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Review Article

Basics on Pre-formulation Research: For Formulation Scientists

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ABSTRACT

Preformulation research were evolved in 1950 and early 1960. Preformulation testing is the first step in the rational development of dosage forms for a drug substance. The study covers drug discovery to drug development. It is a systematic and multidisciplinary study or research. The main objective is to develop a suitable dosage form for a drug substance with maximum safety, efficacy and bioavailability and at the same time to avoid the risk-chance for reformulation which causes loss of money, labor and raw materials to the industry. The author has discussed on relationship between preformulation formulation and reformulation in dosage form development, characteristics of drug substance, stability analysis, significance of biopharmaceutical classification system, applications of preformulation and formulation recommendations etc. The knowledge of preformulation studies is an essential part for a formulation scientist.

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INTRODUCTION

It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients in order to rationally develop a stable, safe and effective dosage for with safety and maximum therapeutic efficacy. Prior to the development of dosage forms, it is essential that certain fundamental physicochemical properties and stability analysis of potential drug molecules and other derived properties of drug powder are determined. Preformulation studies help in assessing the 'drug-ability" of a molecule. Thus, it can be considered as critical decision-making tool during both drug discovery and development phase. Preformulation will give pointers to the feasibility of various possible dosage forms and to any potential problems of instability and poor in vivo dissolution and thus bioavailability. [1]

GOALS AND OBJECTIVES [2]

The goals and objectives of pre-formulation studies cover:

- To formulate an elegant, safe and efficacious dosage form with good bioavailability.
- To establish the kinetic rate profile of a new drug substance.
- To establish the compatibility of the new drug substances with the common excipients.
- To choose the correct from of the drug substance.
- To establish the physical characteristics of a new drug substances.
- To establish physicochemical parameters of new drug substances.

DISCOVERY TO DEVELOPMENT

Previously, animal tissue and whole animal screen had been used to find new chemical entities (NCE) that had been therapeutic potential. The discovery of mechanism based on mass screening of small molecules discovered in late 1980. Today even newer technologies are being used increase the speed and reduce material consumption. All of these innovative changes have had a cascading impact on development. There are various unpredictable in vitro activities and can now be found. As a result, although many initial promising NCEs are extremely potent in the in vitro enzyme assays, they are inactive in the in vivo because of their unfavorable solubility and dissolution characteristics in the aqueous media of the body. This provides demanding challenges for the preformulation scientist because, with mechanism-based therapy, testing in human is often the only means of evaluating the efficacy of a new therapeutic strategy. [3]

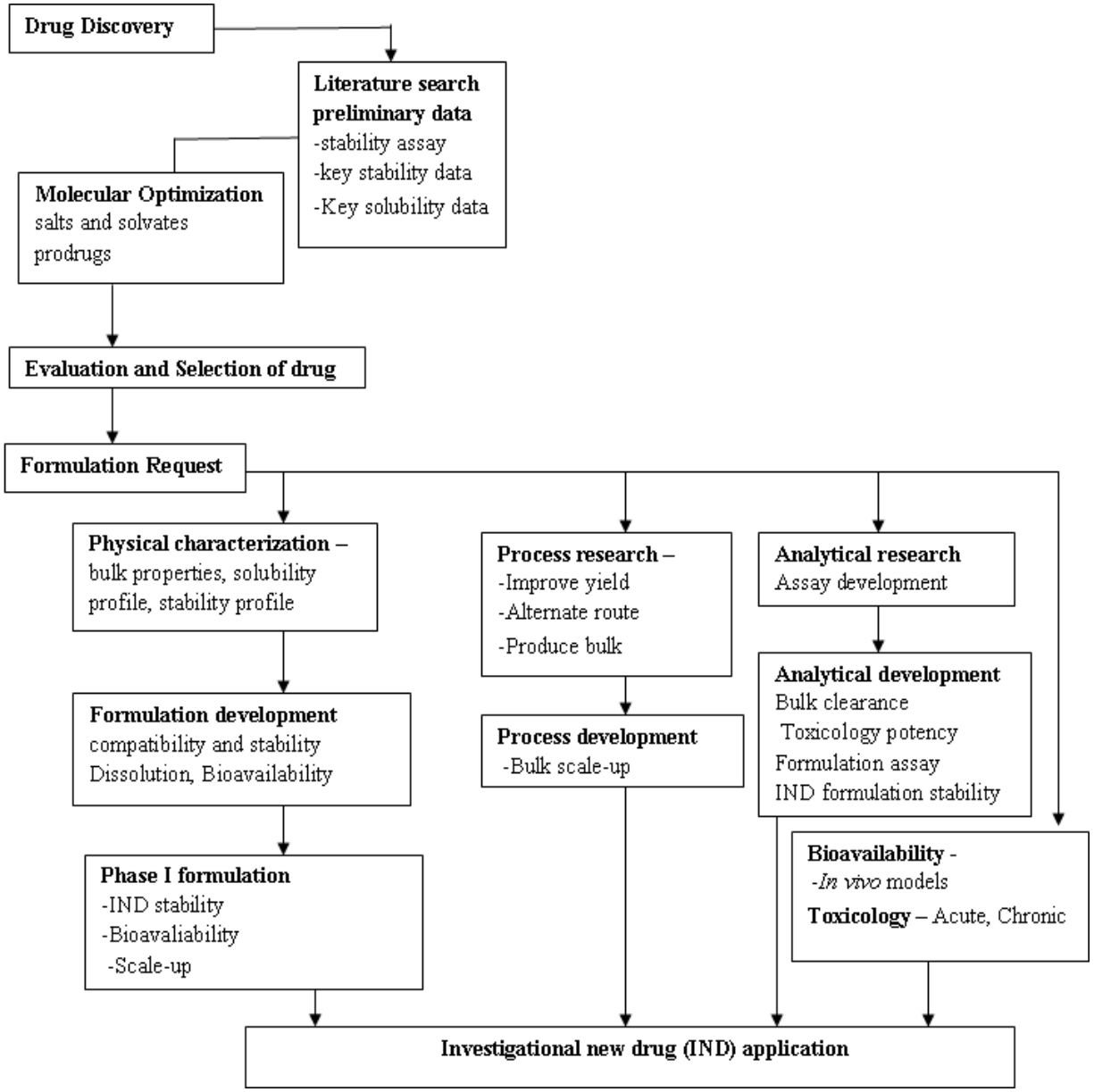

Figure 1: Flow diagram illustrating the multidisciplinary development of a drug candidate [4]

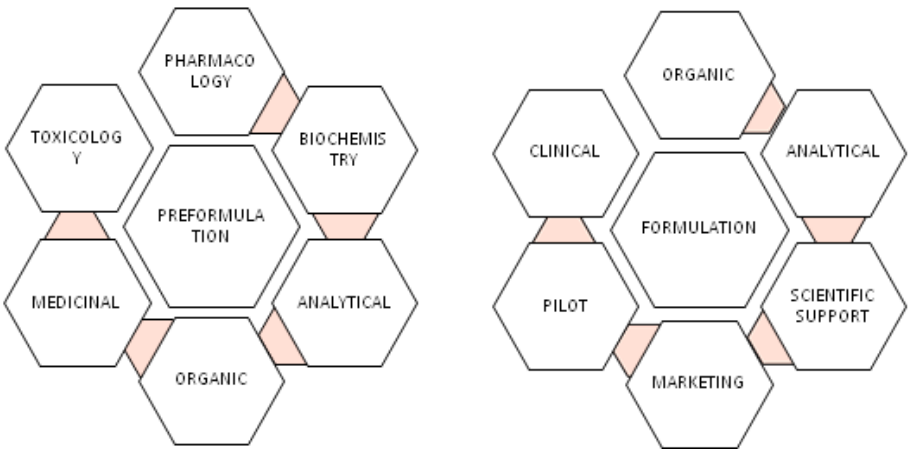

Figure 2: The wheels of product development [5]

RELATIONSHIP BETWEEN PRE-FORMULATION AND FORMULATION IN DOSAGE FORM DEVELOPMENT

Formulations studies aim to develop a drug preparation which is both stable, safety and acceptable to the patient whereas the preformulation studies are essential component of drug development process, and it provides the scientific basics for formulation development. [6]

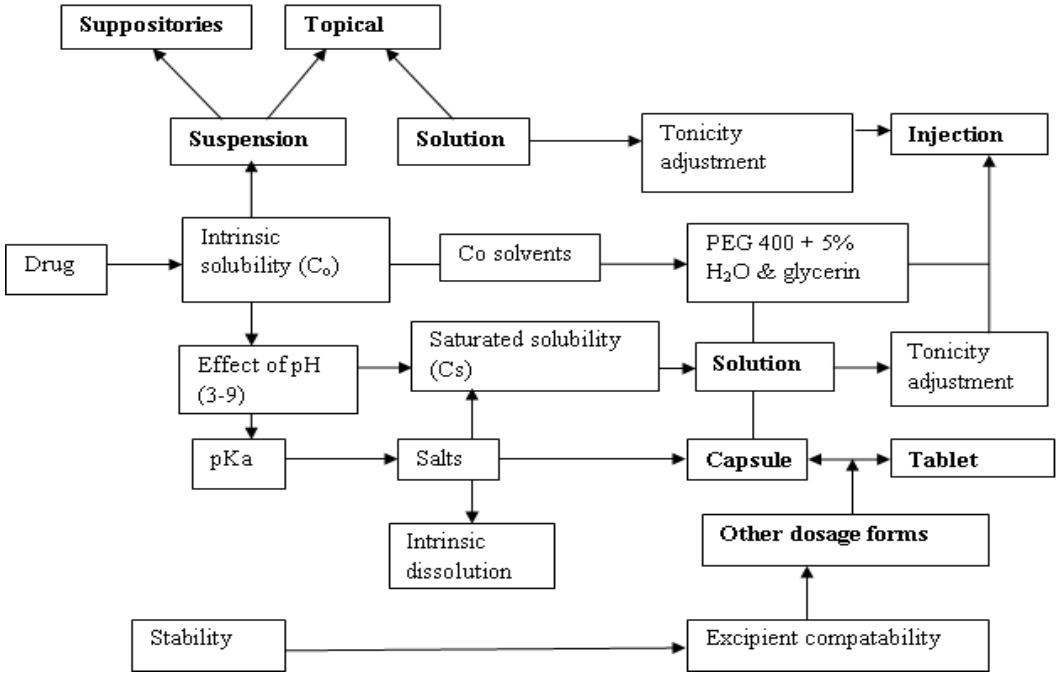

Figure 3: Flow diagram of relationship between preformulation and formulation in dosage form development.

FOCUSED AREAS OF THE STUDY [7-9]

I. **Bulk characterization**

Bulk properties for solid form may likely change during process development hence bulk characterization of bulk lots avoid misleading predictions of stability or solubility, which depend on particular crystalline form.

Bulk characterization study under preformulation research covers study on: crystallinity and polymorphism, hygroscopicity, fine particle characterization, different densities, flow properties etc.

II. **Solubility analysis**

Solubility analysis includes study on: ionization or dissociation constant-pKa, pH solubility profile, commonion effect, effects of heat on solubility, solubilization, partition coefficient, dissolution property etc.

III. **Stability analysis:** Mainly includes solid state stability and solution stability analysis.

A substance can be outlined as

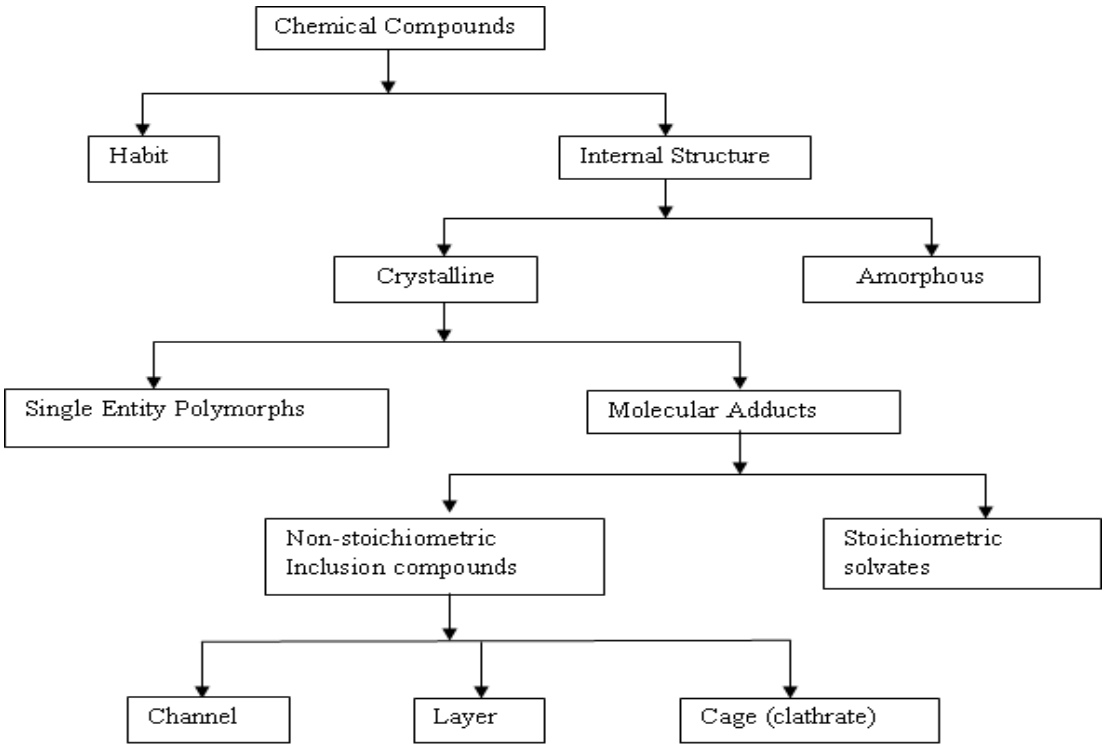

Figure 4: Outline of differentiating habits and crystal chemistry of a compound.

CRYSTAL MORPHOLOGY

Crystal habit and internal structure affects bulk and physico-chemical properties, from flowability to chemical stability. Habit is a description of outer appearance whereas internal structure is the molecular arrangement within the solid. Changes in internal structure alter the crystal habit. Different habits of crystals may be platy, equant or massive, acicular or needle, bladed, prismatic and tabular etc.

INTERNAL STRUCTURE

May be crystalline or amorphous. Crystals have repetitious spacing of constituent atoms or molecules in a three-dimensional array. Amorphous forms have randomly placed atoms or molecules as in a liquid. Amorphous forms are prepared by rapid precipitation, lyophilization or rapid cooling of liquid melts. Amorphous form possesses higher thermodynamic energy than corresponding crystalline form hence shows greater solubility and dissolution rates and on storage reverts to more stable forms. This thermodynamic instability during processing or within dosage forms is a major disadvantage for amorphous state of a drug substance and is more important while formulating a suspension.

Table 1: Difference between crystalline and amorphous Substances

Crystalline	Amorphous
1. Crystalline solids have definite shape and an orderly arrangement of units (molecules or atoms or ions).	1. No definite arrangement of constituent units.
2. The repetition with arrangement exists for long distance of angstrom units.	2. The repetition with arrangement does not exist for long distance of angstrom units.
3. Crystalline substances have a definite or sharp melting point	3. No definite or sharp melting point, are called super cooled liquids
4. Less thermodynamic energy	4. Possesses more thermodynamic energy than corresponding crystalline form.
5. More stable	5. Less stable
6. Shows less solubility and dissolution rates	6. comparatively shows more solubility and dissolution rates
7. Shows X- ray diffraction	7. Do not shows X- ray diffraction

CRYSTALLIZATION SOLVENT

Crystalline compound may contain stoichiometric or non-stoichiometric amount of crystallization solvent. Non-stoichiometric adducts like inclusions or clathrates involve entrapped solvent molecules within the crystal lattice, exhibit lack of reproducibility in formulation hence these adducts are undesirable - should be avoided. Stoichiometric adducts are known as solvates. These are molecular complexes that have incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called hydrate. Hemi, mono, dihydrates correspond to half, one and two molar equivalents of water. A compound without water in the crystal structure is called anhydrous. Solubility of hydrates can be less than the anhydrous forms due to less affinity for water. Conversion of anhydrous form to hydrous within the dosage form may reduce dissolution rate and the extent of absorption.

Polymorphism (Poly- many, morph- physical form, ism- is the phenomenon)

Polymorphism is defined as existence of a single chemical substance of the same molecular composition in more than one crystalline and or amorphous form. The various forms are called polymorphs and

the phenomenon is called as polymorphism. The different polymorphic forms vary in their ability to interconvert at different temperature and pressure.

It is a characteristic of most solid substances. Many drug substances can exist in more than one crystalline form with different space lattice arrangements. Polymorphic forms may be two types basing on, some systems can reversibly interconvert and some cannot

1. Enantiotropic: Reversibly inter-conversion between the different forms is possible.
2. Monotropic: For monotropic polymeric systems, inter-conversion is only possible in one direction, from a meta-stable form to a more stable form.

Different polymorphic forms may differ with respect to: melting points, densities, optical properties, vapor pressure, hardness, x-ray diffraction patterns, solubility and dissolution, even though they are chemically identical. Differences in the dissolution rates and solubilities are an important pharmaceutical stand point of different polymorphic forms of a given drug. When the absorption of a drug is dissolution rate limited, a more soluble and faster-dissolving form may be utilized to improve the rate and extent of bioavailability. Selection of a polymorph that is chemically more stable is a solution in many cases in formulation development.

Example of substances showing polymorphism are chloramphenicol polymorphs, that exists in A, B,C and an amorphous form, most steroids, antibiotic novobiocin (C and A), sulphur and sulphonamides etc. Different polymorphs also lead to different morphology, tensile strength and density of powder bed which all contribute to compression characteristics of materials. Although a drug substance may exist in two or more polymorphic forms, only one form is thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with time. In general, the stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability.

Metastable form may revert to stable form with time (conversion depends on temperature and pressure)

The existence of an elemental substance in more than one crystalline form are said to be allotropic and the different forms are called allotropes.

The formation of polymorphs of a compound may depend upon several variables pertaining to the crystallization process, including

- Solvent differences (the packing of a crystal might be different from a polar versus non polar solvents)

- Impurities that may favor a metastable polymorph due to specific inhibition of growth pattern.
- The level of super saturation from which the material is crystallized (generally the higher the concentration above the solubility, the more chance a metastable form is seen)
- The temperature at which crystallization is carried out.
- Geometry of the covalent bonds (are the molecules rigid and planar or free and flexible)
- Attraction and repulsion of cations and anions (x-ray crystallography is used to define an electron density map of a compound)

Nearly all long chain organic compounds exhibit polymorphism.

Theobroma oil or cocoa butter is a natural substance exhibit polymorphism. The different forms are:

α form, unstable, M.P is of 22 ˚C

β form, stable, M.P is of 34.5 ˚C, that matches with body temperature and

γ form, unstable M.P is of 18 ˚C

Enantiotropy: One polymorphic form can be reversibly changed into another by varying temperatures or pressure e.g., Sulphur

Monotropy: One polymorphic form is unstable at all temperatures and pressures ex: Glycerol stearate.

Allotropy: Existence of an elemental substance in more than one crystalline form are said to be allotropic. The meta stable form, with changing temperature and pressure may convert to stable form. They show different melting points, X-ray diffraction patterns and solubility.

During preformulation, it is important to identify the polymorphic form that is stable at room temperature. Evaluation of stability of metastable polymorph and its rate of conversion within dosage form is a difficult task.

Rate of polymorphic conversion:

The rate of polymorphic conversion depends on several variables. In case of solid dosage forms like tablets/capsules the rate of polymorphic conversion depends on particle size, moisture and excipients. In suspensions it includes drug solubility within the vehicle, presence of nucleated seed for stable form, temperature, agitation, particle size etc.

Crystalline solids have definite shape and an orderly arrangement of units (molecules or atoms or ions). The repetition with arrangement exists for long distance of angstrom units. Crystalline substances have a definite or sharp melting point. The morphology of a crystalline form is often referred to as its habit, where the crystal habit is defined as having the same structure, but different outward appearance. The binding force of the crystals may be-electrostatic attraction of the oppositely

charged ions, covalent bonds, Van der Walls forces, Coulombic forces or hydrogen bonding etc. Type of crystals and stability of crystals depend on solvents, temperature and pressure used for their preparation, the crystalline arrangement patterns and salts (if crystallization is occurring through the formation of insoluble salt complexes that precipitate)

Different polymorphic forms show different solubility and affect the dissolution rate. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug. Selection of a polymorphic form is an important factor in suspension technology. During storage a metastable polymorphic form may change to stable form leading to caking of crystals. Hence it should be in the form of the stable polymorph before the suspension is prepared. Variability in hydrogen bonding contributes to polymorphism in the sulphonamides. Tamoxifen citrate an anti-estrogenic and anti-neoplastic drug used in the treatment of breast cancer and post-menopausal symptoms exists in two different polymorphic forms A and B. Form-A is meta stable form and the molecular structure is less organized. Form-B is stable polymorph, is dominated by H-bonding. An ethanolic suspension of polymorph-A spontaneously rearranges into polymorph-B.

Differentiation of pseudo polymorphs from true polymorphs can be done by

- Melting behavior in silicon oil using hot stage microscopy
- Pseudo polymorphs evolve gas (steam or solvent vapors)
- True polymorphs merely melt, forming second globular phase

Analytic Methods for Characterization of Solid Forms

Table 2: Quantity of material required for the study

Method	Approximate Sample Quantity required
Microscopy	1 mg
Fusion method (hot-stage microscopy)	1mg
Infrared spectrophotometry	2 – 20 mg
Single-crystal X-ray and X-ray powder diffraction (XRD)	500 mg
Differential scanning calorimetry/ Differential thermal analysis (DSC/DTA)	2- 5 mg
Thermogravimetri analysis (TGA)	10 mg
Scanning electron microscopy (SEM)	2 mg
Dissolution/ solubility analysis	mg to g

Characterization of substances [14-16]

Particle size

A term which is used to measure the dimension of particle like solid, liquid and gases. Particle size affects solubility, dissolution, and bioavailability. It can be determined by microscopic sieving method, light scattering method etc.

Type of powder according to particle size –

Mono-disperse powder- All particles are of same size.

Poly-disperse powder- Particles are of different size.

Generally, powder sample contains no. of irregular shape three dimensional particles so generally we consider average particle size (which is distributed in system).

Method for particle size analysis:

a) Microscopy
b) Sieving method
c) Sedimentation
d) Coulter counter
e) Cascade impaction

(a) Microscopy

Range of analysis,

TEM- 0.0001- 0.1 micron.

SEM- 0.01-1000 micron.

Light microscope - 1-1000 micron.

Light microscope - Two dimensional images.

Alternative technique:

1) Scanning electron microscopy (SEM)
2) Transmission electron microscopy (TEM)

SEM gives three dimensional images. It has more resolution power then light microscopy.

Both SEM and TEM analysis use for lower particle size.

(b) Sieving method

Standardized by international organization for standardization (ISO).

Lowest sieve diameter - 45 micron and maximum sieve diameter 1000 micron.

This method obtains particle range 5-12000 micron.

Sample preparation and analysis condition:

Sieve analysis is usually carried out using dry powders although for powder in liquid suspension or which agglomerate during dry sieving a process of wet sieving can be used.

(c) Sedimentation method

Range- 1- 200 mm.

Andresen pipette is used.

Particles size is calculated by Stoke's law.

(d) Electronic scanning zone (coulter counter)

Fastest counting method.

1000 particle count in one second.

More reliable since no. of particles are counted.

(e) 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 air stream. [10-13]

Particle shape

Particle shape is defined by the relative dimensions of the long, intermediate, and short axes of the particle. It affects the flow properties. Particle shape can influence variety of important factors;

(A) Dissolution rate

(B) Girthness

(C) Penetrability

(D) Uniform distribution

Flow properties

It is an ability of particles to flow. Powder flow properties can be affected by change in particle size, shape and density.

The flow properties depend upon following

1. Force of friction

2. Cohesion between one particle to another.

Fine particles possess poor flow by filling a void space between larger particles causing packing and densification of particles. The powder flow is affected by the changes in density, particle size, shape, electrostatic charge. Free flowing drug may become cohesive and necessitates an entirely new formulation.

Angle of Repose

Determination of powder flow properties can be obtained by angle of repose. A greater angle of repose indicates poor flow. It should be less than 30° and can be determined by following equation;

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

where, θ = angle of repose

h = height of pile

r = radius

μ= frictional force

Table 3: Flow properties of particle on the basis of their angle of repose.

Angle of repose; In degree	**Type of flow**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Carr's compressibility index

Measurement of free-flowing powder by compressibility also known as Carr's index. It is simple fast and popular method of predicting powder flow characteristics.

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

Table 4: Table showing compressibility and flowability of pharmaceutical excipients

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fair-passable
23-35	Poor
33-38	very poor
Greater than 40	Very, very poor

Hausner ratio

It is defined as the ratio of powders original bulk volume to its poured final tapped volume.

i.e., Hausner ratio =Original bulk volume (V_o/ V_f)
Final tapped volume

Table 5: Powder flow properties.

Carr's index	Hausner ratio	Angle of repose	Flowability
5 - 15	1.05 - 1.18	25 - 30	Excellent
12 - 16	1.14 - 1.20	31 - 35	Good
18 - 21	1.22 - 1.26	36 - 45	Fair to passable
23 - 35	1.30 - 1.54	46 - 55	Poor
33 - 38	1.50 - 1.16	56 - 65	Very poor
>40	>1.67	>66	Extremely poor

Solubility profile (pKa, pH, partition coefficient)

The solubility of drug is an important physicochemical property because it effects the bioavailability of the drug, the rate of the drug release into dissolution medium and the consequently, the therapeutic efficiency of the pharmaceutical product. When solubility is greater than 1 % w/v, there is no dissolution, which results in an adsorption issue. The solubility of less than 1 mg / ml indicates the need for salt, particularly if the drug will be formulated as tablet or capsules. The solubility of every new drug must be determined as a function of pH over the physiological pH range of 1- 8. Solubility should be ideally being measured at 2 °C temperature. Until more conclusive information is known, 40 °C ensures physical stability, extended short-term storage, and chemical stability. The maximum density of water occurs at 4 °C and 37 °C to support biopharmaceutical evaluation. [17]

Solubility analysis-

1. Aqueous Solubility
(a) Intrinsic solubility
(b) Ionization constant
2. Solubilization
3. Partition coefficient
4. Thermal effect
5. Common ion effect
6. Dissolution

Aqueous solubility

The solubility of a candidate drug molecule is the amount of drug (solute) that dissolves in a given solution (solvent) to produces a saturated solution at constant temperature and pressure. The availability of a drug is always limited and the preformulation scientist may only have 50 mg.

Intrinsic solubility

An increase in solubility in acid compared to aqueous solubility suggests a weak base and an increase in alkali, weak acid. An increase in acidic and alkaline solubility suggests either impotence or zwitter ion behavior. When the fundamental solubility is completely unionized, the intrinsic solubility should ideally be measured at two temperatures i.e.

1. 40 °C to ensure physical and chemical stability (made density of water occur at 4 °C, leads to minimum aq. solubility)
2. 37 °C to support biopharmaceutical evaluation.

Ionization constant (pKa)

Determination of dissociation content 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 orders of magnitude with changing pH. 75 % of all drugs are weak bases, 20 % are weak acids and only and 5 % are nonionic amphoteric or alcohol. Ionization constant (pKa) can be calculated by Henderson-Hasselbalch equation.

For acidic drugs,

pH = pKa + log [ionized drugs]/ [unionized drugs]

For basic drugs,

pH = pKa + log [unionized drug]/ [ionized drug]

Henderson-Hasselbalch equation for weak bases and acids can be used to;

1. To determine pKa by following changes in solubility.
2. To predict solubility at any pH provided that the intrinsic solubility and pKa are known.
3. To facilitate the selection of suitable salt forming compounds and predicts the solubility and pH properly.[18]

Methods to determine pKa: This includes

- Potentiometric method
- Conductivity method
- Dissolution rate method
- Liquid-liquid partition method
- Spectro photometric method

Table 6: Descriptive terms of solubility (Martin, 2006; IP, 1996; Remington, 2000)

Descriptive Term	**Parts of solvent per one part of solute**
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Very insoluble	1000 to 10,000 parts
Insoluble	More than 10,000 parts.

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 is thought to occur by virtue of the solute dissolving in or being adsorbed on to the surfactant. Solubilization of any material in any solvent depends on paper selection of solubilizing agent.

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.

Partition coefficient

When a solute is added to two immiscible liquids it will distribute between the two phases in a fixed ratio which is referred to as partition or distribution coefficient. Various organic solvents used in determination of partition coefficient include chloroform, ether annyl acetate etc. Partition coefficient (Oil/ Water) is a measure of drugs lipophilicity and an indication of its ability to cross cell membranes. Thus, it is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium.

Po/w = (Coil / Cwater) equilibrium

In formulation development the octanol/ water and chloroform/ water partition coefficient is commonly used.

Po/w = concentration of drug in octanol/ concentration of drug in water (Unionized drug)

Po/w = concentration of drug in octanol/ (1-α) concentration of drug in water (Ionized drug)

Thermal effect

Effect of temperature on the solubility of drugs can be determined by measuring heat of solution i.e., Hs

$$\ln S = \Delta HS/ RT + C$$

Where, S = molar solubility at temp (T) (°K)

R = gas constant

ΔHS = heat of solution represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent. Typically, the temperature range should include 15°C,

25°C, 37°C, and 59°C. Thus, the increasing solution temperature increased drug solubility. Most of the substances are endotherms absorbing heat in the process of dissolution.

Importance

Determination of temperature effect on solubility helps in predicting story condition and dosage form designing.

Application

Pharmaceutical solutions must be administered at are near room temperature, so it is more important factors for product storage than the formulation.

1. To increase the solubility of sparingly soluble solute.
2. To increase the stability by reducing the moisture.

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 form of the substance. This can be shown as:

pH = pKa + log [A]/ [HA]

If the substance is brought outside 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 increased then COOH is converted in to –COO. This may interest with H+ of water. The effect of pH on solubility for weak electrolytes can be described by

pH = pKa + log S-So/ So

where,

S = total solubility

So= molar solubility of the un-dissociated acid

For poorly soluble, weakly acidic drugs;

pH = pKa + log [(S+So)] So

For poorly soluble, weakly basic drugs;

pH = pKa + log [So/ (S - So)]

Where, So= Solubility of unionized free acid or base

St = Total solubility (Unionized + Ionized)

Common Ion effects (Ksp)

A common interaction with solvent, which often overlooked, is the common ion effect. It reduces the solubility of a slightly soluble

electrolyte scuting it results from the removal of water molecules as solvent owning to the competing hydration of other ions. Scuting in arises with larger anions (e.g., Benzoate salicylate) which open the water structure. The hydro tropes increase the solubility of poorly water-soluble compounds such as diazepam.

Hydrochloride salts often exhibit sub optional solubility in gastric juice owning to the abundance of chloride ions. Examples of weakly basic through which decrease solubility in acidic and chloride solution; chlortetracycline, dimethyl chlortetracycline, methacycline, demeclocycline, phenazopyridine. [19-20]

Dissolution

Dissolution of drug particle is controlled by several physicochemical properties like chemical form, crystal habit particle size, solubility and surface area. Dissolution experiment can help to identify potential bioavailability problem areas. The absorption of solid drugs administered oral can be understand by following flowchart;

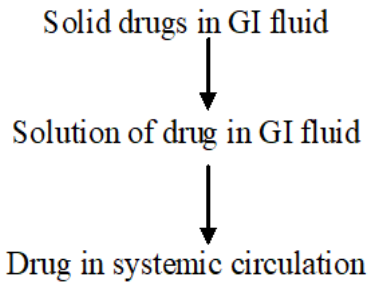

Figure 5: Adsorption of solid drugs through dissolution.

Where, kd……ka adsorption is dissolution rate limited.

The process of dissolution is considered to involve the relocation of a solute molecule from an environment where it is surrounded by other identical molecules with its forms. The dissolution rate of a drug substance in which surface area is constant during dissolution is described by the modified Noyes-Whitney equation i.e., Dc/ dt = da/ hv (Cs – C)

Gibb's free energy, [$\Delta G = \Delta H - T\Delta S$]

where,

ΔH = which is known as the change in the enthalpy of the system.

T = Thermodynamic temperature.

ΔS = Change in entropy, which measures the degree of dissolution randomness in the system.

The process involved in dissolution of solid dosage:

Tablet Granules or Aggregates Fine particles

Study on physico-chemical Properties

1. Microscopy

Materials with more than one refractive index are anisotropic and appear bright with brilliant color against black polarized back ground whereas isotropic material has single refractive index and this substance does not transmit light with crossed polarizing filter and appears black. Hence the thickness of the crystal affects the intensity of colors.

Advantages: By this method we can study crystal morphology and difference between polymorphic forms.

Disadvantages: This requires a well-trained optical crystallographer as there are many possible crystal habits and their appearance at different orientation.

2. Hot stage microscopy

The polarizing microscope fitted with the hot stage is useful for investigating polymorphism, melting point and transition temperature, and rates of transition at control heating rates. In addition, the hot-stage microscope facilitates differentiation of DSC endotherms for polymorphic transitions from desolvation processes.

Advantages: It can be used to observe crystallization process, desolvation, polymorphism, phase transitions etc.

Disadvantages: In this technique the molecules can degraded during melting process.

3. Thermal analysis

Differential scanning calorimetry (DSC) and Differential thermal analysis (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 temperature.

Endothermic processes- Fusion, boiling, sublimation, vaporization, desolvation, solid-solid transition.

Exothermic processes- Crystallization and degradation occur, similarly heat of transition from polymorphs to another may be calculated. A sharp symmetric curve indicates presence of impurities.

4. X-ray diffraction

When beam of homogenous x-ray is allowed to pass through the crystal x-rays beam is diffracted and it is recorded by means of photographic plate. Diffraction is due to crystal which acts as 3-dimensional diffraction grating towards x-ray. The diffraction pattern is characteristic of a specific crystalline lattice for a given compound. An amorphous form does not produce a pattern mixture of different crystalline forms. Single crystal x-ray provides the most complete information about the solid state. [21]

Hygroscopicity

It is the tendency of the materials to absorb moisture from atmosphere and be dynamic equilibrium with water in atmosphere.

Deliquescent

It is the hygroscopic substances which absorb moisture from air and they can be liquified by particularly or wholly forming solution.

Efflorescent

A substance which loses water to form a lower hydrate or become anhydrous it term as efflorescent, e.g., ephedrine, hyoscyamine, phenobarbital, pilocarpine, physostigmine, atropine, cocaine, codeine, scopolamine, caffeine etc.

Methods of determination of hygroscopicity

To carry out study, sample of compound are accurately weighed into container and placed at various humid conditions for period of up to 2 weeks. If weight gain-deliquescent or hygroscopic, if weight loss-efflorescent. It is also determined by Thermo gravimetric analysis, Gas chromatography, and Karl Fischer titration. [22]

Importance of hygroscopicity

1. It affects the flow property.
2. It also affects compaction.
3. Important is aerosol.
4. It affects chemical stability of hydro stable drug.
5. It affects compression characteristics, granulation and hardness of final tablet.

Methods of improvement hygroscopicity

1. For granulation of hygroscopic materials use non-aqueous solvent.
2. For efflorescent material use anhydrous salts.
3. Add finely powdered adsorbents like MgO or MgCo3.
4. Store in desiccant, foil, blister, glass bottle.
5. Use of ion-exchange resins.
6. e.g., complexation of ranitidine with indion 234.

CHEMICAL PROPERTIES

Hydrolysis

Hydrolysis is a chemical reaction of the interaction of chemicals with water, leading to the decomposition of both the substance and water. Drugs with functional group such as ester, amide, lactones or lactones may be susceptible to hydrophilic degradation. It is probably the most commonly encounter made of drug degradation because of the prevalence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.

Oxidation

In contrast to hydrolysis, oxidation mechanism is complex, moving removal of electropositive atom, radical or electron or conversely addition of an electro negative moiety. Loss of electron, gain of electron, auto oxidation also is responsible, e.g., tetracycline, vit-A, vit-D, morphine. Oxidation reaction can be catalyzed by oxygen, heavy metal ions and light leading

to free radical formation free radicals which in turn reacts with oxidizable compound to generate additional free radical to give further reaction, e.g., aldehyde, alcohol, phenol, alkaloid.

Reduction

Any of a class of chemical reactions in which the number of electrons associated with an atom or a group of atoms is increased. It is a relatively more common pathway of drug metabolic process. Hepatic microsomes catalyze diverse reductive chemical reaction and require NADPH for this purpose. Azo and nitro reduction is catalyzed by cytochrome P450. Chloral hydrate is reduced to its active metabolite trichloroethanol by alcohol dehydrogenase.

Racemisation

It is the process in which one enantiomer of a compound is converting into another. This can alter pharmacokinetic, pharmacological and toxicological properties. It depends upon temperature, solvent, catalyst, and presence and absence of light, e.g., L-epinephrine is 5 - 20 times more active than D- epinephrine.

Polymerisation

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer, e.g., darkening of glucose solution is attributed to polymerization of breakdown product [5-(hydroxyl methyl) furfural], Polymerisation of HCHO to para-HCHO which crystallizes out from the solution. [23-26]

STABILITY ANALYSIS

Preformulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include both solution and solid-state experiment under conditions typical for the handling, formulation, storage, and administer of a drug candidate.

Stability in toxicology formulation

Because toxicological studies are generally started early in the drug development process, it's common to test samples of toxicological preparations for stability and potential homogeneity issues. The drug is given as a feed as an oral gavage of a solution or as a suspension in an aqueous medium. Minerals, vitamins, enzymes, and a variety of functional groups included in feed lower the drug's shelf life.

1. To be used a fresh sample of feed.
2. Checked for ease of production of solutions or suspension.
3. At varying temperatures, store in flame-sealed ampoules.
4. Shaking every now and dispersibility.

Solution stability

Effects of pH, ionic strength, co-solvent, light, temperature, and oxygen are all investigated. Experiments were carried out at pH and temperature extremes to see what would happen. Assay specificity and maximal degradation rates. The pH rate profile in its whole - the pH of maximum

stability. Aqueous buffers are utilized to give a wide range of medication concentrations, co-solvent concentrations, and ionic strength. Physiological media are compatible.

pH rate profile

1. Data on stability for each pH and temperature.
2. Kinetic analysis - apparent decay constant.
3. Arrhenius plot - log apparent degradation is constant vs. absolute temperature reciprocal activation energy.

Solid state stability

Solid-state stability is impacted by changes in purity and crystallinity. Both the original bulk lots and more current lots need to be studied. Compared to solution state TLC, UV-Vis, and fluorescence, solid-state TLC, UV-Vis, and fluorescence are slower and more challenging to interpret. Examples of polymorphic variations include DSC, IR, or visible changes like oxidation, which causes surface discoloration.

Storage condition:

Refrigerator – 5 °C

Room temperature – 22 °C

Studies at elevated temperatures: Commonly utilized elevated temperatures include 40 °C, 50 °C, and 60 °C with ambient humidity. Physical and chemical changes in the sample held at a higher temperature are monitored weekly and compared to a suitable control.

Stability under high humidity conditions: Solid medication samples can be kept in laboratory desiccators containing saturated solutions of various salts to be exposed to varying relative humidity levels. Closed desiccators are then placed in the oven to maintain a steady temperature.

Bulk stability

During the development phase, bulk parameters for the solid form, such as particle size, bulk density and surface shape are likely to change.

Compatibility

Knowing how drug excipients interact might help you choose the right excipients for your formulation. To enhance the chance of hiding an interaction, the reported pre formulation screening of drug excipients interaction requires only 5 mg of drug in a 50 % mixture with the excipients. Physicochemical features such as appearance, assay, and degradation products should be evaluated in mixtures. [26-27]

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

The biopharmaceutical classification system is a system to differentiate the drugs on the basis of their solubility and permeability.

Table 6: Biopharmaceutical classification

CLASS-1 High solubility. High permeability.	CLASS-2 Low solubility. High permeability.
CLASS-3 High solubility Low permeability	CLASS-4 Low solubility Low permeability

Significance of BCS

The drugs are classified in BCS on the basis of solubility, permeability and dissolution. This was given by Amidon et al. Solubility class boundaries are based on the highest dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical bio equivalence study protocols that prescribe administration of a drug product to testing human volunteers with a glass of water. Permeability class boundaries are based indirectly on the extent of adsorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. [28]

APPLICATIONS OF PREFORMULATION

1. Physical properties of the studied API influence on its physical and chemical stability.
2. It influences on the route of administration, delivery system and the drug activity.
3. Moreover, chemical stability of the drug is affected by the physical properties.
4. Crystal morphology, polymorphism, amorphous forms and hygroscopicity are usually studied.
5. Certain properties are studied in preformulation stage of the solid dosage forms. [29]

FORMULATION RECOMMENDATIONS

After the preformulation evaluation of a new drug candidate, it should be necessary that a report prepared regarding the process by which preformulation studies done. Which specifying the pharmaceutical problems associated with the new drug molecule. These reports should conclude with recommendations for developing phase 1 formulation. These reports are extremely important in preparing regulatory points 2 was eventually recommended for development. [30]

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