PHYSICOCHEMICAL PARAMETERS OF PREFORMULATION STUDIES

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INTRODUCTION

WHAT IS PREFORMULATION?

"It is the study of the physical and chemical properties of the drug prior to compounding process".

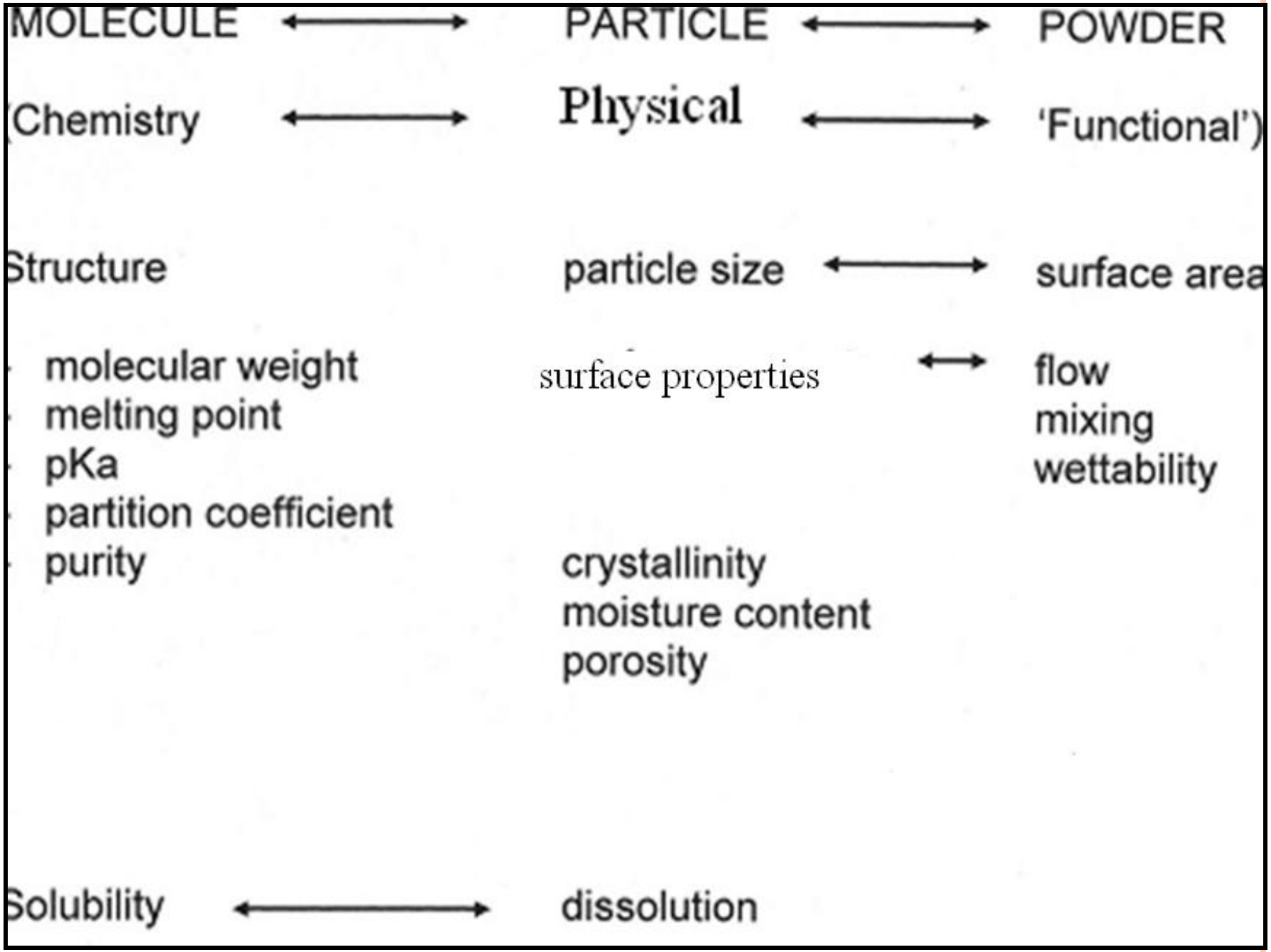
- Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrant evaluation in man.
- These studies should focus on physicochemical properties of new compound that affect drug performance & development of efficacious dosage form.
- This properties may provide;
  - A rationale for formulation design
  - Support the need for molecular modification

Goals of preformulation

- To establish the physicochemical parameters of a new drug.
- To establish its physical characteristics .
- To establish its compatibility with common excipients.
- Providing a scientific data to support the dosage form design and evaluation of the product efficacy and stability.

In short

- Quantization of physical and chemical properties will assist in developing a;
  a. Stable
  b. Safe
  c. Effective formulation


MOLECULE
PARTICLE
POWDER
(Chemistry
Physical
'Functional')
Structure
particle size
surface area
molecular weight
melting point
pKa
partition coefficient
purity
surface properties
flow
mixing
wettability
crystallinity
moisture content
porosity
Solubility
dissolution

THE MAJOR AREAS OF PREFORMULATION STUDY

I. Physical description and Bulk Characterization:

- Crystallinity and Polymorphism
- Hygroscopicity
- Fine Particle Characterization
- Thermal Effects
- Powder Flow Properties

II. Solubility Analysis :

- Ionization Constant- pKa
- pH Solubility Profile
- Common Ion Effect
- Solubilization
- Partition Coefficient
- Dissolution

III. Stability Analysis :

- Solid-State Stability
- Solution-Phase Stability
- Compatibility Studies: Stability in the Presence of Excipients

PHYSICAL CHARACTERIZATION

- Drugs can be used therapeutically as solids, liquids and gases.
- Liquid drugs are used to a much lesser extent than solid drugs and even less frequently than gases.
- Solid materials are preferred in formulation work because of their ease of preparation into tablets and capsules.
- The majority of drug substances in use occur as solid materials.
- Most of them are pure chemical compounds of either:

  Amorphous or Crystalline in nature

PHYSICAL DESCRIPTION AND BULK CHARACTERIZATION

- Bulk properties for the solid form such as particle size, bulk density and surface morphology are likely to change during process of development.
- The various physical and bulk characteristics are explained as follows:

CRYSTALLINITY AND POLYMORPHISM

- Solid drug materials may occur as:
  a. Amorphous (higher solubility)
  b. Crystalline (higher stability)

- The amorphous or crystalline characters of drugs are of great importance to its ease of formulation and handling, its chemical stability and its biological activity.

AMORPHOUS DRUGS

- Amorphous drugs have randomly arranged atoms or molecules.
- Amorphous forms are typically prepared by ; precipitation, lyophilization, or rapid cooling method.

Advantage:

- Amorphous forms have higher solubilities as well as dissolution rates as compared to crystalline forms.

Disadvantage:

- Upon storage, sometimes amorphous solids tend to revert to more stable forms. This instability can occur during bulk processing or within dosage forms.

E.g. Novobiocin :

- It is inactive when administered in crystalline form, but when they are administered in the amorphous form, absorption from the gastrointestinal tract proceeds rapidly with good therapeutic response.

CRYSTALLINE DRUGS

- Crystals are characterized by repetitious spacing of constituent atoms or molecules in a three dimensional array.
- Crystalline forms of drugs may be used because of greater stability than the corresponding amorphous form.
- **For example:** the crystalline forms of penicillin G as potassium or sodium salt is considerably more stable and result in excellent therapeutic response than amorphous forms.

POLYMORPHISM

- Polymorphism is the ability of a compound to crystallize as more than one distinct crystalline species with different internal lattices or crystal packing arrangement even they are chemically identical depending on the variation in ;

  a. Temperature

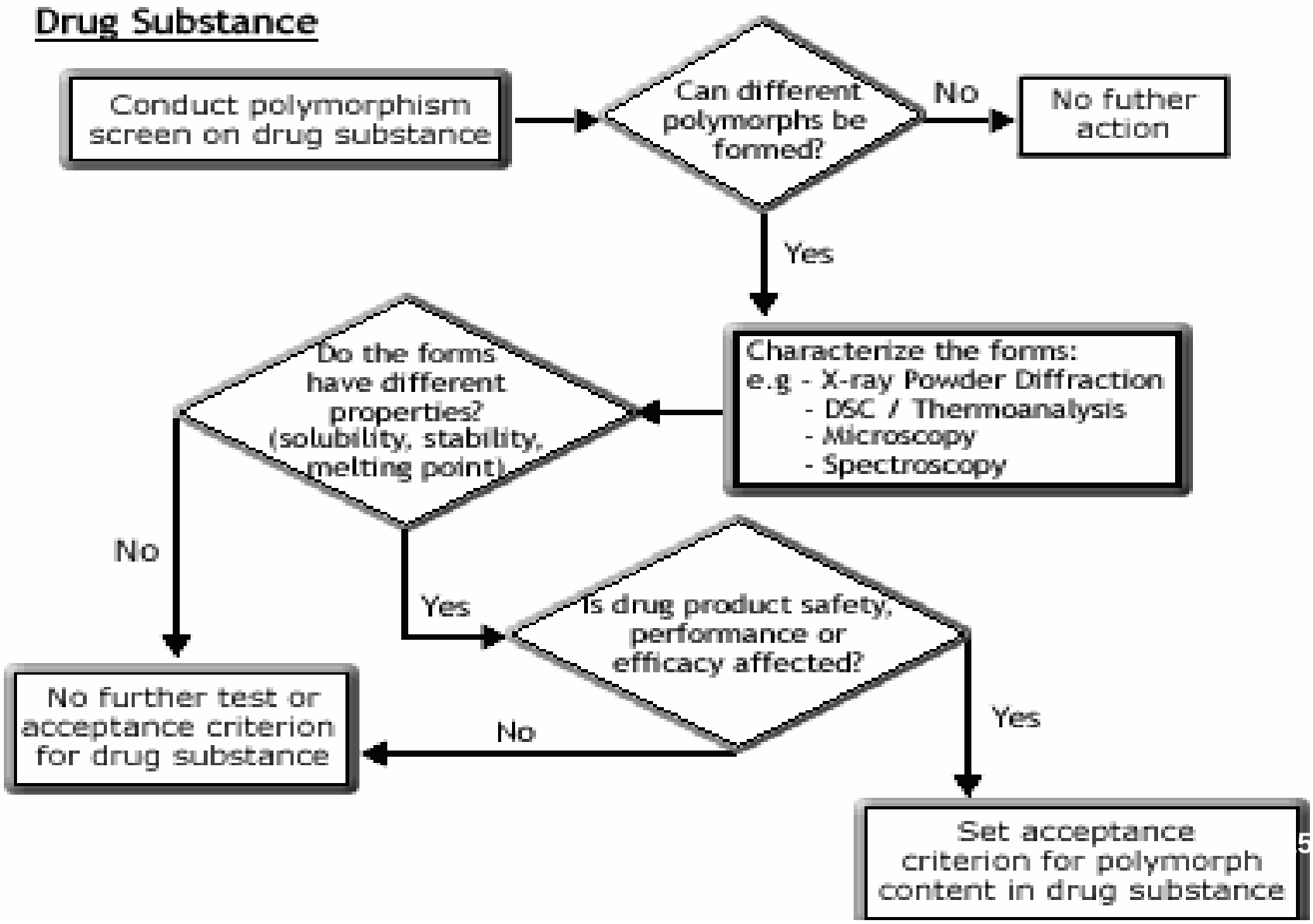
  b. Solvent

  c. Time

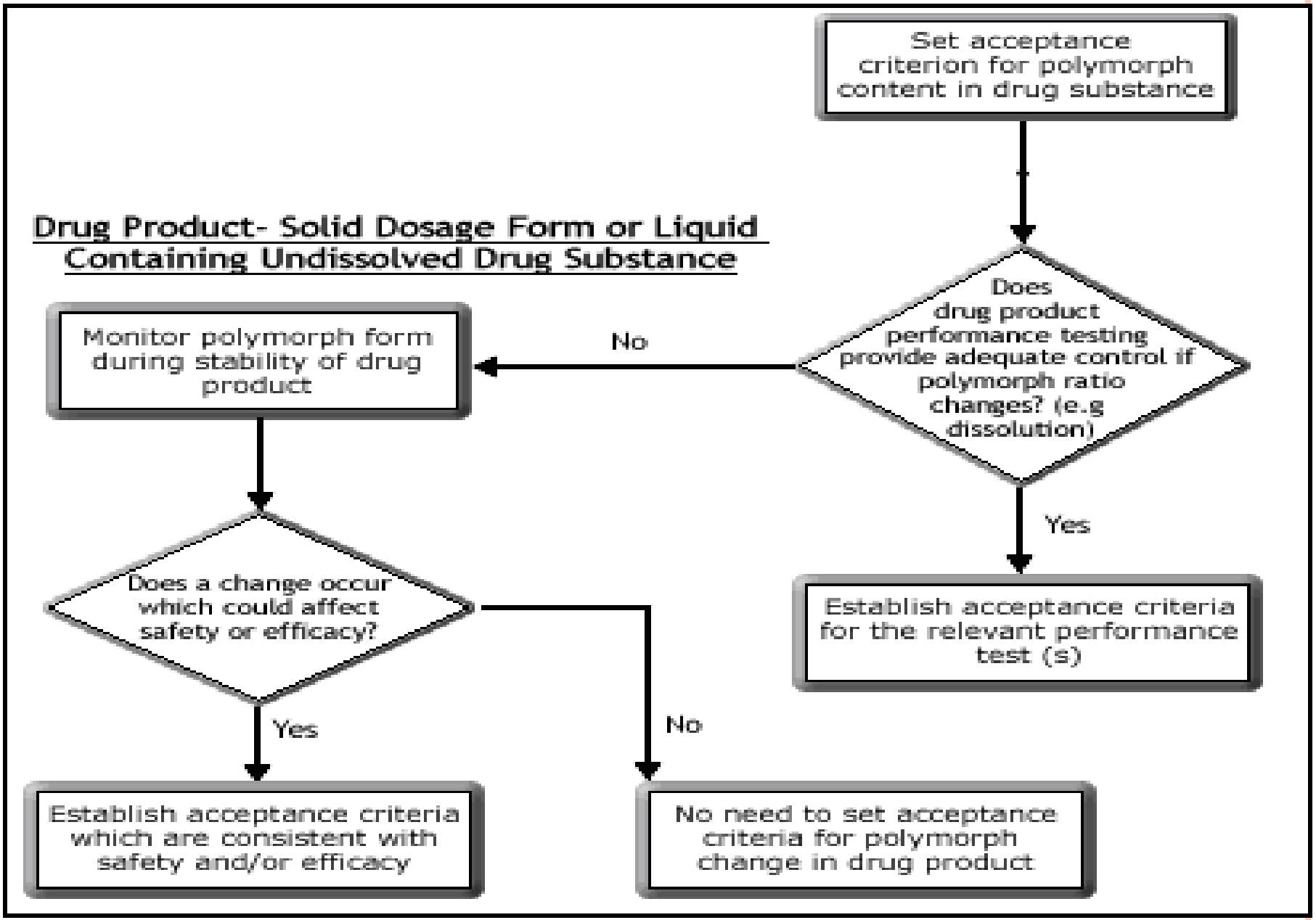
Significance of polymorphism:

- Different polymorphs exhibits different solubilities, therapeutic activity and stability.
- Chemical stability and solubility changes due to polymorphism can have an impact on drug's activity.

Setting Acceptance Criteria for Polymorphism in Drug Substances



Setting Acceptance Criteria for Polymorphism in Drug Products



THERMAL ANALYSIS

- **Differential scanning calorimetry and Differential thermal analysis: [DSC & DTA]**

  Measure the heat loss or gain resulting from physical or chemical changes within a sample as function of temperature.

- **Thermo gravimetric analysis (TGA):**

  It measure changes in sample weight as a function of time (isothermal) or function of time (isothermal) or temperature.

- Desolvation and decomposition processes are frequently monitored by TGA.

Applications:

- Purity, polymorphism, solvation, degradation, and excipient compatibility.
- Thermal analysis can be used to investigate and predict any physicochemical interactions between components in the formulation.
- It is used for selection of chemically compatible excipients.

X-RAY DIFFRACTION

- It is an important technique for establishing the batch-to batch reproducibility of a crystalline form.
- Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound.

Applications:

- Quantitative ratios of two polymorphs and their percentages of crystallinity may be determined.
- Mixtures of different crystalline forms can be analyzed using normalized intensities at specific angles, which are unique for each crystalline form.

HYGROSCOPICITY

- Many drugs , particularly water-soluble salts, have a tendency to adsorb atmospheric moisture.
- Changes in moisture level can greatly influence many parameters such as ; chemical stability, flowability, and compatibility.
- Adsorption and equilibrium of moisture content can depend upon ; atmospheric humidity, temperature, surface area, exposure, and the mechanism for moisture uptake.

Hygroscopic substances:

It adsorbs water because of hydrate formation or specific site adsorption.

Deliquescent materials:

Adsorb sufficient water to dissolve completely, as observed with sodium chloride on a humid day.

- Analytic methods for monitoring the moisture level are ; gravimetric (weight gained), Karl Fischer titration, or gas chromatography) according to the desired precision & the amount of moisture adsorbed onto the drug sample.

FINE PARTICLE CHARACTERIZATION

- Size, shape & surface morphology of drug particles affect the flow property, dissolution &chemical reactivity of drugs.

Significance of Particle Size:

- Particle size of drugs may affect formulation and product efficacy.
- Certain physical and chemical properties of drug substances are affected by the particle size distribution including; drug dissolution rate, content uniformity, texture, stability, flow characteristics, and sedimentation rates.

- Particle size significantly influences the oral absorption profiles of certain drugs.
- Satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.

METHODS TO EVALUATE PARTICLE SIZE AND DISTRIBUTION

1. Sieving or screening
2. Optical microscopy
3. Sedimentation
4. Stream scanning.

Sieving or screening:

Disadvantage: It requires a relatively large sample size.

Advantage: Simplicity in technique and equipment requirements.

Optical microscopy:

It is the first step in the determination of particle size and shape for new drug substance.

Disadvantage: Quantitative evaluations need minimum 1000 particles (tedious and time consuming). The slide must be representative of the bulk of the material.

Sedimentation:

- It utilize the relationship between rate of fall of particles and their size.

Disadvantage:

- Proper dispersion, consistent sampling temperature control, must be carefully controlled to obtain consistent and reliable results.

Stream scanning:

- Technique utilizes a fluid suspension of particles which pass the sensing zone where individual particles are sized, counted & tabulated.
- Sensing units are based on ; light scattering transmission, as well as conductance.
- The popular unit in the pharmaceutical industry for this purpose is the Coulter Counter

Advantages:

- The unit electronically size, count and tabulate the individual particles that pass through the sensing zone and data is obtained in a short time with reasonable accuracy.

- Thousands of particles can be counted in seconds and used to determine the size distribution curve.
- It is a powerful tool and can be used for evaluation of parameters as crystal growth in suspension formulation.

SURFACE MORPHOLOGY

- It is observed by Scanning Electron Microscopy (SEM), which serves to confirm the physical observations related to surface area.
- Surface morphology of drug can provide greater area for various surface reactions such as; degradation, dissolution, or hygroscopicity.
- Surface roughness leads to poor powder flow characteristics of powders due to friction and cohesiveness

BULK DENSITY

- Bulk density of a compound varies with the method of crystallization, milling, or formulation.

Importance of bulk density:

- Knowledge of the true and bulk densities of the drug substance is useful in forming idea about the size of the final dosage form.
- The density of solids also affects their flow properties.

POWDER FLOW PROPERTIES

- Flow properties are significantly affected by:

  Changes in particle size, density, shape, and adsorbed moisture, which may arise from processing or formulation.

- The powder flow properties can be characterized by the following methods:

The Angle Of Repose:

- It is the maximum angle between the surface of a pile of powder and horizontal plane

$$\text{Tan } \theta = h/r$$

- The rougher and more irregular the surface of the particles, the higher will be the angle of repose.
- Lower values indicates better flow characteristics.

- The acceptance criteria for angle of repose are:

Angle of repose	Type of flow
< 20	Excellent flow
20-30	Good flow
30-34	Passable
>40	Poor flow

- **Compressibility:**

It can be characterized by the following methods;

1. Carr's compressibility index
2. Hausner`s ratio

1. Carr's compressibility index:

$$\text{Carr's index (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

- By decreasing the bulk and tapped density good flow properties can be obtained.

The acceptance criteria for carr`s index are :

Carr's index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

2. Hausner `s ratio:

- Hausner `s ratio = $\frac{\text{Tapped density}}{\text{bulk density}} \times 100$

The acceptance criteria for Hausner`s ratio are :

:

Hausner`s ratio	Type of flow
< 1.25	Good flow
> 1.5	Poor flow
1.25-1.5	Glidant addition required
>1.5	Glidant doesn't improve flow

SOLUBILITY

- The solubility of drug is an important physicochemical property because it affects the rate of drug release into the dissolution medium and consequently, the therapeutic efficacy of the pharmaceutical product.
- The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved.
- General rules –
  - 1. Polar solutes dissolve in polar solvents
  - 2. Non-polar solutes dissolve in non-polar solvents

Common solvents used for solubility determination are:

- Water
- Polyethylene Glycols
- Propylene Glycol
- Glycerine
- Sorbitol
- Ethyl Alcohol
- Methanol
- Benzyl Alcohol
- Isopropyl Alcohol
- Tweens
- Polysorbates
- Castor Oil
- Peanut Oil
- Sesame Oil
- Buffers at various pHs

SOLUBILITY DETERMINATION

Description	Approximate weight of solvent(g) necessary to dissolve 1g of solute	Solubility(%w/v)
Very soluble	<1	10-50
Freely soluble	1-10	3.3-10
Soluble	10-30	1-3.3
Sparingly soluble	30-100	0.1-1
Slightly soluble	100-1000	0.01-.1
Very slightly soluble	1000-10000	0.01-0.1
Poorly soluble	>10000	<0.01

Ionization constant (pKa)

- For a compound containing basic or acidic functional groups, solubility at a given pH is influenced by the compound's ionization characteristics.
- The solubility of a compound in aqueous media is greater in the ionized state than in the neutral state.
- Thus, solubility of ionizable compounds is dependent on the pH of the solution.
- The method for the determination of pKa according to the nature of drug can be explained as:

pKa Determination By Nature of Drug

Nature of drug	Ionization	pKa
Very weak acid	Unionized at all pH	>8
Moderately weak acid	Unionized at gastric pH-1.2	2.5-7.3
Strong acid	Ionize at all pH	<2.5
Very weak base	Unionize at all pH	<5
Moderately weak base	Unionize at intestinal pH	5-11
Strong base	Ionize at all pH	>11

- Determination of the dissociation constant for a drug capable of ionization within a pH range of 1 to 10 is important since solubility, and consequently absorption, can be altered by changing pH.
- The Henderson-Hasselbalch equation provides an estimate of the ionized and un-ionized drug concentration at a particular pH.
- *For acidic compounds*:

  pH = pKa + log ([ionized drug]/[un-ionized drug])
- *For basic compounds*:

  pH = pKa + log ([un-ionized drug]/[ionized drug])

Methods for determination of pKa:

The various methods for the determination of pKa are;

a. Potentiometric method
b. Spectrophotometric method
c. Solubility method
d. Conductometric method

Partition coefficient

- Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes.

Define:

It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = (C_{oil}/C_{water})_{equilibrium}$$

Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug

Stability studies

- Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug.
- These studies include both solution and solid state experiments under conditions typical for the handling, formulation, storage, and administration of a drug candidate as well as stability in presence of other excipients.
- Factors affecting chemical stability critical in rational dosage form design include ;
  - Temperature
  - pH
  - Dosage form diluents

- The effect of pH on drug stability is important in the development of both oral and parenteral dosage forms

  e.g. acid labile drugs intended for oral administration must be protected from the highly acidic environment of the stomach.

- Buffer selection for parenteral dosage forms will also be largely based on the stability characteristics of the drug.

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Thank you