic camera, allowing the particles to be individually imaged & sized.

Methods to Determine Particle Size

6. Cascade impaction :

- The principle that a particle driven by an airstream will hit a surface in its path, provide that its inertia is sufficient to overcome the drug force that tends to keep in it in airstream.

POWDER FLOW PROPERTIES

- Powder flow properties can be affected by change in particle size, shape & density.

- The flow properties depends upon following-

1. Force of friction.
2. Cohesion between one particle to another.

- Fine particle posses poor flow by filling void spaces between larger particles causing packing & densification of particles..
- By using glident we can alter the flow properties.

eg. Starch, Talc

Determination Of Powder Flow Properties

- By determining **Angle Of Repose.**
- A greater angle of repose indicate poor flow.
- It should be less than 30°. & can be determined by following equation.

$$\tan \theta = h/r.$$

where, θ = angle of repose.

h=height of pile.

r= radius.

Angle Of Repose (In degree)	Type Of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Determination Of Powder Flow Properties

- Measurement of free flowing powder by *compressibility.*
- Also known as *Carr's index.*

$$\text{CARR'S INDEX}(\%) = \frac{(\text{TAPPED DENSITY} - \text{POURED DENSITY})}{\text{TAPPED DENSITY}} \times 100$$

- It is simple, fast & popular method of predicting powder flow characteristics.

Determination Of Powder Flow Properties

- Carr's Index
  - 5-15
    - 12-16
    - 18-21
    - 23-35
    - 33-38
    - >40
- Type of flow
  - Excellent
  - Good Fair To Passable
    - Poor Very Poor
  - Extremely Poor

PARTICLE SHAPE

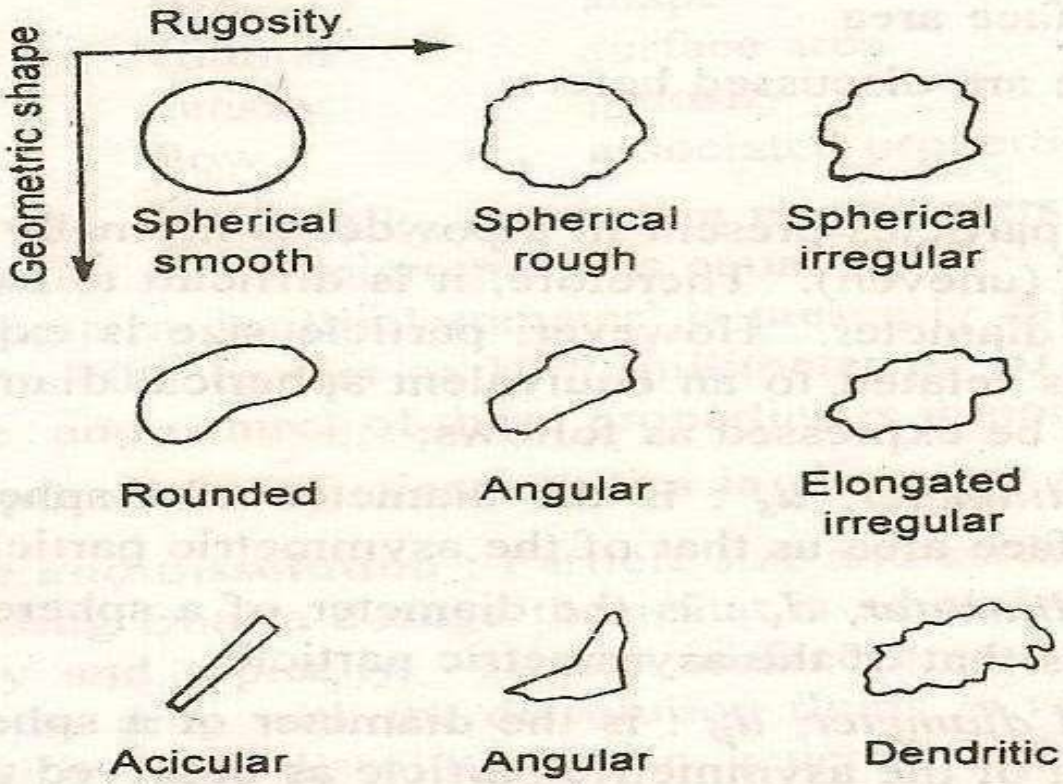


Figure 6-1. Characteristic particle shapes related to geometric shape and surface irregularity.

PARTICLE SHAPE

- Particle shape will influence the surface area, flow of particles, packing & compaction properties of the particles.
- A sphere has minimum surface area per unit volume.
- Therefore, these properties can be compared for spheres & asymmetric particles, in order to decide the shape.
- The following expression can be obtained:

Property	Sphere	particle
surface area	πd_{s_2}	$\alpha_s x\, d_{p2}$
volume	$(1/6)\pi d_{s3}$	$\alpha_v x\, d_{p3}$

Cont…

PARTICLE SHAPE

- When particle shape is spherical, the $d_s = d_p$
- Thus, $\alpha_s = \pi = 3.124$ & $\alpha_v = \pi/6 = 0.524$
- Therefore, Shape factor $= \dfrac{\alpha_s}{\alpha_v} = \dfrac{3.124}{0.524} = 6$

SURFACE AREA

- Particle size & surface area are inversely related to each other.
- Smaller the drug particle, greater the surface area.

Specific surface is defined as the surface area per unit weight (Sw) or unit volume (Sv) of the material.

SURFACE AREA

Estimation of S_v:

$$S_v = \frac{\text{Surface area of the particles}}{\text{Volume of particles}}$$

$$= \frac{n \alpha_s d^2}{n \alpha_v d^3}$$

$$= \frac{\alpha_s}{\alpha_v d}$$

- According to shape factor,

$$\frac{\alpha_s}{\alpha_v} = 6$$

- So, $S_v = 6 / d$.

SURFACE AREA

- Estimation of S_w:

$$S_w = \frac{\text{Surface area}}{\text{Weight}} = \frac{\text{Surface area}}{\text{density x volume}}$$

$$= \frac{S_v}{\rho}$$

$$= \frac{6}{\rho d}$$

Methods for determining surface area

1. Adsorption method :

- Particles with a large specific surface are good adsorbents for the adsorption of gases & of solutes from solution.
- The volume of nitrogen gas, V_m, in cm^3 that 1 g of the powder can adsorb when the monolayer is complete is more accurately given by using the BET equation, however, which can be written as:

$$\frac{P}{V(P_0 - P)} = \frac{1}{V_m b} + \frac{(b-1)}{V_m b} \cdot \frac{P}{P_0}$$

Cont...

Methods for determining surface area

- Where,

V = Volume of gas in cm^3 adsorbed per gram of powder at pressure P.

P = Pressure of the adsorbate, in mmHg.

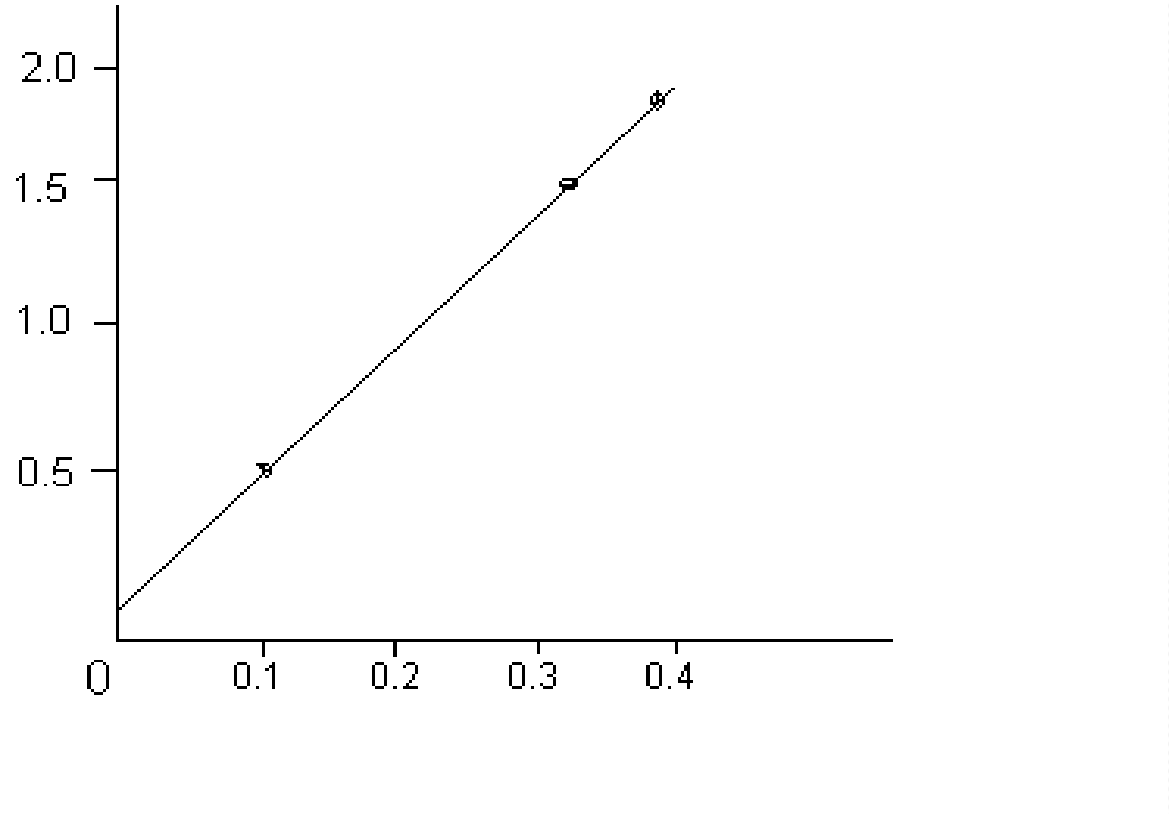
P_o = Saturation vapor pressure (monolayer)

V_m = Amount of vapor adsorbed per unit mass adsorbent, when the surface is covered with monomolecular layer

b = Constant that express the difference between the heat of adsorption & heat of liquefaction of the adsorbate (nitrogen).

Quantasorb QS – 16 instrument

$$\frac{P}{V(P_0 - P)}$$



P/P_0

Air permeability method :

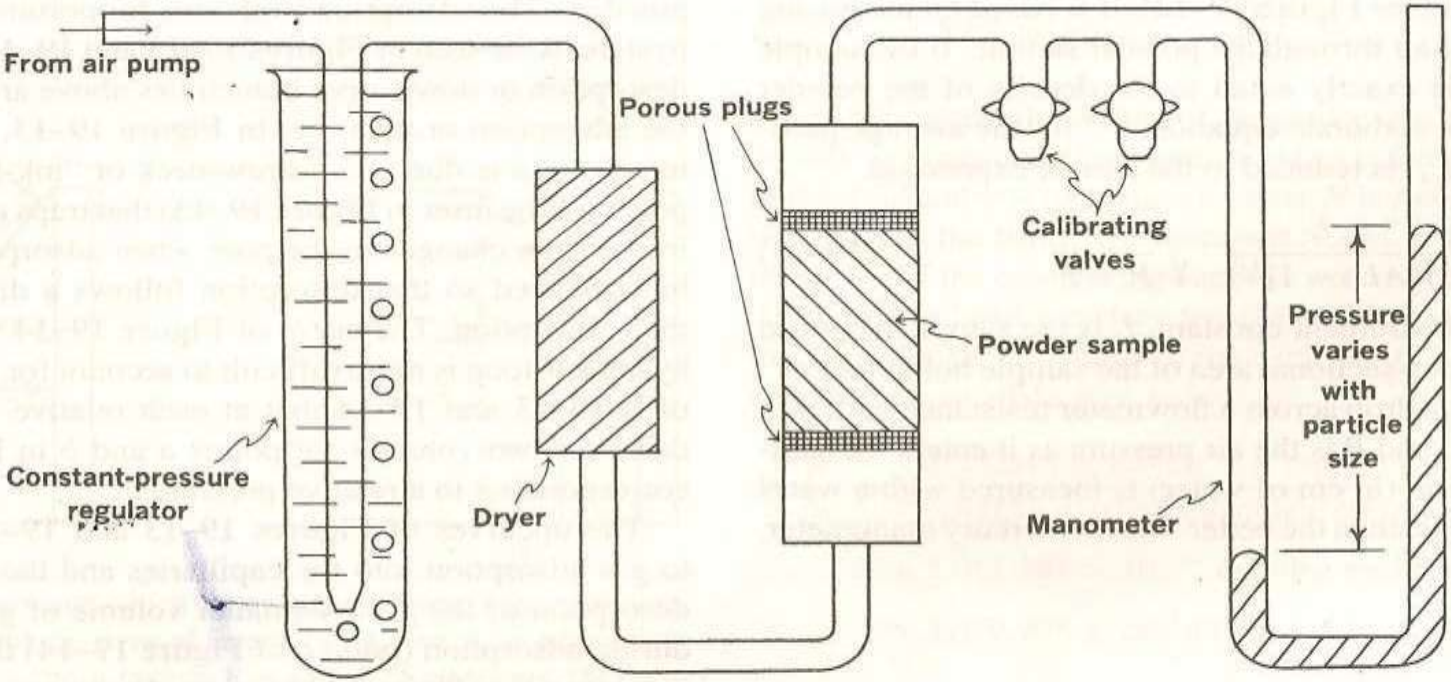


Fig. 19–12. The Fisher subsieve sizer. An air pump generates air pressure to a constant head by means of the pressure regulator. Under this head, the air is dried and conducted to the powder sample packed in the tube. The flow of air through the powder bed is measured by means of a calibrated manometer and is proportional to the surface area or the average particle diameter.

HOWEVER SIZE REDUCTION IS NOT REQUIRED IN FOLLOWING CASES

- WHEN DRUG IS UNSTABLE.
- DEGRADE IN SOLUTION FORM.
- PRODUCE UNDESIRABLE EFFECTS.
- WHEN SUSTAINED EFFECT IS DESIRED.

SOLUBILIZATION

“ Solubilization is defined as the spontaneous passage of poorly water soluble solute molecules into an aqueous solution of a soap or detergent in which a thermodynamically stable solution is formed ”.

SOLUBILIZATION

- **It is the process by which apparent solubility of an otherwise sparingly soluble substance is increased by the presence of surfactant micelles .**

- ***MICELLES: -***

- **The mechanism involves the property of surface active agents to form colloidal aggregates known as micelles .**

SOLUBILIZATION

- When surfactants are added to the liquid at low concentration they tend to orient at the air-liquid interface .
- On further addition of surfactant the interface becomes completely occupied and excess molecules are forced into the bulk of liquid.
- At very high concentration surfactant molecules in the bulk of liquid begin to form micelles and this concentration is know as *CRITICAL MICELLE CONCENTRATION {CMC}*

SOLUBILIZATION

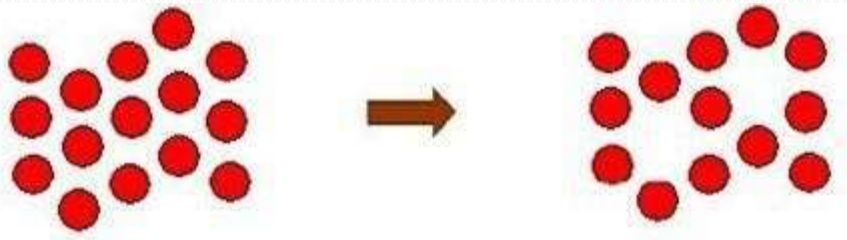
- Solubilization is thought to occur by virtue of the solute dissolving in or being adsorbed onto the micelle.
- Thus the ability of surfactant solution to dissolved or solubilize water insoluble materials starts at the CMC and increase with increase in the concentration of micelles.

- Solubilization of any material in any solvent depends on proper selection of solubilising agents.

Process Of Solubilization

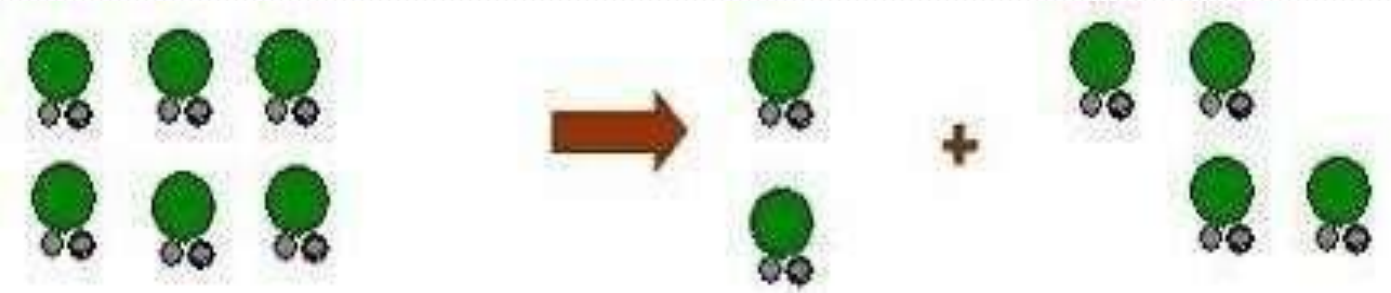
- The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Step 1: Holes opens in the solvent

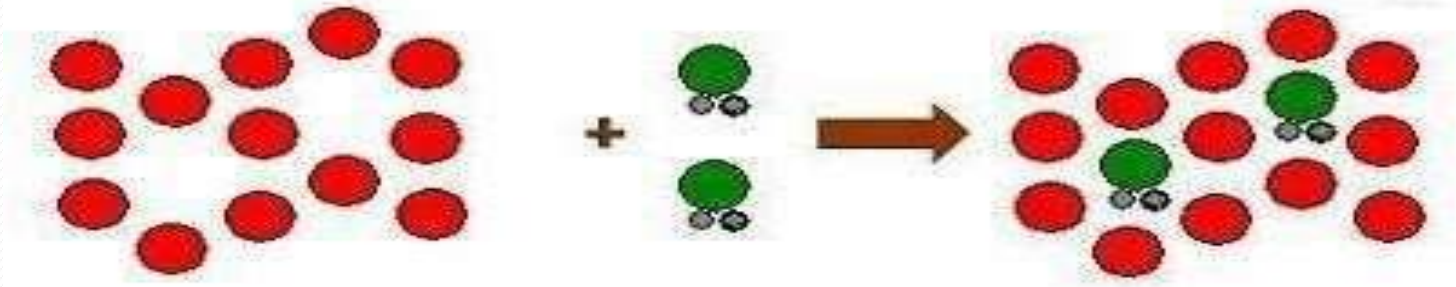


Process Of Solubilization

Step2: Molecules of the solid breaks away from the bulk



Step 3: The free solid molecule is intergraded into the hole in the solvent



SOLUBILITY

- **The amount of substance that passes into solution in order to establish equilibrium at constant temperature and pressure to produce a saturated solution.**

SOLUBILITY

- If solubility is <1mg/ml indicates need for salt formation to improve solubility.
- If solubility is <1mg/ml in pH= 1 to 7, preformulation study should be initiated.
- Solubility should ideally be measured at two temperatures: 4°C and 37°C.
  - 4°C to ensure Physical stability.
  - 37°C to support Biopharmaceutical evaluation.

DESCRIPTIVE SOLUBILITIES (I.P.)

Description	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 - 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

SOLUBILITY ANALYSIS

- **Preformulation solubility studies focus on drug solvent system that could occur during the delivery of drug candidate.**

- **For e.g. A drug for oral administration should be examined for solubility in media having isotonic chloride ion concentration and acidic pH.**

SOLUBILITY ANALYSIS

- **Analytic method that are particularly useful for solubility measurement include HPLC, UV spectroscopy, Fluorescence spectroscopy and Gas chromatography.**

- **Reverse phase HPLC offer accurate and efficient mean of collecting solubility data of drug.**

Ionization constant (pKa)

Can be calculated by Henderson Hasselbach equation-

For acidic drugs….pH= pKa+ log [ionized drug] / [unionized drug]

For basic drugs….pH= pKa+ log [unionized drug] / [ionized drug]

pH Solubility Profile

- **The solubility of acidic or basic drug will show difference in solubility with changes in pH.**

- **pH solubility profile of a drug can be established by running the equilibrium solubility experiment within pH range of 3-4.**

Partition Coefficient

- **It is the ratio of unionized drug distributed between organic and aqueous phase at equilibrium.**

$$\mathbf{P}\ o/w = (\ \mathbf{C}\ oil\ /\ \mathbf{C}\ water\ )equilibrium$$

Effect Of Temperature

- **The heat of solution ΔHs, represents the heat released or absorbed when a mole of solute is dissolved in large quantity of solvent.**

- **Endothermic reaction**
- **Exothermic reaction**

Determination of solubility

- **The following points should be considered**
- **The solvent & solute must be pure.**
- **A saturated solution must be obtained before any solution is removed for analysis.**
- **The method of separating a sample of saturated solution from undissolved solute must be satisfactory.**
- **The method of analyzing solution must be reliable**
- **Temperature must be adequately controlled .**

Solubility Determination Method

- **Solubility is normally depends on temperature, so temperature is recorded in each solubility measurement.**
- **Plot of solubility against temperature is commonly used for solubility determination.**
- **Two methods are available for determination are as follow.**

I.Analytical method

II.Synthetic method

Analytical method

- **Temperature of equilibrium is fixed and concentration of the solute in the saturated solution is determined at equilibrium by a suitable analytical procedure.**

- **In other words a saturated solution in the presence of an excess of the undissolved solute is prepared at an accurately known temperature. This situation can be achieved by suitable contact b/w solute and solvent.**

Synthetic method

- **In this method a weighed amount of solute is placed in the vessel.**
- **While agitating the system at constant temperature known amount of solvent is added gradually until the solubility limit is reached.**
- **At equilibrium, temperature and content of the system is recorded.**
- **This method is carried out at micro scale level by examining the small amount of the system under hot stage microscope.**

General Method of Increasing the Solubility

- **Addition of co-solvent**
- **pH change method**
- **Reduction of particle size**
- **Temperature change method**
- **Hydotrophy**
- **Addition of Surfactant**
- **Dielectrical Constant**
- **Complexation**

Addition Of Co-Solvent

- **Weak Electrolyte :- Phenobarbitone**
- **Non polar :- Nitro Cellulose**

These are poorly soluble in given solvent.

For such poorly soluble materials, to enhance their solubility, the water miscible solvents are used in which the drug has good solubility.

This process of improving solubility is known as co-solvency and the solvent used is known as co-solvents.

Addition Of Co-Solvent

e.g. **Phenobarbitone is insoluble in water. A clear solution is obtained by dissolving in mixture of Alcohol, Glycerin, Propylene glycol.**

e.g. Of Cosolvents:-

PG, glycerin, sorbitol, PEG, Glyceryl formal, glycofurol, ethyl carbamate, ethyl lactate and dimethyl acetamide.

pH change Method

- **Weak base:- Alkaloids, Local Anaesthesia**
- **Weak acid:- Sulphonamides, Barbiturates**
- **In aqueous medium they dissociate poorly and undissociated portion is insoluble.**

e.g. **Benzoic acid, Phenobarbitone**

- **So, solubility of the undissociated portion is improved by pH control.**
- **For weak acidic drug:- increase pH, solubility is increase.**
- **For weak base drug:- decrease pH, increase solubility.**

Reduction Of Particle size

- **Reduction in Particle size improve solubility of drug.**

- **Basically reduction in particle size increase contact surface area of the particle, there by ultimately it increase rate of solubility of drug.**

Temperature Change Method

- **In endothermic reaction by increasing temperature solubility is increase.**

- **In exothermic reaction by increasing temperature solubility is decrease.**

e.g. **Methyl Cellulose when mixed with water and temperature is raised, it becomes insoluble. To dissolve it cold water is added.**

HYDROTROPHY

The term Hydotrophy has been used to designate the increase in solubility in water of various substances due to the presences of large amount of additives.

e.g. **Solubilization of Benzoic acid with Sodium benzoate.**

Addition of Surfactant

Surfactants are molecules with well defined polar and non-polar region that allow them to aggregate in solution to form micelles. Non polar drugs can partition into micelles and be solubilized.

e.g. **Surfactant based solution of Taxol, that is solubilized in 50% solution of Cremophor.**

Dielectrical Constant

Dielectrical Constant is the effect that substances has, when it acts as a solvent on the case with which it separates oppositely charged atoms.

e.g. **DEC of Water- 80**

Kerosene- 2

Glycerine- 48

Benzene- 2.2

Complexation

- For the Complexation occur both drug and ligand molecule should be able to donate or accept electrons.
- The solubility of compound is the sum of solubility of the compound and its complex.

e.g. HgI_2 (Mercuric Iodide) is sparingly soluble in water. Its solubility in water is increased by forming complex with KI.

$$HgI_2 + 2KI \longrightarrow K_2HgI_4 \text{ (water soluble)}$$

Applications of solubilization

- **Drugs with limited aqueous solubility can be solubilized. These include oil-soluble vitamins, steroid hormones and antimicrobial agents etc.**
- **Solubilization of orally administered drugs results in an improved appearance and improves unpleasant taste.**
- **Both oil-soluble and water-soluble compounds can be combined in a single phase system as in case of multivitamin preparations.**

Applications of solubilization

- **Solubilization may lead to enhanced absorption and increased biological activity.**
- **Improves the intestinal absorption of vitamin A.**
- **Drug absorption from ointment bases and suppositories also increased.**
- **Liquid preparations with small quantity of preservative can be prepared by solubilization.**

Applications of solubilization

- **Aqueous concentrates of volatile oils can be prepared by solubilization.**

Example: soaps used for solubilising phenolic compounds for use as disinfectants- Lysol, Roxenol etc.

- **Barbiturates, anticoagulant, alkloidal drugs are dissolved with polysorbate by solubilization.**

SURFACTANT

- ***Surfactants:-***

are wetting agents that lower the surface tension of a liquid, allowing easier spreading, and lower the interfacial tension between two liquids.

- **Classification**

Some commonly encountered surfactants of each type include:

1. Ionic
- **Cationic**
- **Anionic**
- **Zwitterionic**

2. Non ionic

IONIC

Cationic Surfactants:-

Quaternary ammonium salts are more preferred because they are less affected by pH.

e.g. **Cetyl Trimethyl Ammonium Bromide (CTAB) Hexadecyl Trimethyl Ammonium Bromide, and other Alkyltrimethyl Ammonium Salts, Cetylpyridinium Chloride (cpc)**

IONIC

Anionic Surfactants:-

They are the most commonly used surfactants, containing Carboxylate, Sulfonate, Sulfate ions.

e.g. **Sodium Dodecyl Sulphate (SDS), Ammonium Lauryl Sulphate and other alkyl sulfate salts, Sodium Laureth Sulphate, also known as Sodium Lauryl Ether Sulphate (SLES).**

IONIC

Zwitterionic:-

When a single surfactant molecule exhibit both anionic and cationic dissociations it is called amphoteric or Zwitterionic.

The anion include carboxylates and phosphate group and the cation include quaternary ammonium group.

e.g. **Dodecly Betamine**

Dodecly Dimethylamine Oxide

NONIONIC

- **These are most widely used because they are free from non compatability, stability and potential toxicity and classified as water soluble and water insoluble non ionic surfactants.**

- ***e.g.*** **Long chain fatty acids, fatty alcohols**

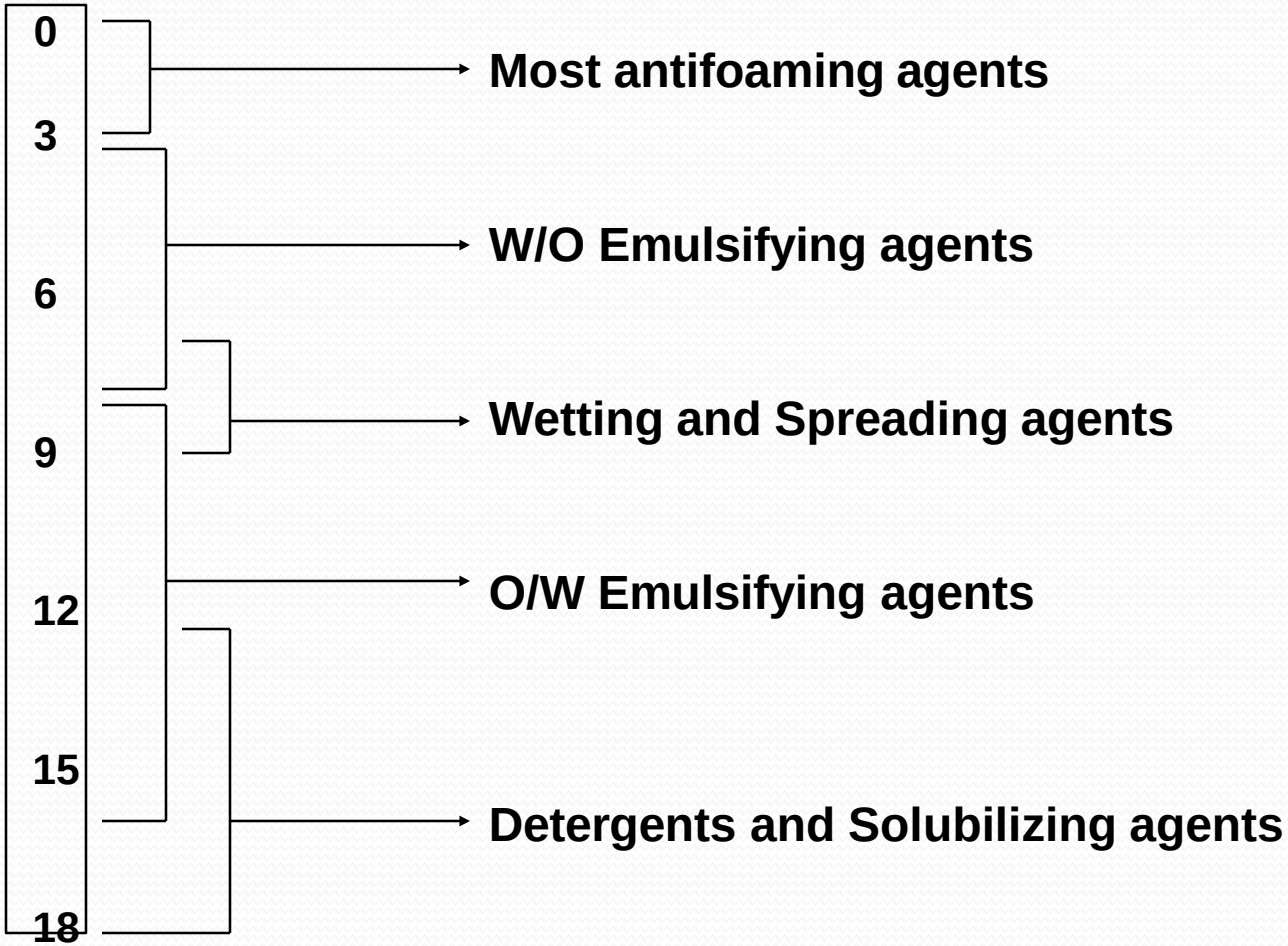
Water solubility of these agents is further increased by addition of polyoxyethylene groups through ether linkage with one of the alcohol group.

e.g. **spans**

HLB SCALE

- Griffin in 1947 developed the system of the hydrophilic-lipophilic balance [HLB] of surfactant.
- The higher the HLB of the an agent, the more hydrophilic it is.
- Tween, polyoxyethylene derivative of the spans are hydrophilic and have high HLB value (9.6-16.7)
- The lower the HLB of the agent, the more lipophilic it is.
- The sorbitan ester are lipophilic and have low HLB value (1.8-8.6)

HLB SCALE


0
3
6
9
12
15
18
Most antifoaming agents
W/O Emulsifying agents
Wetting and Spreading agents
O/W Emulsifying agents
Detergents and Solubilizing agents

HLB SCALE

- The HLB of non ionic surfactant whose only hydrophilic portion is polyoxyethylene is calculated using the formula

- HLB = E/5

  Where, E = Percentage weight of ethylene oxide

Importance Of Surfactant

- **Surfactants play an important role in many practical applications and products, including:**

- **Detergents**
- **Fabric Softener**
- **Emulsifier**
- **Paints**
- **Adhesive**
- **Inks**
- **Soil remediation**
- **Wetting**

Importance Of Surfactant

- **Ski Wax**
- **Snowboard Wax**
- **Foaming**
- **Defoaming**
- **Laxatives**
- **Agrochemical formulations Herbicides Insecticides**
- **Quantum dot coating**
- **Biocides (Sanitizers)**
- **Hair Conditioners (after shampoo)**
- **Spermicide (Nonoxynol 9)**

TEMPARATURE ,pH, COSOLVANCY, SOLID DISPERSIONS

Effect of Temperature

- The solubility of a solute in a solvent is dependent on temperature, nature of solute and nature of solvent.
- Heat of solution represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.
- Most of the substances are endothermic, absorbing heat in the process of dissolution.

Effect of Temperature

- For this substances, an increase in temperature results in an increase in solubility.
- Exothermic substances give off heat in the process of dissolution. The solubility of such substances would decrease with increase in temperature.
- Care should be taken as heat may destroy a drug or cause other changes in the solution.

e.g. On excess heating the sucrose solution it can get converted in to the invert sugar.

Effect of Temperature

- Depending on the type of reactions weather it is exothermic or endothermic heat is either released or absorbed.

  e.g. Mixture of chloroform and acetone. The heat produced by the solute-solvent interaction is so much greater than the heat necessary to separate the molecules of acetone and chloroform, which can be detected as a rise in temperature of the liquid.

Effect of Temperature

- Applications:
- Pharmaceutical solutions must be administered at or near room temperature. So, it is more important factor for product storage than the formulation.
- To increase the solubility of sparingly soluble solute.
- To increase the stability by reducing the moisture content.

Effect of pH

- Weak electrolytes undergo ionization and are more soluble when in ionized form. The degree of ionization depends on dissociation constant (pKa) and the pH of the medium.
- Solubility is a function of pH, that is related to its pKa which gives ratio of ionized and unionized forms of the substance.

  This can be shown as:

$$pH = pKa + \log \frac{[A^-]}{[HA]}$$

Effect of pH

- If the substance is brought outside its pKa, i.e. the pH value where half the substance is ionized and half is not, than solubility will be changed because we are introducing new intermolecular forces, mainly ionic attraction.

- e.g. –COOH has pKa value at pH around 4. If pH is increased then –COOH is converted into $–COO^-$. This may interact with the H^+ of water.

Effect of pH

- The effect of pH on solubility for weak electrolytes can be described by:

$$pHp = pKa + \log \left[\frac{S - S_0}{S_0} \right]$$

- Where,

pHp = pH below which the drug precipitates from solution as the undissociated acid.

S = total solubility.

S_0 = molar solubility of the undissociated acid.

Effect of pH

- It is to be ensured that pH change for one single compound should not affect the other requirements of product.

- e.g. the chemical stability of drug may depend on pH, and this pH of optimum stability should not coincide with the pH of other ingredients specially colors, preservatives and flavors.

Cosolvancy

- To enhance the solubility of poorly soluble materials, the water miscible solvents are used in which the drug has good solubility. This process of improving solubility is known as co-solvency.

- Solvents used to increase the solubility are known as co-solvents.

Cosolvancy

- The mechanism for solubility enhancement by co-solvency is not clearly understood. But it is proposed that, solubility is increased may be by reducing the interfacial tension between the solvent and hydrophobic solutes and decreasing dielectric constant of solvent.

Cosolvancy

- The commonly used and acceptable co-solvents in formulation of aqueous liquids for oral solutions are Ethanol, Sorbitol, Glycerin, Several members of PEG series.

- For parenteral products, Dimethylacetamide is widely used. But in case of oral liquids its application is limited, because of its objectionable odour and taste.

Cosolvancy

- Some characteristics of co-solvent, which are used in preparation:

  1.It must be non-toxic. Non-irritating.

  2.It should be able to solubilize the drug in given solvent.

  3.It should be able to cross the membrane.

- Apart from increasing solubility, they are also used to improve the solubility of volatile constituents used to impart a desirable flavour and odour to the product.

Solid – Dispersion System

- Definition :

Solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting, solvent or melting solvent method.

Classification (Based on FastRelease mechanism)

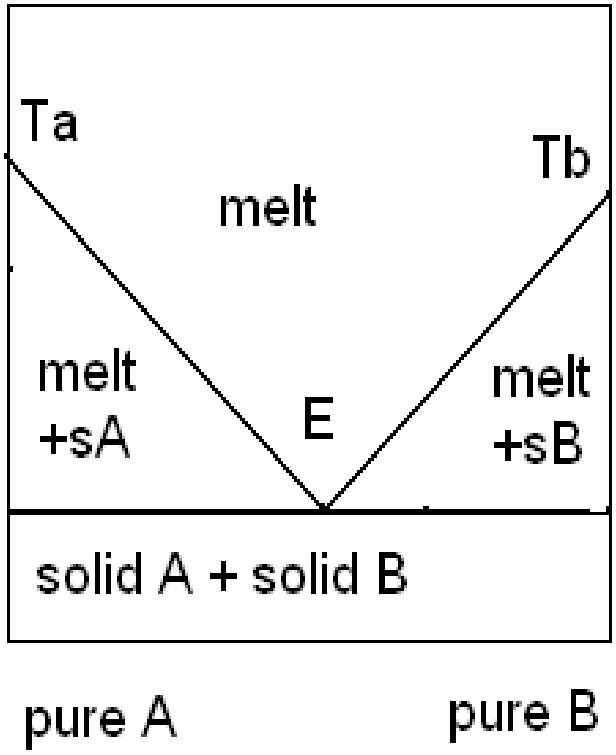
- Simple Eutectic Mixtures
- Solid Solutions
- Glass Solutions and Glass Suspensions
- Amorphous precipitation of drug in crystalline carrier
- Compounds or Complex formation between drug and carrier
- Any combination among the above

A. Eutectic Mixtures

- When two or more substances are mixed together they liquefy due to the lowering of melting point than their individual melting point. Such substances are called as eutectic substances.

  e.g. paracetamol-urea, griseofulvin-urea

A. Eutectic Mixtures



- Simple binary phase diagram showing eutectic point E.
- The eutectic composition at point E of substance A and B represents the melting point.
- T_A and T_B are melting point of pure A and pure B.

A. Eutectic Mixtures

- The following factors may contribute to faster dissolution rate of drug dispersed in the eutectic mixtures:-

  1.Increase in drug solubility.

  2.Solubilization effect by the carrier which completely dissolves in a short time in diffusion layer surrounding drug particles.

  3.Absence of aggregation and agglomeration between fine crystallites of pure hydrophobic drug.

A. Eutectic Mixtures

4. Excellent wettability and dispersibility of a drug as the encircling soluble carrier readily dissolves and causes water to contact as wet drug particles.

5. Crystallization of drug in a metastable form after solidification from fused solution, which has high solubility.

A. Eutectic Mixtures

- Eutectics are easy to prepare and economical with no solvents involved. The method however cannot be applied to:

  - Drugs which fail to crystallize from mixed melt.

  - Thermolabile drugs.

  - Carriers such as succinic acid that decompose at melting point.

B. Solid Solutions

- It is made up of a solid solute dissolved in a solid solvent. It is often called a “mixed crystal” because the two components crystallize together in a homogenous phase system.
- It is prepared by fusion method.
- A solid solution of poorly soluble drug in a rapidly soluble carrier achieves a faster dissolution because particle size of drug is reduced to molecular size.

Classification

- According to extent of miscibility :

1. Continuous (iso-morphous, unlimited, complete) solid solution.
2. Discontinuous (limited, restricted, incomplete) solid solution.

- According to crystalline structure of solid solutions :

1. Substitutional solid solutions.
2. Interstitial solid solutions.

Classification

a) Continuous Solid Solutions :-

The two components are miscible or soluble at solid state in all proportions.

No established solutions of this kind has been shown to exhibit fast release dissolution properties.

The faster dissolution rate would be obtained if the drug is present as a minor compartment.

b) Discontinuous Solid Solutions :-

There is only limited solubility of a solute in a solid solvent in this group of solid solutions.

C. Glass Solutions and Glass Suspensions

- A glass solution is a homogenous, glassy system in which a solute is usually obtained by abrupt quenching of the melt.

- Many compounds have been shown to be able to form glasses readily upon cooling from liquid state.

- These compounds include sucrose, glucose, ethanol and 3- methyl hexane.

C. Glass Solutions and Glass Suspensions

- It is presumably due to their strong hydrogen bonding which may prevent their crystallization.
- Polymers possessing linear, flexible chains can freeze into a glass state to transparency and brittleness.
- The strength of chemical binding in a glass solution is much less compared to that in a solid solution.
- Hence, dissolution rate of drugs in the glass solution is faster than in solid solution.
- e.g. Glass solution of citric acid

D. Amorphous Precipitation of Drug in Crystalline Carrier

- Instead of forming a simple eutectic mixture in which both drug and the carrier crystallize simultaneously from a solvent method of preparation, the drug may also precipitate out in an amorphous form in crystalline carrier.

- It has faster dissolution and absorption rates than crystalline form.
- e.g. Amorphous novobicin has 10 fold higher solubility than its crystalline form.

E. Compound or Complex Formations

- Dissolution and absorption of a drug can occur from a complex or a compound formed between the drug and an inert soluble carrier.
- Complexation also implies that dissolution could be retarded as observed with PEG 4000 - phenobarbital.
- However, the formation of a soluble complex with a low association constant results in increased rates of dissolution and absorption.

F. Combinations and Miscellaneous Mechanisms

- A solid dispersion entirely belongs to any five groups discussed so far, but it can also be made up of combinations of different groups.

- These combinations increase the dissolution and absorption rate.

- The griseofulvin dispersed at high concentrations in PEG may exist as individual molecules and as micro-crystalline particles.

Methods of Preparations

- Melting Method
- Solvent Method
- Melting - Solvent Method
- Hot Melt Extrusion Technique

1. Melting Method or Fusion Method

- The physical mixture of a drug and water soluble carrier is heated until it melts.
- The melt is then cooled and solidified rapidly in an ice bath with vigorous stirring .
- The final solid mass is crushed, pulverized and sieved.
- To facilitate faster solidification, the homogenous melt is poured in the form of a thin layer onto stainless steel plate and cooled by flowing air or water on the opposite side of the plate.

1. Melting Method or Fusion Method

- Advantages :
- Simplicity of method.
- Supersaturation of a solute or a drug in a system can often be obtained by quenching the melt rapidly from high temperature.
- Disadvantage :
- Some drugs or carriers may decompose or evaporate during fusion process at high temperatures .

  e.g. succinic acid used as a carrier for griseofulvin is quite volatile and may also partially decompose by dehydration near its melting point.

2. Solvent Method

- They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent.

- The method is used to prepare solid dispersions of griseofulvin-polyvinylpyrrolidone, sulphathiazole - pvp.

2. Solvent Method

- Advantage :
  - Thermal decomposition of drugs or carriers can be prevented because of low temperature required for the evaporation of organic solvents.

- Disadvantages :
  - High cost of preparation.
  - Difficulty in completely removing the solvent.
  - Difficulty in producing crystal forms.

3. Melting Solvent Method

- It is prepared by first dissolving the drug in a suitable solvent and then incorporating this solution in a melt of PEG without removing the solvent.

- Advantages :

  Same as above two methods

- Disadvantage :

  From practical stand point, it is only limited to drugs with a low therapeutic dose, e.g. below 50mg.

4. Hot Melt Extrusion Method

- In this method, a blend of active ingredients, polymeric carrier and other processing aids like plasticizers and antioxidants is heated and softened.
- This softened material is called as extrudate.
- When the extrudate is cooled at room temperature, the polymeric thermal binder solidifies and bonds the excipients together to form a matrix.

4. Hot Melt Extrusion Method

- Advantages :
  - There are no concerns with solvent handling or recovery after processing

  -It is simple and continuous process for preparation of tablets and granulations.
  - The process is faster and there were fewer steps than the wet granulation method.

  -Can be used for formulating sustained release granules.

  e.g. Diltiazem granules.

Methods of Determination of Solid Dispersion Systems

- Thermal analysis

  a) Cooling curve method

  b) Thaw-melt method

  c) Thermoscopic method

  d) Differential thermal analysis (DTA)

  e) Zone Melting Method

Methods of Determination of Solid Dispersion Systems

- X-Ray diffraction Method
- Microscopic method
- Spectroscopic method
- Thin layer chromatography
- Solubility determinations

A. Thermal Analysis

b) Thaw-melt method

- Here a sample of solidified mixture in a capillary melting point tube is heated gradually till the thaw point.

- The thaw point is referred to as crossing solidus line.

- It is useful in differentiating between a simple eutectic system and a limited solution.

A. Thermal Analysis

c) Thermoscopic method :

- Polarized microscopy is used with hot stage to study phase diagrams of binary systems.

- The physical mixture is gradually heated on a slide until it completely liquefies.

- After cooling, the mixture is heated at rate of 4 degree per minute.

- The thaw and melting points are determined by visual observations.

A. Thermal Analysis

d) Differential thermal analysis (DTA) :

- An effective thermal method for studying phase equilibria of either pure compound or mixture.

- Different effects, associated with physical or chemical changes are automatically recorded as function of time or temperature as the substance is heated in uniform rate.

- In addition; evaporation, sublimation, polymorphic transition, desolvation can be detected.

B. X-Ray Diffraction Method

- In this method the intensity of x-ray diffraction or reflection from a sample is measured as a function of diffraction angles.
- Counter and film methods detect diffraction intensity.
- Counter method provides better resolution of diffraction and relative intensity which can be easily compared.
- This method is used to characterize physico-chemical properties of Griseofulvin dispersed in PEG 4000 and 6000.

C. Microscopic Method

- It has been used to study polymorphism and morphology of solid dispersion.
- The fine particles of crystallization in glass PVP can be easily detected by polarizing microscope.
- The resolution of electron microscope was used to study dispersed particle size of iopanic acid in PVP.

D. Spectroscopic Method

- In the UV study, the spectra of pure drug and the dispersed drug are scanned.
- e.g. The spectrum of the dispersed beta – carotene resembles that beta–carotene is dissolved in organic solvents but do not indicate the molecular dispersion of drug in polymer.

E. Thin Layer Chromatography

- TLC characteristics of pure and dispersed drugs are studied to test whether the drugs are decomposed by process.

- A single spot with same 'R_f'value is expected for both the pure and processed samples in thin layer plate.

F. Solubility determinations

- Results from aqueous solubility studies of drug in various concentrations of carrier would indicate interactions between drug and carrier.
- Such studies indicated weak or insignificant interactions between griseofulvin and PEG 6000.
- Increased rate of dissolution due to solubility of the drug by carrier can be predicted by this method.

Pharmaceutical Applications

- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.
- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs by using poorly soluble or insoluble carriers.

β-cyclodextrin drug dispersion system,

techniques for studies of crystals, polymorphism

β-cyclodextrin drug dispersion system

- The poorly dissolution of relatively insoluble drug has for long been a problem in the formulation of oral dosage form.

- This limits the aspect such as
  - Absorption &
  - Bioavailability

β-cyclodextrin drug dispersion system

- Several approach have been followed in improving the solubility of drug, one of them being complexation using cyclodextrin.

- Cyclodextrin is cyclic structure oligomers of glucose which are obtained from the starch digests of the bacteria Bacillus macerans.

Method of preparation of β-cyclodextrin complex

- Physical mixture method
- Kneading method
- Co-evaporation method
- Solid dispersion method
- Spray drying method
- Neutralization method

Physical mixture method

- Here the drug and b-cyclodextrin (1:2) are mixed physically with spatula & then the pulverized powder is passed through 100#.

- Eg. Diclofinac sodium

Kneading method

- Here the b-cyclodextrin is dissolved in small vol. of water-methanol solution(6:4).
- To the above solution required drug is added in small amount.
- The slurry is then kneaded for 45 min. & dried at 45^{o}c.
- The dried mass is pulverized and sieved through 100#.
- Eg. Nimesulide , Omeprazole

Co-evaporation method

- In this method, aq. solution of b-cyclodextrin is added to an alcoholic solution of drug.
- The resulting mix. is stirred for 1 hr. & evaporated at 45°c until it is dried.
- The dried mass is pulverized and sieved through 100#.
- Eg. Steroids & Diclofenac sodium

Solid dispersion method

- Here the drug & molar qty. of b-cyclodextrin is dissolved in methanol.
- The solution is then evaporated in vacuum at 40℃ with rotatory evaporator.
- The powder is stored under vacuum in dessicator for 3 days & analysed.
- Eg. Rifampicin

Spray drying method

- In this, the drug & double molar of β-cyclodextrin are dissolved in methanol.

- The solution was then spray dried under foll. conditions –

  Feed rate – 10 ml/min

  Inlet temp. - 95^{o}c

  Outlet temp. - 65^{o}c

  Press. – 5 bar

  Drying air – 35 m^3

Spray drying method

- The powder is then collected & stored under vacuum in dessicator for 3 days & analysed.

- Eg. Naproxene

Neutralization method

- Here the drug & b-cyclodextrin are dissolved in 0.1N HCl & then 0.1N NaOH is added to precipitate the complex at pH-7.5.
- The ppt. is washed with distilled water.
- Then it is pulverized & sieved through 90# and stored in dessicator over fused $CaCl_2$.
- Eg. Ketoconazole

Applications

- To increase aq. solubility
- To increase dissolution rate of drug
- To improve bioavailability of drug
- To increase chemical/physical stability
- To decrease drug irritation

Crystallinity

- Crystal habit & internal structure of drug can affect bulk & physicochemical property of molecule.
- Crystal habit is description of outer appearance of crystal.
- Internal structure is molecular arrangement within the solid.

Crystallinity

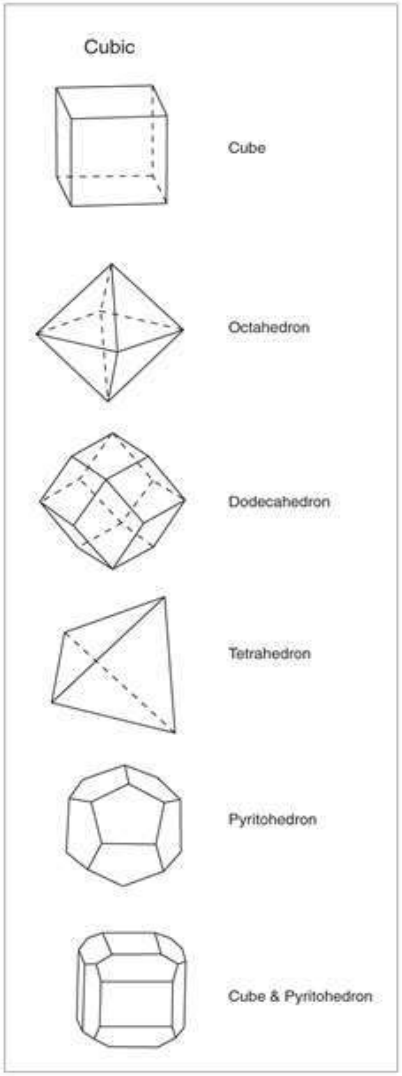
- Change with internal structure usually alters crystal habit.

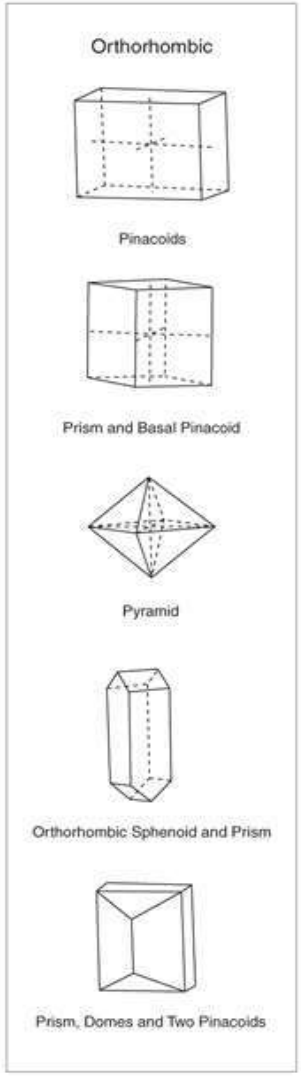
  Eg. Conversion of sodium salt to its free acid form produce both change in internal structure & crystal habit.

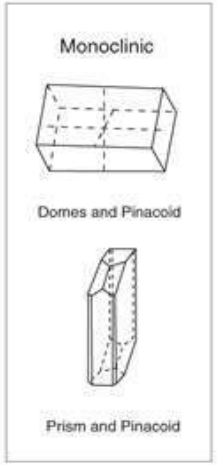
Different shapes of crystals

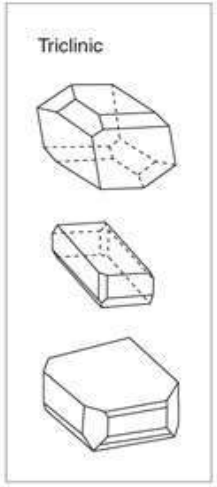
- **Cubic or isometric** - not always cube shaped. Also find as octahedrons (eight faces) and dodecahedrons (10 faces).
- **Tetragonal**- similar to cubic crystals, but longer along one axis than the other, forming double pyramids and prisms.
- **Orthorhombic** - like tetragonal crystals except not square in cross section (when viewing the crystal on end), forming rhombic prisms or dipyramids (two pyramids stuck together).
- **Hexagonal** - six-sided prisms. When you look at the crystal on-end, the cross section is a hexagon.
- **Trigonal** - possess a single 3-fold axis of rotation instead of the 6-fold axis of the hexagonal division.
- **Triclinic** - usually not symmetrical from one side to the other, which can lead to some fairly strange shapes.
- **Monoclinic** - like skewed tetragonal crystals, often forming prisms and double pyramids.

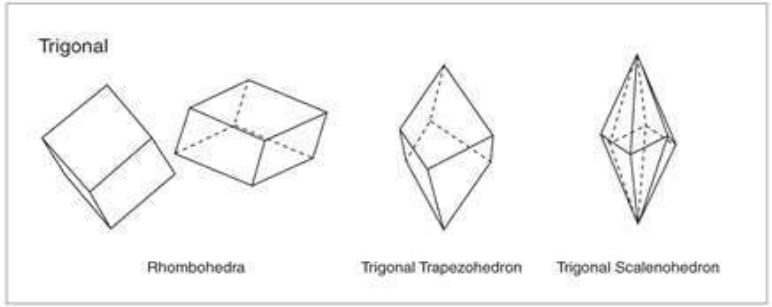
Different shapes of crystals

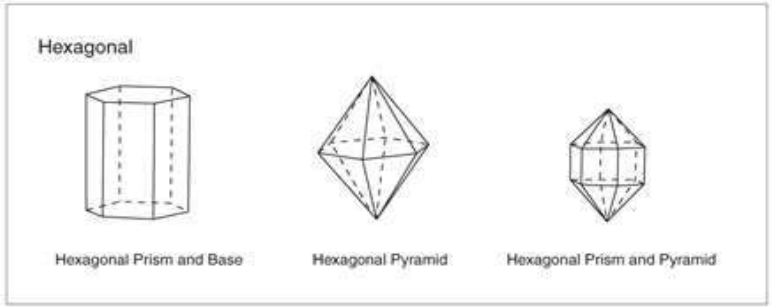


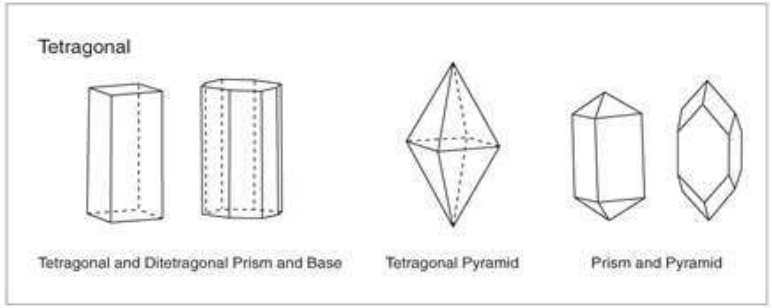












Different shapes of crystals

- Depending on internal structure compounds is classified as
  1. Crystalline
  2. Amorphous
- Crystalline compounds are characterized by repetitious spacing of constituent atom or molecule in three dimensional array.
- In amorphous form atom or molecule are randomly placed.

Different shapes of crystals

- Solubility & dissolution rate are greater for amorphous form then crystalline, as amorphous form has higher thermodynamic energy.

Eg. Amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption.

Polymorphism

- It is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice.
- Different crystalline forms are called polymorphs.
- Polymorphs are of 2 types
  1. Enatiotropic
  2. Monotropic

Polymorphism

- The polymorph which can be changed from one form into another by varying temp. or pressure is called as Enantiotropic polymorph.

  Eg. Sulfur.

- One polymorph which is unstable at all temp. & pressure is called as Monotropic polymorph.

  Eg. Glyceryl stearate.

Polymorphism

- Polymorph differ from each other with respect to their physical property such as
  - Solubility
  - Melting point
  - Density
  - Hardness
  - Compression characteristic

Polymorphism

- During preformulation it is important to identify the polymorph that is stable at room temp.

  Eg. 1)Chloromphenicol exist in A,B & C forms, of these B form is more stable & most preferable.

  2)Riboflavin has I,II & III forms, the III form shows 20 times more water solubility than form I.

Techniques for studies of crystals

- Microscopy
- Hot stage microscopy
- Thermal analysis
- X-ray diffraction

Microscopy

- Material with more than one refractive index are anisotropic & appear bright with brilliant colors against black polarized background.
- The color intensity depends upon crystal thickness.
- Isotropic material have single refractive index and this substance do not transmit light with crossed polarizing filter and appears black.

Microscopy

- Advantage :

  By this method, we can study crystal morphology & difference between polymorphic form.

- Disadvantage :

  This require a well trained optical crystallographer, as there are many possible crystal habit & their appearance at different orientation.

Hot stage microscopy

- The polarizing microscope fitted with hot stage is useful for investigating polymorphism, melting point & transition temp.

- Disadvantage :

  In this technique, the molecules can degrade during the melting process.

Thermal analysis

- Differential scanning calorimetry (DSC) & Differential thermal analysis are (DTA) are particularly useful in the investigation of polymorphism.

- It measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temp.

Thermal analysis

- For characterizing crystal forms , the heat of fusion can be obtained from the area under DSC- curve for melting endotherms.
- Similarly, heat of transition from one polymorph to another may be calculated.
- A sharp symmetric melting endotherm can indicate relative purity of molecule.

Thermal analysis

- A broad asymmetric curve indicates presence of impurities.

- Disadvantage :

  Degradation during thermal analysis may provide misleading results.

X-ray diffraction

- Working :

  When beam of nonhomogenous X-ray is allow to pass through the crystal, X-ray beam is diffracted & it is recorded by means of photographic plate.

- Diffraction is due to crystal which acts as 3 dimensional diffraction grating toward X-ray.

X-ray diffraction

- Random orientation of crystal lattice in the powder causes the X-ray to scatter in a reproducible pattern of peak intensities.

- The diffraction pattern is characteristic of a specific crystalline lattice for a given compound.

X-ray diffraction

- An amorphous form does not produce a pattern mixture of different crystalline forms.

- Single – Crystal x-ray provide the most complete information about the solid state.

Stability testing….

Why Stability?

- Provide a evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as….. temperature, Humidity and light.

- Establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.
- Because physical, chemical or microbiological changes might impact the efficiency and security of the final product

Where and Why?

Stability Studies are preformed on ...

- **Drug Substances (DS)** The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

- **Drug Products (DP)** The dosage form in the final immediate packaging intended for marketing…….

- controlled and documented determination of acceptable changes of the drug substance or drug product

What are changes?

- Physical changes
  - Appearance
  - Melting point
  - Clarity and color of solution
  - moisture
  - Crystal modification (Polymorphism)
  - Particle size
- Chemical changes
  - Increase in Degradation
  - Decrease of Assay
- Microbial changes

Forced degradation studies

- Acidic & Basic conditions.
- Dry heat exposure
- UV radiation exposure
- Influence of pH
- Influence of temperature
- Influence of ionic strength

Arrhenius Equation

- $K = Se^{+Ha}/RT$

where..k = specific rate of degradation.

R = gas constant (1.987 calories degree $^{-1}$mole)

T = absolute temperature.

S = frequency factor.

Logarithmically ,

$\ln k = -Ha/ RT + \ln S$

converting to log $_{10}$

$\text{Log } k = -\Delta Ha/2.303\ R\ .1/T + \log S$

log k = specific rate of degradation

S = constant

Arrhenius Equation

- Plot of log K v/s 1/T….yields a slope equal to -ΔHa/2.303 R ….. From which heat of activation (ΔHa) can be calculated.

- Log k2/k1 = ΔHa/2.303 R . (T2 – T1)/ T2.T1

Mean Kinetic Temperature

Clasius – Clapeyron equation

- $\ln = P_2 / P_1 . \Delta H V (T_2 – T_1) / R (T_2 – T_1)$

where…. P_2 & P_1 = vapour pressure at T_1 & T_2

ΔH =molar (latent) heat of evaporation

Relative humidity

Q =PD / PS . 100

RH is expressed in percentage (%)

Q = Relative humidity

PD = partial pressure of unsaturated air

PS = saturation pressure

Chemical degradation studies

- Hydrolysis
- Oxidation
- Reduction
- Decarboxylation
- Photolysis

Stability studies at different stages

- Stress- and accelerated Testing with drug substances
- Stability on pre-formulation batches
- Stress testing on scale-up Batches
- Accelerated and long term testing for registration
- On-going Stability testing
- Follow-up Stabilities

Testing scope for Solid dosage

Tablet & Capsule

- **Physical-chemical properties**
  - Appearance
  - Elasticity
  - Mean mass
  - Moisture
  - Hardness
  - Disintegration
  - Dissolution
- **Chemical properties**
  - Assay
  - Degradation
- **Microbial properties**

- **Container closure system properties**
  - Functionality tests (e.g. extraction from blister)

Testing scope for Oral liquid form

- Physical-chemical properties
  - pH
  - Color & clarity of solution
  - Viscosity
  - Particle size distribution (for oral suspensions only)
- Chemical properties
  - Assay
  - Degradation products
  - Degradation preservatives
  - Content antioxidants
- Microbial properties
- Container closure system properties
  - Functionality tests

Testingscope for *liquid forms* for inj. And parenterals

- Physical-chemical properties
  - pH
  - Loss on weight
  - Color & clarity of solution
- Chemical properties
  - Assay
  - Degradation products
  - Degradation preservatives
  - Content antioxidants
- Microbial properties
- Container closure system properties
  - Functionality tests

Testing scope for *SEMI LIQUID FORMS*

- Physical-chemical properties
  - Appearance, odor, homogenesity, consistency
  - Loss on weight, Viscosity
  - Content uniformity (within the container)
- Chemical properties
  - Assay
  - Degradation products & preservatives
  - Content preservatives
  - Degradation– Content antioxidants
- Microbial properties

- Container closure system properties
  - Functionality tests

Climatic Zones / Storage conditions

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	humidity % r.h.	Temp °C	humidity % r.h.
Climatic Zone I "Temperate" Japan, United Kingdom, Northern Europe, Canada, Russia, United States	**20**	**20**	**42**	**21**	**45**
Climatic Zone II "Mediterranean, Subtropical" Japan, United States, Southern Europe	**26.4**	**22**	**52**	**25**	**60**

Climatic Zones / Storage conditions

Climatic Zone Countries	Calculated data			Derived data	
	Temp. °C	MKT °C	humidity % r.h.	Temp °C	humidity % r.h.
Climatic Zone **III** "Hot, dry" Iran, Iraq, Sudan	**26,4**	**27,9**	**35**	**30**	**35**
Climatic Zone **IV** "Hot, humid" Brazil, Ghana, Indonesia, Nicaragua, Philippines	**26,7**	**27,4**	**76**	**30**	**70**

What or Who is ICH?

- **ICH** stands for **I**nternational **C**onference on **H**armonization of Technical Requirements for Registration of Pharmaceuticals for Human use

- **Objectives of ICH**
- Harmonization of registration applications within the three regions of the EU, Japan and the United States.
- ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess
- The quality ,safety and efficasy of the product.

What or Who is ICH?

There are Six Parties directly involved in the decision making process

- **EU: European Commission - European Union**
- **EFPIA: European Federation of Pharmaceutical Industries and Associations**
- **MHLW: Ministry of Health, Labor and Welfare, Japan**
- **JPMA: Japan Pharmaceutical Manufacturers Association**
- **FDA: US Food and Drug Administration**
- **PhRMA: Pharmaceutical Research and Manufacturers of America**

There are additionally observers installed to act as a link with non-ICH countries and regions

- WHO
- The European Free Trade Area (EFTA), represented by Swissmedic Switzerland
- Health Canada
- Global guidelines

ICH Guidelines

- Quality Guidelines "**Q**" (chemical and pharmaceutical QA)
  - details see next slide
- Safety Guidelines "**S**" (in vitro and in vivo pre-clinical studies)
  - covering Carcinogenicity Testing, Genotoxicity Testing, Toxicokinetics and Pharmacokinetics ….. etc.
- Efficacy Guidelines "**E**" (clinical studies in human subject)
  - Covering clinical safety, Dose Response Studies, Good Clinical Practices, Clinical evaluation …. etc.
- Multidisciplinary Guidelines "**M**"
  - Covering Medical Terminology, Electronic Standards for Transmission of Regulatory Information …… etc.
  - Important for Stability !
    - » Guideline **M4**: The Common Technical Document (CTD)

ICH Q-Guidelines (Quality)

-
- Stability Testing in Climatic Zone I and II (Q1A)
- Photostability Testing (Q1B)
- Stability Testing for New Dosage Forms (Q1C)
- Bracketing and Matrixing Designs (Q1D)
- Evaluation of Stability Data (Q1E)
- Stability Testing in Climatic Zones III and IV (Q1F)
- Validation of Analytical Procedures (Q2)
- Impurities (Q3)
- Biotechnological Products (Q5)

Specifications (Q6)

New Drug Substances & Products

- Stability Testing in Climatic Zone I and II (Q1A)
- Photostability Testing (Q1B)
- Stability Testing for New Dosage Forms (Q1C)
- Bracketing and Matrixing Designs (Q1D)
- Evaluation of Stability Data (Q1E)
- Stability Testing in Climatic Zones III and IV (Q1F)
- Validation of Analytical Procedures (Q2)
- Impurities (Q3)
- Biotechnological Products (Q5)
- Specifications (Q6)

Drug substances - General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	**25°C ± 2°C / 60% ± 5% r.h or 30°C ± 2°C / 65% ± 5% r.h.**	**12 months**
Intermediate	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**
Accelerated	**40°C ± 2°C / 75% ± 5% r.h.**	**6 months**

Drug substances - intended for storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	**5°C ± 3°C**	**12 months**
Accelerated	**25°C ± 2°C / 60% ± 5% r.h.**	**6 months**

Drug substances/Product- intended for storage in Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	**-20°C ± 5°C**	**12 months**

Drug products - General case

Study	Storage condition	Minimum time period covered by data at submission
Long term	**25°C ± 2°C / 60% ± 5% r.h. or 30°C ± 2°C / 65% ± 5% r.h.**	**12 months**
Intermediate	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**
Accelerated	**40°C ± 2°C / 75% ± 5% r.h.**	**6 months**

Drug products - packaged in Semi-permeable containers

Study	Storage condition	Minimum time period covered by data at submission
Long term	**25°C ± 2°C / 40% ± 5% r.h. or 30°C ± 2°C / 35% ± 5% r.h.**	**12 months**
Intermediate	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**
Accelerated	**30°C ± 2°C / 65% ± 5% r.h.**	**6 months**

Drug products - intended for storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	**5°C ± 3°C**	**12 months**
Accelerated	**25°C ± 2°C / 60% ± 5% r.h.**	**6 months**

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Thank You