CRYSTALLINITY & PARTICLE SIZE,PARTICLE SIZE DISTRIBUTION

(AS A PART OF PREFORMULATION STUDIES)

CRYSTALLINITY

CONTENTS:-

1. INTRODUCTION

1.1 WHAT IS A CRYSTAL?

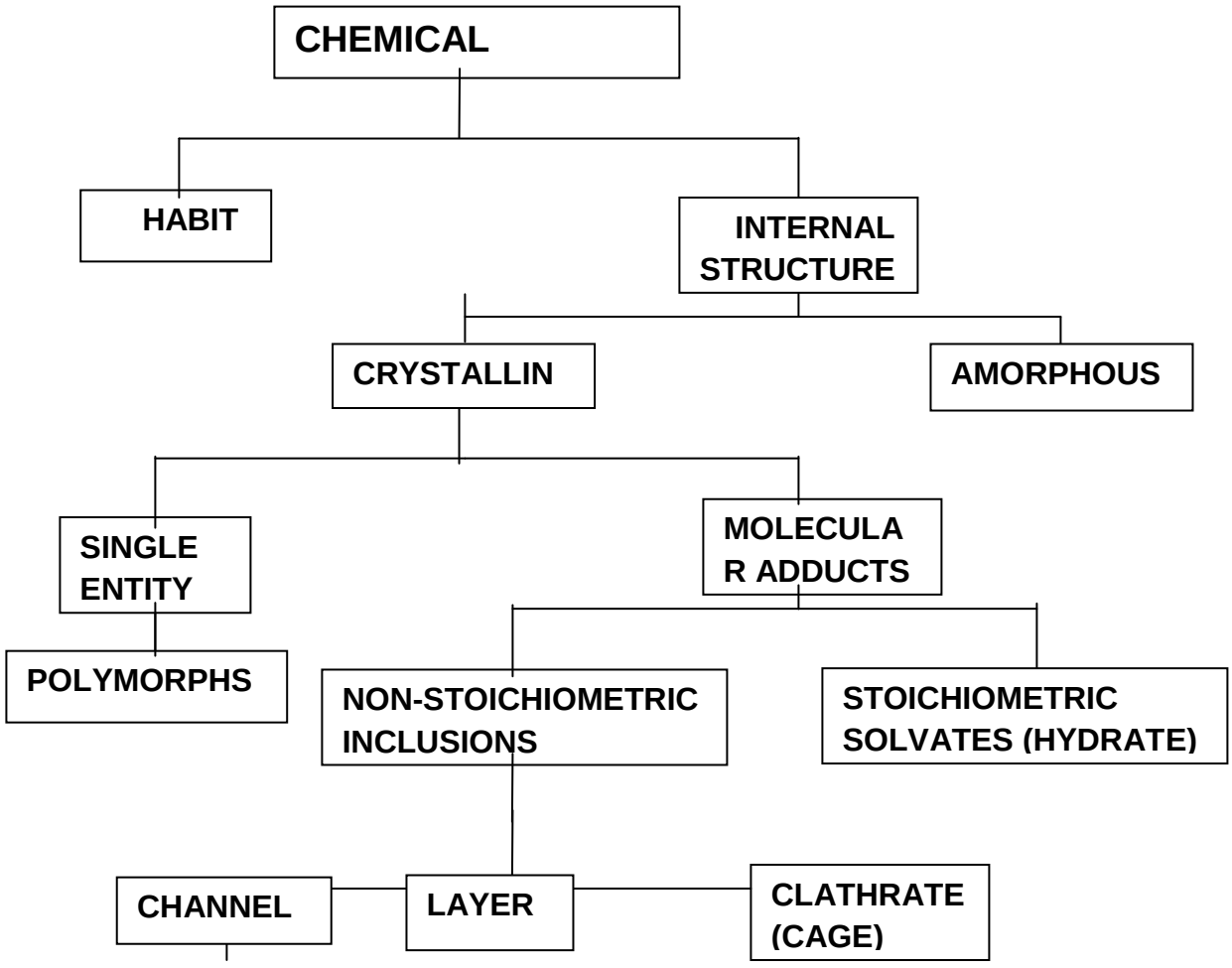
A crystal is a solid in which the constituent atoms, molecules, or ions are packed in a regularly ordered, repeating pattern extending in all three spatial dimensions.

The interatomic distance in a crystal of any material are constant .It can be used for the identification of material the crystal shape independent of size.eg.sugar crystal

1.2 ADVANTAGE OF CRYSTAL

- Better appearance
- Easy of filtering and washing
- Solubity ,density will be same no batch varition
- Crystal are always pure &attractive
- Easy to store,not form cake on storage.

2. CLASSIFICATION OF CHEMICAL COMPOUND:-



2.1 AMORPHOUS COMPOUND:

They have atoms or molecules randomly placed as in a liquid. They are typically prepared by:-

- Lyophilization. E.g. Fluprednisolone in tert-butanol.
- Rapid quenching of chloramphenicol palmitate solution in hydrophilic solution.
- Rapid quenching of melted chloramphenicol palmitate in the refrigerator to -10°
- Precipitation is also used to prepare the amorphous prompt insulin zinc suspension.

Amorphous forms are usually of higher thermodynamic energy than corresponding crystalline forms, so solubilities as well as dissolution rates are generally greater but due to high energy they are unstable and tend to revert back to a stable form. This is particularly true for formulations like aqueous suspensions.

In case of amorphous novobiocin suspension it slowly converts to a crystalline form and thus becomes less and less absorbable and finally looses therapeutic effect.

The best agents found were methylcellulose, polyvinylpyrollidone, and several alginic acid derivatives such as sodium alginate and propylene glycol algin.

2.1.1 Characterization of amorphous solids:-

The only positive way to differentiate amorphous from crystalline solids is by means of X-ray powder diffraction. This technique gives very diffuse reflections of amorphous compounds, where the d distances, the distance between parallel planes in which the atoms of the crystal lie, cannot be determined as is done with crystalline solids.

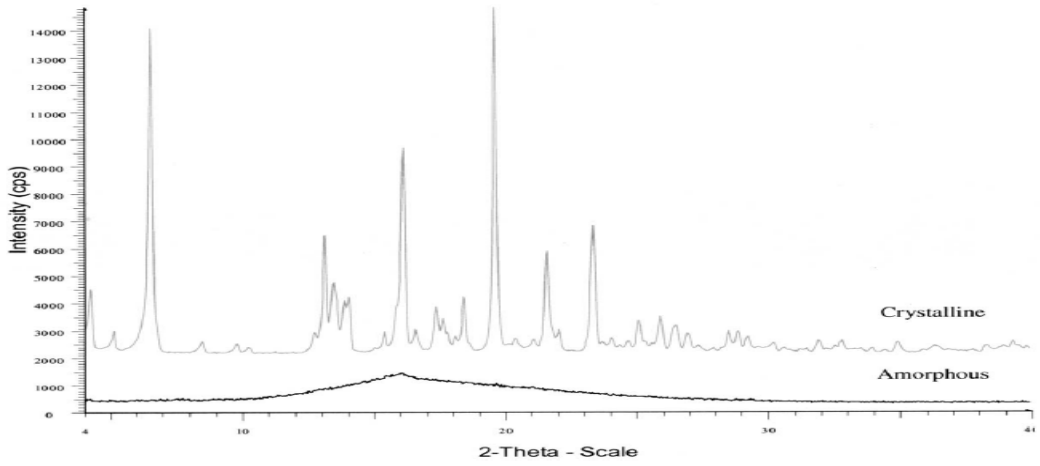


Fig. 3. Powder X-ray diffractograms for the crystalline and amorphous forms of the drug substance.

2.2 POLYMORPHS:-

Many drug substances can exist in more than one crystalline form with different space-lattice arrangements. This phenomenon is known as polymorphism and the different crystalline forms as polymorphs. Drugs like barbiturates and steroid hormones have polymorphic forms.

2.3 SOLVATES (PSEUDOPOLYMORPHISM):-

During crystallization from a solution , crystal separating may consist of pure component or be a molecular compound .The molecular compound may contain two or more constituents that have completely satisfied classical "Valance force" and are crystallize together as new single crystalline entity.

Solvates are molecular complexes that have incorporated the crystallizing solvent molecule in their specific lattice position and in fixed stoichiometry. When the solvent incorporated in the solvate is water, it is called a hydrate.

A classical method for distinguishing solvates from polymorphs involves observation of the melting behaviour of crystals embedded in silicon oil using"HOT STAGE MICROSCOPY", where upon heating, bubbles of solvent are generated by solvates. In case of polymorphs, no such generation occurs.

Example **:- Steroid**

Estradiol form solvates with 30 solvent
Hydrocortisone acetate
Fluprednisolone

Antibiotics

Erythromycin
Grmicidin
Ampicillin
Chlormphenicol
Sulphanilamide

METHOD USED TO IDENTIFICATION OF SOLVATES

1.Thermogravimetric analysis :
Thermograms of different solvates shown different steps of desolvation which corresponds at a certain interval of temp. and pressure to the stable solvates .

2.Differential thermal analysis :
Identify different hydrates of Phenobarbital , theophylline and other organic pharmaceuticals .

3.Differential scanning calorimetric :
Identify the chloroform solvates of Griseofulvin and gas evaluation analysis can be done simultaneously with differential scanning calorimetry.

4.X-ray diffraction :
This is used to differentiate fluprednisolon polymorph from solvate.

APPLICATION OF SOLVATES

- ✓ Disolution :- The dissolution rate of solvate is many time greater than the anhydrous form on the other hand dissolution rate of hydrate is less than anhydrous form .The effect of the concentration of solvating solvent in dissolution medium when measuring dissolution of the pentanol solvate of fludrocortisone acetate , the dissolution rate was retarded by the addition of pentanol in dissolution medium .
- ✓ Bioavailability :- The difference seen in ampicillin bioavailability were due to the hydration of ampicillin since they found that solubility of two phase in dilute Hcl at 370 . It suggest that difference in bioavailability are related to formulation factor rather than when hydration state of the raw material .

2.4 CLATHRATES:-

A clathrate is a single-phased solid with two distinct components: the host and the guest. The guest is retained in the closed cavities provided by the crystalline structure of the host. Thus it is a non-stoichiometric molecular adduct. The major classes of clathrates are hydroquinone clathrates, water clathrates, phenol clathrates etc.

2.4.1PHARMACEUTICAL APPLICATIONS OF CLATHRATES:-

■ PURIFICATION- Benzene was purified of one of its usual contaminants thiophene by clathrate formation. Although both form clathrates with monoaminenickel cyanide, benzene is more firmly held in cage structure, so it is preferentially clathrated and separated from solution by filtration.

■ SEPARATION OF RARE GASES- Argon is separated from neon by adjusting the pressure conditions in which hydroquinone-argon clathrate is formed, while neon do not form.

■SEPARATION OF OPTICAL ISOMERS- Inclusion complexing substance that will separate optical isomers is tri-o-thymotide.

■STORAGE OF INERT GASES- They are used for convinient storage of inert gases like hydroquinone or to introduce such gases into fairly inaccessible locations. The gas can be released by heating or dissolving the clathrates.

■MODE OF ACTION OF ANESTHETICS- Non-hydrogen bonding anesthetics work primarily due to clathrate formation of molecules of anesthetic agent with water contained in the neurons and around the neural network.

3. COMPARISON OF THE MECHANICAL PROPERTIES OFTHE COMPACTS OF THE CRYSTALLINE ANDAMORPHOUS FORMS OF A DRUG SUBSTANCE:-

AMORPHOUS FORM	CRYSTALLINE FORM
Least ductile (highest indentation hardness value)	More ductile (Low indentation hardness value)
Form compacts with lower tensile strength.	Form compacts with high tensile strength.
Compacts have high brittleness value.	Compacts have low brittleness value.
Require lower compression stress to form compacts.	Higher compression stress is required.

4. COMPARISON OF SOLUBILITY OF CRYSTAL, SOLVATE AND HYDRATE:-

Amorphous form is always more soluble than a corresponding crystalline form.
The dissolution rates of hydrates are less than corresponding anhydrous crystalline form. E.g gluthethimide, theophylline, caffeine, succinyl sulphathiazole, phenobarbitol.

The dissolution rates for organic solvates are higher than corresponding pure crystaline form. E.g. 1,4-dioxane solvate of nifedipine shows better solubility than dihydrate form.

So organic solvates should be preferred in place of pure crystals which solves both problems, solubility and stability, but only if ICH guidelines about limits of organic residues permit

MECHANISM OF CRYSTAL GROWTH

The formation of crystal nuclei can be consider as a process that determine the size of the product .Control of the crystallization process to obtain a consitent and uniform crystal form, habit,density and size distribution is particularly critical for drug substance to be utilize in suspension and powdered . Eg. When the crystallization of sterile ceftazidine pentahydrate or modify to significantly increase the density to reduce the volume of the fill dose. The rate of

dissolution increase significantly .Many dry solid parenteral product such as the cephalosporin are prepared by the sterile crystallization techanique.

To obtain a uniform product from lot to lot , strict adherence to procedure develop for particular crystallization must be followed .

Control of pH
Rates of addition
Solvent concentration & purity
Temperature & mixing rate

Each crystallization procedure has to design to ensure sterility and minimize particulate contamination .Eg. Changing the absolute ethyl alcohol instead of 95 % ethanol during washing procedure can desroy the crystalline structure .

The size distribution of dispersed system may increase during aging to three principle mechanism :

Ostwald ripening
Polymorphic transformation
Temperature cycling
Ostwald ripening

For Kelvin equation ,

$$\ln s/s' = 2y V/rRt$$

Where,

s' = Solubility of infinitely large particle
s = Solubility of small particle of radius r
y = Surface tension
V = Molar volume of solid

Polymorphs exhibit different equilibrium solubility

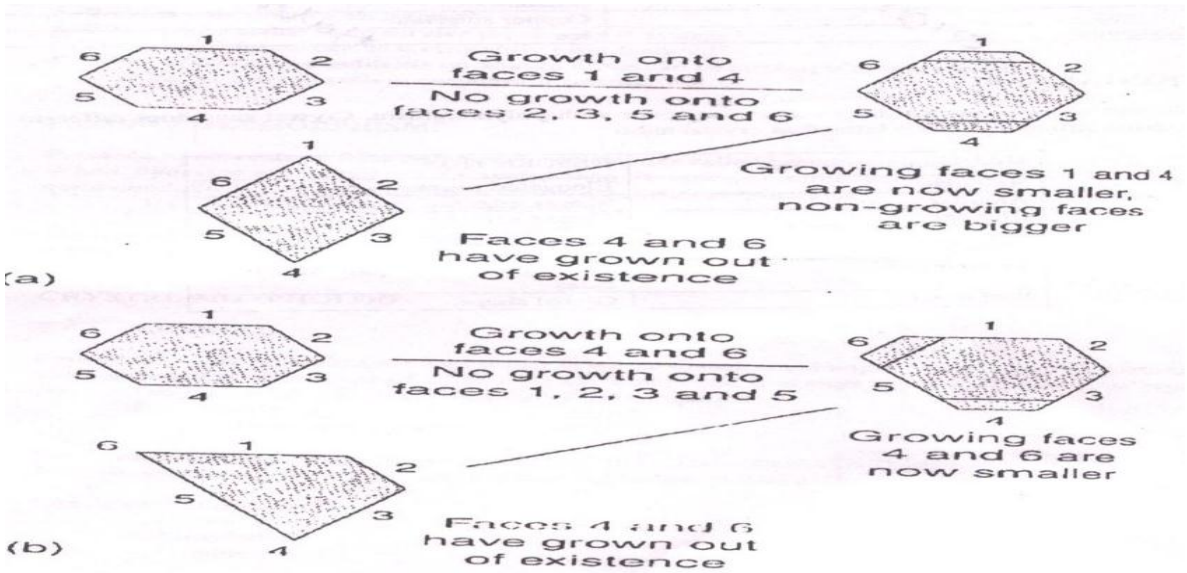
For Example Phenylbutazone identified by X-ray diffraction. The difference in solubility is driving force of crystal growth of suspension as the particle of more soluble form of polymorph go into solution and reprecipitate as less solution ie. More stable

Temperature cycling may lead to crystal growth depending on temperature

Solubility is directly related to temperature so slighst rise in temperature lead to increase equilibrium solubility. Precipitation occur to release the upersaturation and crystal growth occur.

HOW THE CRYSTAL HABIT IS ARISES?

- It is possible to change the external shape of the crystal by changing the crystallization condition.With any crystalline material , the largest face is always slowest growing.the reason for that can be seen from the figure.
- If the drug is deposited on the two faces of the hexagonal crystal habit, then the first consequences is that the face where drug is deposited actually becomes a smaller part of the crystal, whereas the other faces become larger. Eventually the fastest growing faces will no longer exist.
- The growth on different faces will depend on the relative affinities of the solute for the solvent and the growing faces of the crystal.



5. CRYSTAL STRUCTURE & MORPHOLOGY:-

A crystal structure is a unique arrangement of atoms in a crystal. A crystal structure is composed of a motif, a set of atoms arranged in aparticular way, and a lattice

Any crystal is characterized by its internal structure and habit. Habit is the description of the outer appearance of a crystal whereas the internal structure is the molecular arrangement within the solid.

5.1 Crystals are of two types:-

- ✓ Irregularly shaped crystals known as **anhedral or allotriomorphic.**
- ✓ Definite shaped crystals bound by plane faces known as **euhedral or idiomorphic.**

Anhedral crystals, although irregularly shaped, have a regular arrangement of building units which may be proved by X-ray diffraction.

5.1.1 crystal can be classified by the type of bonds between two particles in a crystal.

Metallic crystals having strong metallic bond.

Ionic crystals having electrostatic ionic bond.

Crystals having strong carbon covalent bond.

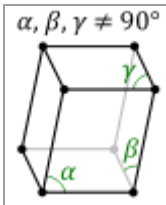
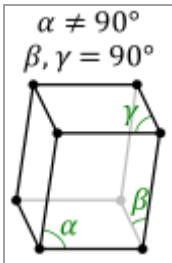
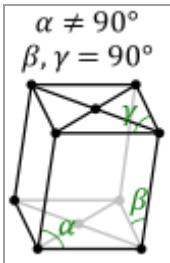
Crystals bonded by vanderwaal forces.

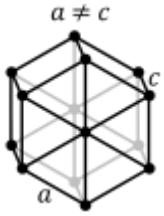
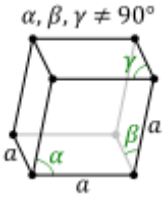
5.2 CRYSTAL SYSTEM :- (INTERNAL STRUCTURE)

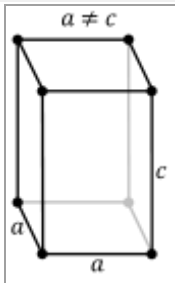
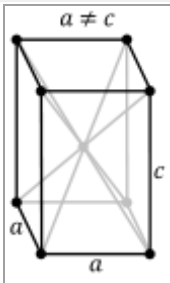
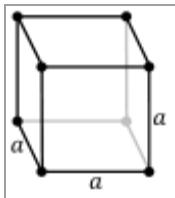
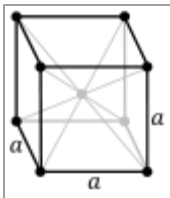
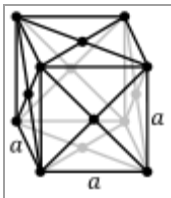
For all crystals there are seven basic or primitive unit cells, as shown in Fig.1. We represent the side lengths as a, b and c and the angles as α (between sides b and c), β (between sides a and c) and γ (between sides a and b). The structure have atoms or molecules at each corner of unit cell. It is also possible to find unit cells with atoms or molecules at the centre of the top and bottom faces (end-centered), at the centre of every face (face-centered) or with a single atom in centre of crystal (body-centered). The most symmetric system is cubic system. The other six systems, in order of decreasing symmetry, are hexagonal, tetragonal, rhombohedral (also known as trigonal), orthorhombic, monoclinic and triclinic. Thus there are fourteen types of unit cell and we call these the Bravais lattices. For drugs there are only three common types of unit cell: triclinic, monoclinic and orthorhombic.

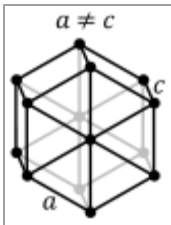
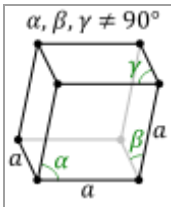
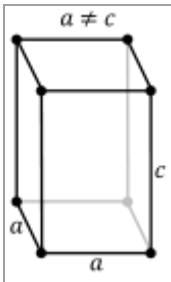
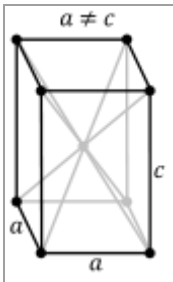
We can identify the various planes of crystal using the system of *Miller indice*

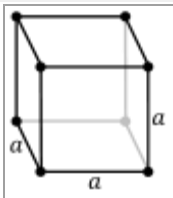
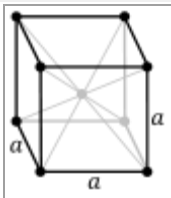
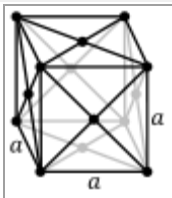
- **Cubic:** sodium chloride
- **Hexagonal:** iodoform
- **Tetragonal:** urea
- **Orthorhombic:** iodine
- **Monoclinic:** sucrose
- **Triclinic:** boric acid

Crystal system	Lattices:		
triclinic			
monoclinic	Simple 	base-centered 	
orthorhombic	Simple	base-centered	body-centered

hexagonal			
rhombohedral (trigonal)			
tetragonal	Simple	body-centered	

			
cubic (isometric)	Simple	body-centered	face-centered
			

hexagonal			
rhombohedral (trigonal)			
tetragonal	Simple	body-centered	
			
cubic	Simple	body-centered	face-centered

(isometric)			

5.3CRYSTAL HABIT:-

Crystal habit is the description of the outer appearance of a crystal.

There are five types of crystal habit widely recognized:

Platy: plates

Tabular: moderate expansion of two parallel faces

Prismatic: columns

Acicular: needle-like

Bladed: flat acicular

These occur in all the six system.

5.3.1 METHODS OF MODIFICATIONS OF CRYSTAL HABIT:-

Excessive supersaturation. E.g. transform a prism or isodiametric crystals to needle shape.

Cooling rate and agitation. E.g. naphthalene gives thin plates if rapidly cooled whereas slow evaporation yields prisms.

The crystallizing solvent. E.g. resorcinol produces needles from benzene and squat prisms from butyl acetate. Similarly, iodoform crystallizes as hexagonal bipyramids from aniline and as prisms from cyclohexane.

Addition of co-solvents or solutes. E.g. sodium chloride is cubic but urea produces octahedral habit.

Crystal habit can also be modified by adding impurities or 'poisons'; for example, sulphonic acid dyes alter the crystal habit of ammonium, sodium and potassium nitrates.

It can be quantitatively expressed in terms of aspect ratio (AR), defined as the ratio of length to width and values of AR approaching 1 (spherical or cube shape) are considered to be pharmaceutically good. It is preferable to keep the AR values below 5 so as to avoid problems with flow. AR in polar solvents was as high as 9.4 in comparisons with 5-6 in non-polar solvents.

6. CRYSTALLIZATION

6.1 DEFINITION

Crystallization is the (natural or artificial) process of formation of solid crystals from a uniform solution. Crystallization is also a chemical solid-liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs.

6.2 The crystallization process consists of two major events.

Nucleation is the step where the solute molecules dispersed in the solvent start to gather into clusters, on the nanometer scale (elevating solute concentration in a small region), that becomes stable under the current operating conditions. These stable clusters constitute the nuclei. Nucleation can occur spontaneously or induce artificially by any foreign surface. These two cases are referred as homogenous and heterogenous nucleation respectively.

The crystal growth is the subsequent growth of the nuclei that succeed in achieving the critical cluster size.

Occur through 4 stages-

transport through or from the bulk solution to an impingement site, which is not necessarily final site

Adsorption at impingement site, where precursors may shed solvent molecules. Hence solvent must be transported back in soln.

Diffusion of growth units of precursors from site of impingement to growth site.

incorporation into lattice; for precursors, after desolvation. Thus, the growth site may also be a source of solvent that has possibility of, again, being adsorbed before escaping into soln.

Nucleation and growth continue to occur simultaneously while the supersaturation exists. Supersaturation is the driving force of the crystallization, hence the rate of nucleation and growth is driven by the existing supersaturation in the solution. Depending upon the conditions, crystals with different sizes and shapes are obtained. Once the supersaturation is exhausted, the solid-liquid system reaches equilibrium and the crystallization is complete, unless the operating conditions are modified from equilibrium so as to supersaturate the solution again.

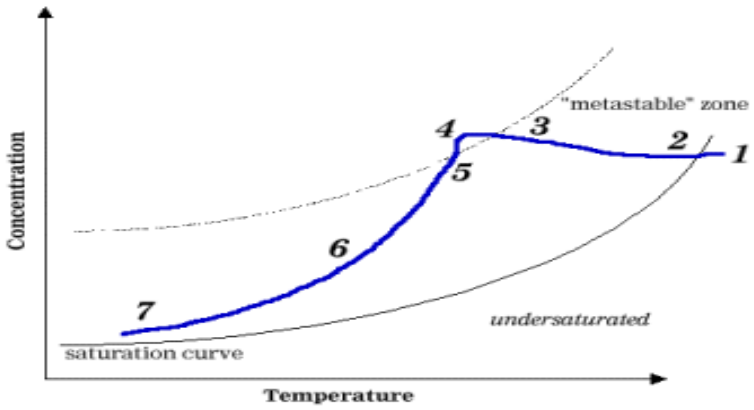
6.2.1 Crystallization can be achieved by various methods, with

1) Solution cooling
2) Addition of a second solvent to reduce the solubility of the solute.
   (technique known as anti-solvent or drown-out)

3) Chemical reaction

4) Change in pH being the most common methods used in industrialpractice.

Other methods, such as solvent evaporation, can also be used.



1 Feed location, undersaturated
2 Solution cools to saturation
3 Enter "metastable" zone, nucleation begins
4 Rapid nucleation
5 Concentration decreases with crystal growth
6 Crystal growth during main cooling cycle
7 Exit location, supersaturated

FIG.1

PROGRESSION OF CRYSTALLIZATION

Measurements of crystal growth rate:-

Divided into two groups, direct and indirect methods.

DIRECT MEASUREMENTS OF LINEAR CRYSTAL GROWTH RATES-

Single crystals are always used for this purpose.

Direct measurement of crystal dimensions under microscope (at beginning & after ending of experiment).

Measurements using a travelling microscope, permitting continous observation of growth during experiment.

Measurements using a screw micrometer.

In addition, the growth rate can be calculated from measured increase in mass or volume.Gravimetric measurements with single crystals, in which increase in crystal mass is determined. The crystal is either weighed before or after ending experiment or weighed continously by suspending it on one arm of an analytical balance.

The fluidised layer method, where the increase in mass of a greater number of crystals in fluidised bed in flowing soln is measured.

INDIRECT METHOD OF LINEAR CRYSTAL GROWTH RATE-

Measurement in an agitated batch crystallizer, where the increase in crysta mass in crystalline suspension is measured.

Measurement in a continous MSMPR crystallizer(mixed suspension,mixed product removal).

Measurement of decrease in supersaturation in batch crystallizer.

7. ANALYTICAL METHODS FOR CHARACTERIZATION OF CRYSTAL FORMS :-

METHOD	MATERIAL REQUIRED per SAMPLE
1.Microscopy	1mg
2.Fusion methods (hot stage microscopy)	1mg
3. Differential scanning calorimetry (DSC/DTA)	2-5mg
4. Infrared spectroscopy	2-20mg
5. X-ray powder diffraction	500mg
6. Scanning electron microscopy	2mg
7. Thermogravimetric analysis	10mg
8. Dissolution/solubility analysis	mg to gm

8. IMPORTANCE OF CRYSTALLINITY IN PREFORMULATION STUDIES:-

8.1 EFFECT ON SOLUBILITY & BIOAVAILABILITY

The antibiotic, novobiocin is essentially inactive when administerd in crystalline form, but in amorphous form, absorption from g.i.t proceeds rapidly with good therapeutic response. Thus due to difference in solubility amorphous novobiocin is 10 times more bioavailable.

The hormone insulin presents another striking e.g of different degree of activity that may result from use of different physical forms of it.

Insulin is a protein that forms an extremely insoluble zinc-insulin complex when combined with zinc in presence of acetate buffer. Depending upon the pH of acetate buffer sol, the complex may be an amorphous ppt or crystalline material.

NO.	TYPE OF INSULIN	FORM OF INSULIN	ONSET OF ACTION	DURATION OF ACTION
1	Prompt insulin-zinc suspension (semilente)	Amorphous	fast	Short
2	Extended insulin-zinc suspension (ultralente)	Crystalline	slow	Long
3	Insulin-zinc suspension (lente)	30%amorphous+ 70%crystalline	fast	Intermediate

The more soluble form of chloramphenicol palmitate, form B shows greater bioavailability after oral administration than least soluble form A.

Similarly in chlortetracyclin hydrochloride β form is more soluble and bioavailable than corresponding α form.

8.2 CHEMICAL STABILITY

In other instances, crystalline forms of drugs may be used because of greater stability than corresponding amorphous forms.
e.g. crystalline forms of penicillin G as potassium or sodium salt are more stable.

8.3 SUSPENSION SYRINGEABILITY

It is mostly a mechanical effect. A suspension of plate shaped crystals may be injected through a needle with a greater ease than one with needle shaped crystals of same dimensions.

8.4 EFFECT ON GRANULATION

Sulphathiazole can exist in different crystalline forms out of which form III has water adsorption of 0.046mg/m^2 while form I has water adsorption of 0.031mg/m^2. so form III shows better wetting and so easy granulation.
Use of amorphous form of calcium pentothenate in multi-vitamin tablets prepared by wet granulation process, is not desirable because polymorphic transformation makes the granulation mass sticky, making futher granulation virtually impossible.

8.5 HARDNESS OF TABLET

Sulphamerazine is available in two different crystalline forms SMZ-I & SMZ-II. SMZ-II tablets show faster dissolution rate than SMZ-I due to difference in compressibility of both the forms. SMZ-I forms harder tablets than SMZ-II at same compression pressure and so it shows delayed

release. Both these forms can be used in single tablet by compression coating in which the core is formed of SMZ-I and coat is made up of SMZ-II to get repeat action.

8.6 EFFECT ON CONSOLIDATION

Substances possessing the cubic lattice arrangement were tabletted more satisfactorily than those with rhombohedral lattice. The isotropic nature of former group contribute to better tabletting because no alignment of particular lattice planes is required. In addition provide three equal planes for stress relief at right angles to each other.

8.7 DIRECTLY COMPRESSIBLE EXCIPIENTS

The DC grade excipients are microgranulations, since they consist of masses of small crystallites randomly embedded in a matrix of glue-like (often amorphous) material. Such a combination imparts the desired overall qualities which results in strong tablet by providing a plastically deforming component (the matrix) to relieve internal stresses and strongly bonding surfaces (the faces of crystallites) to enhance consolidation.

8.8 POLYMORPHIC TRANSFORMATION

Many drugs undergo polymorphic transformation during various processes. E.g. during grinding drugs like digoxin, estradiol, spironolactone, phenylbutazone undergo transformation. By granulation of theophylline with water converts into monohydrate from anhydrous form. Similarly by drying and compression also drugs undergo change in their form.

9. LATEST TECHNIQUES DEVELOMENTS IN CRYSTALLIZATION:-

9.1 <u>SPHERICAL CRYSTALLIZATION</u>-

It has been developed by Yoshiaki and co-workers. It is a solvent exchange crystallization method in which crystal agglomeration is purposefully induced through the addition of third solvent termed as “Bridging liquid” which act as granulating agent.

It is a novel technique to improve compressibility, good flowability and bioavailability of pharmaceuticals. In addition to this the tablets manufacture by this technique have greater mechanical strength and lower friability.

Various drugs have been successfully undergone this process to acquire improved micromeritic properties like salicylic acid, mefenemic acid, aminophylline, tolbutamide and thus have shown increased dissolution rate.

METHODS OF SPHERICAL CRYSTALLIZATION

9.1.1 SIMPLE SPHERICAL CRYSTALLIZATION

It is achieved by change of solvent or salting out. It causes formation of fine crystals and agglomeration. E.g. spherical crystallization of salicylic acid from ethanol by addition of water, using chloroform as bridging unit.

9.1.2 QUASI-EMULSION-SOLVENT-DIFFUSION METHOD

Uniformly coated directly compressible agglomerates are obtained by using mixed system of two or three partially miscible solvents, i.e. bridging liquid-poor solvent system or good solvent-bridging liquid-poor solvent system. E.g. antirheumatic drug bucillamine was crystallized as spheres by this method using HPMC.

9.1.3 AMMONIA DIFFUSION METHOD

Useful for amphoteric drugs like enoxacin which is slightly soluble in water but soluble in acidic and alkaline solution. A mixture of three partially immiscible solvents, acetone-ammonia water-dichloromethane, was used.

Here ammonia water acts as a bridging liquid and also good solvent for enoxacin. Acetone is water miscible but poor solvent. Thus enoxacin gets precipitated by solvent exchange without forming ammonium salt.

9.1.4 NEUTRALIZATION METHOD

Tolbutamide dissolved in sodium hydroxide and HPEC aqueous solution was crystallized using this method. Hydrochloric acid was added to neutralize the solution and crystallize out fine crystals of drug.

9.2 CONTROLLED CRYSTALLIZATION-

Very useful method for getting microcrystals in very narrow size range for hydrophobic drugs. It is more effective than micronisation because it gives better bioavailability due to uniform sized particles. E.g. anti-inflammatory drug betamethasone dipropionate, triamcinolone acetonide, beclomethasone. Here the side effects caused by drug deposition in the throat is avoided and administered amount of drug can be lowered.

This method was performed using solvent change method by instataneously mixing two liquids in presence of HPMC as stabilizing agent.

9.3 AMORPHOUS FORM STABILIZATION-

Amorphous forms have highest solubility but it is very unstable and on storage may get convert to crystalline form. So scientist developed a technique to stabilize the amorphous form. Drugs like ketoprofen, indomethacin, naproxen and progesterone were used for this purpose.

NEUSILIN (amorphous magnesium alluminium silicate) was milled in the ball mill with the above drugs. The amorphous form thus formed was more stable than normal amorphous form and did not turned to crystalline form easily. Neusilin is an amphoteric compound so can be combined with both acidic and alkaline groups.

Thus by using additives with high glass transition temperature or by selective hydrogen bonding with the stabilizing additives conversion of amorphous form to crystalline form can be prevented.

9.4 SUPER-CRITICAL FLUID CRYSTALLIZATION-

Useful method for selective production of polymorphs and pseudopolymorphs. In this technique precipitation of small organic molecules from aqueous solution was studied using a mixture of supercritical CO_2 & ethanol as drying medium and as anti-solvent.

Glycine has three polymorphs and can be selectively precipitated to either pure α or β form. When increase the ethanol concentration precipitation of metastable β-glycine was preferred. Similarly increase ethanol concentration in extractant phase favoured precipitation of phenylalanine anhydrate over monohydrate form.

CONCLUSION

Thus, with all examples of the effects of habits, polymorphs, solvates and clathrates on optimising pharmaceutical formulations, the crystal chemistry has become a routine part of every pharmaceutical company's preformulation programme.

PARTICLE SIZE,PARTICLE SIZE DISTRIBUTION

1. **Introduction of Particle size.**
    a. **Definition**
    b. **Classification of powder**
2. **Introduction of particle size distribution.**
    a. **Definition**
    b. **Methods for analysis**
    c. **Properties of drug that are affected by particle size**
    d. **Importance of Particle and particle size distribution.**
3. **Introduction of particle shape.**

PARTCLE SIZE

Definition:-

Particle size is a notion introduced for comparing dimensions of solid particles, liquid particles (called droplets), or gaseous particles (called bubbles) .

The notion of particle size applies to:

Colloidal particles

Particles in ecology

Particles present in particulate matter

Particles that form a granular material

The particle size of a spherical object can be unambiguously and quantitatively defined by its diameter. The above quantitative definition of particle size cannot be applied to non-spherical particles.

GENERAL CLASSIFICATION OF PARTICLES BASED ON THEIR SIZE:-

Type of particle	Mesh opening size
Coarse Powders	> 1000 μm
Conventional Powders	50 μm - 1000 μm
Fine Particles	1 μm - 50 μm
Very fine Particles	0.1 μm - 1 μm
Ultra-fine Particles	< 0.1 μm

TYPE OF POWDER ACCORDING TO PRTICLE SIZE:-

Monodisperse powder:- all particles are of same size.

Polydisperse powder:- particles of different size.

Generally powder sample contains no. of irregular shape three dimensional particles so generally we consider Avg. Ps.

Average particle size: Average size of the particles which are distributed in system.

$$d_{mean} = (\sum nd^{p+f} / \sum nd^{f})^{1/p}$$

p=1-particle length, p=2-surface, p=3-expression of volume, p=+ve -arithmetic mean

p= -ve – harmonic mean, p= zero – geometric mean

PARTICLE SIZE DISTRIBUTION

Definition:- The particle size distribution (PSD) of a powder, or granular material, or particles dispersed in fluid, is a list of values or a mathematical function that defines the relative amounts of particles present, sorted according to size. Systems for Collection of particle are practically always polydisperse.

METHODS FOR PARTCLE SIZE ANALYSIS

METHOD	NOMINAL RANGE (μm)	SIZE DETERMINED
Sieving ⇧ Dry ⇧ Wet	 <0 2-74	Breadth
Microscopic ⇧ Optical ⇧ Electron	 0.5-500 0.002-15	Martin's, Feret's, or equivalent circle diameter
Electrical Zone Sensing	0.05-500	Volume weighted diameter
Photon Correlation Spectroscopy	0.003-3.0	Volume weighted mean diameter
Laser Diffraction	0.1-600	Volume weighted mean diameter
Elutriation ⇧ Laminar flow ⇧ Cyclone	 3-75 8-50	Equivalent Spherical diameter [ESD]
Centrifugal Classification	0.5-50	ESD
Centrifugal Sedimentation ⇧ Mass accumulatiom ⇧ Photo-extinction ⇧ X-ray	 0.05-50 0.05-100 0.01-5	ESD
Gravity Sedimentation ⇧ Pipettes & Hydrometers ⇧ X-ray	 1-100 0.2-65	ESD
Hydrodynamic Chromatography ⇧ Capillary Column	 0.1-6	ESD
Cascade Impactors	0.05-30	Aerodynamic diameter
Gas Permiability	0.01-40	Mean surface weighted diameter
Gas Adsorption	0.005-50	Mean surface weighted diameter
Nephelometry	>0.1	Total light scattering (size dependent)

01] MICROSCOPY:-

RANGE OF ANALYSIS:-

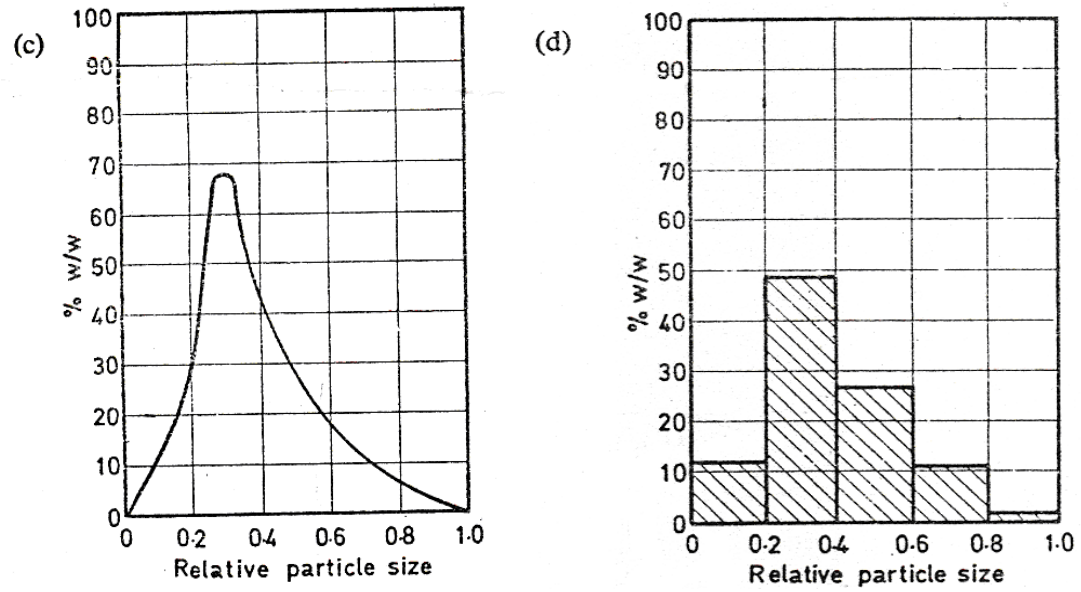
«- By transmission electron microscope 0.001-0.1 micron.
«- By scanning electron microscope 0.01-1000 micron.
«- By light microscope 1-1000 micron.

METHOD:-

«- An emulsion or Suspension in diluted or Undiluted form is mounted on a slide Or ruled cell and placed on a mechanical stage.
«- The microscope eyepiece is fitted with a micrometer by which the size of the particles may be estimated.
«- Sometimes the field can be projected onto a screen where the particles are measured more easily, or a photograph can be taken from which a slide is prepared & projected on a screen for measurement.
«- The popular Measurements for Particle size are

Martin's diameter
Feret's diameter
Projected Area Diameter

«- A Particle Size Distribution Curve is plotted as seen in figure.



Particle size distribution curve

USES:-

«- Scientist named Prasad & Wan used Video Recording equipment to observe, record, store & retrieve particle-size data from a microscopic examination of Tablet excipients including MCC , Na CMC , Na Starch Glycolate & Methyl Cellulose.

ADVANTAGES

- «- Easy and convenient
- «- A size-frequency distribution curve can be plotted.
- «- Can detect the presence of agglomerates.

DISADVANTAGES

- «- Diameter is obtained from only two dimensions - length and breadth
- «- No estimation of the depth (thickness) of particle is available
- «- The number of particles that must be counted to get a good estimate of the distribution makes the method slow and tedious.

02] SIEVING:-

RANGE OF ANALYSIS:- 5-12000 µm.

METHOD:-This method utilizes a series of standard sieves calibrated by the National Bureau of Standards. Methods may be simple shaking of the sample in sieves until the amount retained becomes more or less constant. Alternatively, the sample may be washed through with a non-reacting liquid (usually water) or blown through with an air current.

ADVANTAGES

- «- simplicity, cheapness, and ease of interpretation.

DISADVANTAGES

- «- The smallest practical sieve size is 20-40 µm, and many PSDs are concerned with much smaller sizes than this.
- «- A 20 µm sieve is exceedingly fragile, and it is very difficult to get material to pass through it.
- «- The amount of energy used to sieve the sample is arbitrarily determined. Over-energetic sieving causes attrition of the particles and thus changes the PSD, while insufficient energy fails to break down loose agglomerates.

AIR JET SIEVING METHOD:-

Principle: A reverser air jet circulator beneath the sieve mesh, blowing oversize particles away from the mesh to blocking.

USE:- Impinging Air jet can remove Micrometer-size particles from solid surface. [Chemical Abstracts, 149(3); August 2008:56449r]

03] SEDIMENTATION:-

- «- These are based upon study of the terminal velocity acquired by particles suspended in a viscous liquid.
- «- Sedimentation time is longest for the finest particles.
- «- Stokes given a theoritical description of the motion of falling under the influence

of gravity.

dst=[18 η μ/(Pp-PL) g]½

«- A no. of Techniques based on Sedimentation Methods utilizing devices such as The Andereasen apparatus pipette or Recording Balances.

«- This technique is useful for sizes below 10 μm.

«- For sub-micrometer particles which can't be reliably measured by above method due to the effects of Brownian motion. The Typical apparatus used which diperses the sample in liquid, then measures the optical density of successive layers using visible light or x-rays.

04] ELUTRITION:-

«- Elutriation is a procedure in which the fluid moves in direction opposite to sedimentation movement. For example the particle will move in vertically down wards direction and fluid moves vertically upwards direction. If velocity of fluid is higher then the particle are carried upwards and vice versa.

«- Size of particle that will separate depends on their Viscosity & Density.

«- Separation in to several fractions may be affected by using no. of vessels of increasing diameter with suspension entering through bottom.

05] ELECTRONIC SCANNING ZONE (COULTER COUNTER):-

An example of this is the Coulter counter, which measures the momentary changes in the conductivity of a liquid passing through an orifice that take place when individual non-conducting particles pass through. The particle count is obtained by counting pulses, and the size is dependent on the size of each pulse.

Advantages

«- Fastest counting.

«- 1000 Particle count at one second.

«- More reliable since no of particles are counted.

«- To study particle Growth & dissolution and the effect of antibacterial agent on the growth of micro-organism.

06] CAPILLARY HYDRODYNAMIC FRACTIONATION:-

Sample particles are fractionated according to size as they flow in a capillary tube. The particles are detected at the capillary outlet by an on-line detector, typically an ultraviolet (UV) detector. Particle size is given by the elution or transit time of the particles in the capillary. This elution time depends only on the particle hydrodynamic size and is independent of particle chemical composition and density.

07] LASER LIGHT SCATTERING METHODS:-

«- In this method particle can be presented either in liquid or in air suspension.

«- Both the large particle and small particle analyzers are based on the interaction of laser light with particles.

FRAUNHOFER DIFFRACTION:-

For particles that are much larger than the wave length of light, any interaction with particles causes light to be scattered in a forward direction with only a small change in angle. This phenomenon is known as Fraunhofer diffraction, and produces light intensity patterns that occur at regular angular intervals and are proportional to the particle diameter producing the scatter different diameter particle may be considered to be the sum of all the individual patterns produced by each particle in the size distribution.

08] X-RAY DIFFRACTION METHOD:-

Principle:-

«- An x-ray irradiation produce a highly specific diffraction pattern from a crystal of material. An X-ray diffraction pattern from the crystal is formed a series of dots of varying intensity with fixed angular & recorded on photographic film.

«- It is powerful tool for particle size analysis.

ADVATAGES:-

«- very sensitive

«- use in identification of polimorphs

DISADVANTAGES:-

«- Very expensive

09] NEPHELOMETRY:-

Measurement of the scattered light intensity is the basis of nephelometry.

Method:- A beam of light is directed through the test sample. Detectors are placed to measure the 90-degree scatter, the forward-scattered light, & the light transmitted through the sample. Excellent linearity and colour rejection are attained by electronically comparing the ratio of the output of the 90-degree detector to the sum of the other two detectors. The design of the optical system makes the effect of stray light negligible.

10] CASCADE IMPACTION:-

Size Range:-0.05-30 µm.

Material:-Particle of all kind

Method:-

«- Air samples are withdrawn through device which consist of several stages on which particles are deposited on impaction plate.

«- Particles will impact on certain stage depending on their size.

«- A series of scanning microscopy that may be identified & related to a size range in which elevated counts were noted with a particle counter.

Uses:-

«- In combination with scanning microscopy use to identify small particles present in the air.

«-To determine the distribution of particles of respirable size. E.g Aerosol.

Limitation:-

«- particles bouncing off

«- over loading
«- fluctuation

11] ROTATING DRUM METHOD

Material:-Dry powder, Granulates, Friable products.
Size Range:-0.5-10000 microns
This method is suitable to determine the distribution of particle of respirable or inhalable size.

PROPERTIES OF DRUG THAT ARE AFFECTED BY PARTICLE SIZE AND PARTICLE SIZE DISTRIBUTION

Surface area
Density, Porosity and Compressibility
Angle of repose and Flow property
Bulkiness and Packaging Criteria
Hygroscopicity
Electrostatic charge

SURFACE AREA:-

As particle size decrease the surface area of particle increases.
Surface area is important for drug absorption, dissolution, solubility and bioavailability.

DENSITY: -

The ratio of mass to volume is known as the density.
As bulk density of pwd decrease, decrease PS more air absorbed on to surface.

POROSITY: - Is define as ratio of void volume to bulk volume of Packing.
Particle of very small PS increase porosity through decrease flowability due to absorbed moisture or Vander Walla's force.

FLOW PROPERTY:-

Flow property can be increased by addition of small particles in to larger particle which fill the void space.

ANGLE OF REPOSE:-

As Particle size decreases angle of repose decreases and due to cohesive forces flow property increases.

BULKINESS AND PACKAGING :-

As particle size increase bulkiness decreases. It is a reciprocal of bulk density. Uniformity of powder blend is imp.

HYGROSCOPYCITY:-

Decrease in particles size give larger surface area that will give high susceptibility for moisture absorption.

ELECTROSTATIC CHARGES:-
Particle size, PSD, cohesion, adhesion and electrical double layer property is most affected by it.

IMPORTANCE OF PS AND PSD:-
1. Particle size affects many physical properties of drug like surface area, density, porosity, compressibility, moisture absorption, surface properties like solubility, absorption, dissolution and bioavailability.
2. Tablet: - PS and PSD is important for selecting granulation process it also affect average tablet weight variation, granules properties like uniformity of color, size uniformity, also uniformity of dose, absorption, dissolution and finally bioavailability.
3. Suspension: - Sedimentation Rate, Suspendibility, redispersibility, coalescence and agglomeration.
4. Aerosol:- Particle Size of drug affects site of absorption in the bronchopulmonary tract.
5. Bioavailability:- Drug whose BA is increase by PS reduction are Sulphadiazine, Phenothiazine, Tolbutamide, Spironolactone, Aspirin, Nitrofurantoin.

Griseofulvin: - If micronized than increases rate of absorption and finally the dissolution.
Penicillin-G and Erythromycin if PS decreases, surface area increases if remain more time in contact with GIF so increases degradation.

Poorly soluble hydrophobic drug:- If PS is decreases then increases chance of formation of agglomerates.

In case of Nitrofurantoin increase in bioavaibility may resulted in increase in its side effects.
PS & PSD also affects the porosity and bulkiness so affects packing.

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STUDY QUESTIONS

1.Discuss types of powders according to particle size and enlist methods for method of particle size analysis which properties of drug are affected by particle size and particle size distribution?

2. Explain different phases of powder compaction and its evaluation.
3. Differentiate consolidation and compaction of powders.