***Scope**: Once a person goes through this module he / she will be able to understand about the importance played by various pharmaceutical additives in different dosage forms where they are added and how they play a vital role in work ability of a dosage from.*

***Other highlights that can be understood by students**: 1. The student will also be able to have a clear knowledge about various existing as well as novel manufacturing techniques involved in drug product development. 2. Equip himself / herself with knowledge to overcome few challenges that are other faced during formulation of a potent pharmaceutical dosage form.*

***Contents of the present module**: Preformulation Studies: Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substances. a. Physical properties: Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism b. Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization BCS classification of drugs & its significant Application of preformulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.*

Introduction:

The most challenging situation or night mare for any formulation scientist or pharmaceutical company is the time when the most successful drug or its formulation or promising dosage form has to be recalled due to unexpected changes. One of the recent example in this context is the Ritonavir story which has really posed to be a challenge for Abbott laboratories. This is the stage where a planned preformulation study really helps in avoiding such effects to a larger extent[1]. Preformulation studies found its way in to practical field by 1950 and early 1960.

Preformulation:

This term can be defined as a phase of formulation development process where the formulation chemists analyses and characterizes various properties of the new drug substance in order to figure out a stable, safe and effective dosage form for better management of diseased conditions.

Objectives of Preformulation Studies:

The prior investigations before formulation helps to give an idea that major and significant challenges associated with a potent compound of interest to be developed in to commercial product can be analyzed and removed. Further the formulation chemist can use these information to design and develop a more stable dosage form[2].

Steps of Preformulation Study:

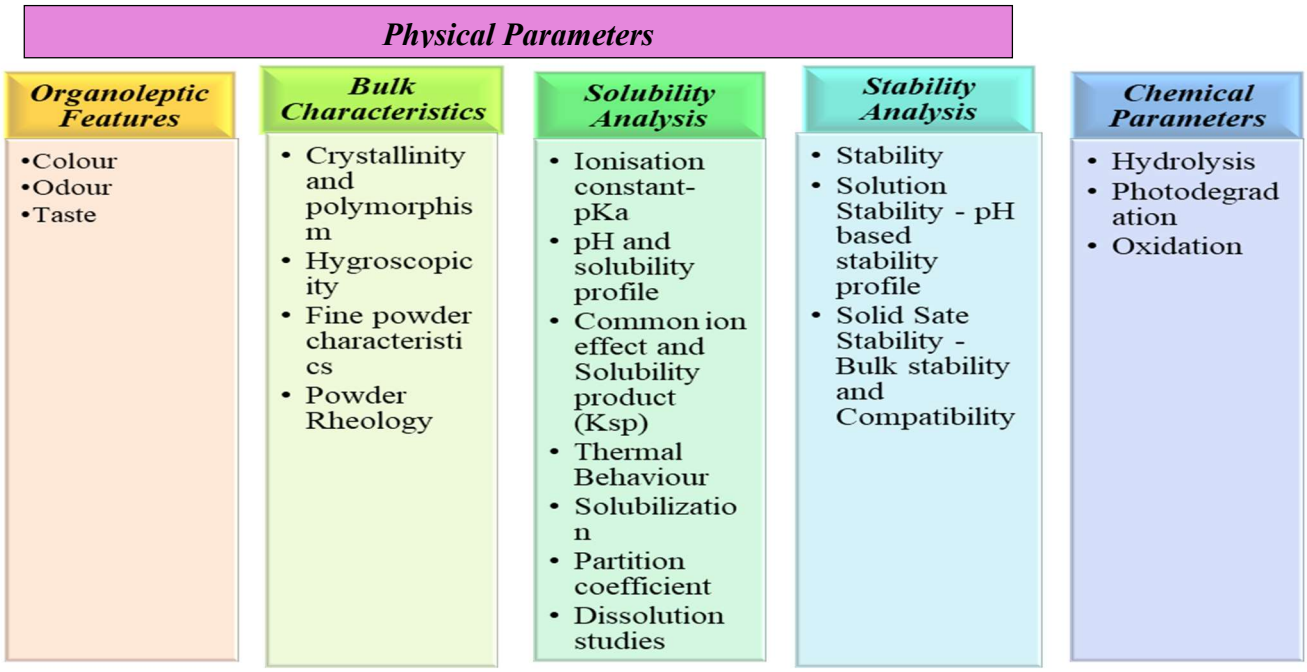


Figure -1: Various steps of preformulation studies.

A detailed description about various parameters:

Organoleptic properties:

Color: A poor visual appealing system is usually not accepted by patients, so a thorough study is needed either based on visual perception or instrumental method to analyses that each formulated batch does not vary with respect to chromatic features. In cases where needed coating with suitable color become mandatory in order to have compliance.

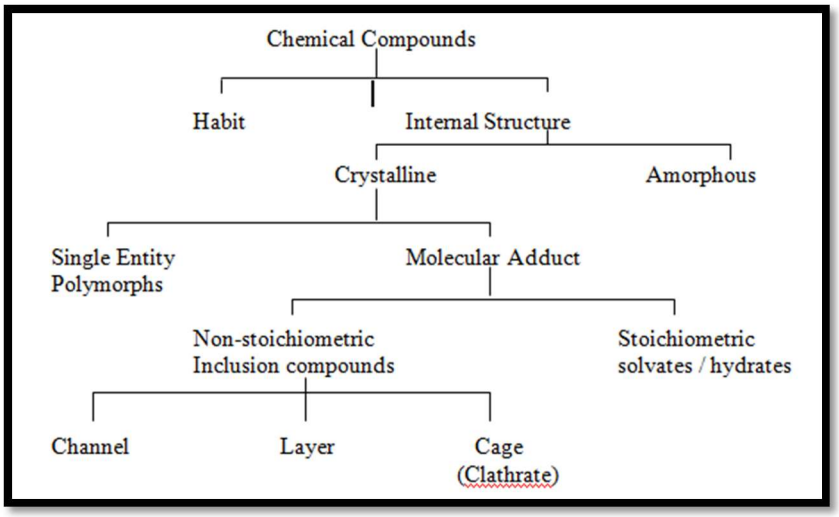
Olfactory perception and palatability: An active ingredient must be palatable as well as have a good aroma in case it's not the case then additives like flavours or coating can be done to mask out the taste or hide the intense smell which is otherwise not acceptable. For example: Pungent or sulphur smelling ingredients must be covered with an acceptable odorous compound similarly bland or bitter drugs can be masked for taste.

Bulk characterization studies:

The need of this study is to identify all possible forms that may exist for a substance at various points of synthesis for example presence of polymorphs (the ritonavir case). Here we normally characterise the bulk properties such as particle size, bulk density, surface morphology which may otherwise lead to an un-predictive phenomenon that may either alter

the efficacy of the drug or the question the stability. The studies undertaken under this head is depicted in Figure-1.

Crystal Morphology, Polymorphism, Hydrates and Solvates:



The active ingredient or the excipients can exist in different crystalline or amorphous states based on their method of synthesis, isolation from mother liquor, phases of crystallizations and geometric configurations. Based on their arrangements sometimes many different physical forms arise and this phenomenon is defined by the term polymorphism. Each polymorph that is obtained is different from the other form significantly which usually influences predominantly the parameters of bioavailability and stability of the drug. Even the polymorphs play a critical role during the compression stage of tabletting in case of few drugs like paracetamol, valsartan etc[3]. In case of paracetamol it is seen that orthorhombic forms are preferred over monoclinic forms during compaction. The crystals that are generally disordered and do not possess sharp melting point like that of crystals as well as demonstrates slow change with rise in temperature are defined amorphous products. The point where amorphous substance exhibits this change is called as glass transition temperature. Thus, it is important to understand crystal habits and other properties to ensure that a dosage form does not deviate from bioavailability or stability.

Factors affecting crystal habit:

1. If super saturation is not controlled it leads to transformation of a prism shaped crystals to a needle shaped one.

2. Similarly if rate of cooling rate and agitation are ultered then crystal habit changes super saturation degree, e.g. thin plates of naphthalene is developed if it gets rapidly recrystallized in cold ethanol or methanol solvent system, whereas controlled evaporation yields prisms.

3. The mother liquor affects habit by preferential assimilation on to certain faces, inhibiting their growth. For example: Resorcinol needles are obtained from benzene while squat prisms from butyl acetate.

4. Poisoning of mother liquor yields orients growth of crystals in different direction. An example to understand this is the Sodium chloride crystal demonstrates usually cubic structure, but in presence of urea produces an octahedral habit.

Amorphous forms:

The solids that exist in this form usually do not have any defined internal structure. They have atoms or molecules randomly placed as in a liquid. For example - Amorphous form of Novobiocin[4].

Glass transition temperature, Tg:

Tg is a characteristics feature of an amorphous form. Below *Tg* the amorphous form are brittle and is defined as glassy state. Above *Tg* the solid tend to behave as to be in plastic or rubbery state. So *Tg* is the minimum temperature at which the solid becomes amorphous i.e. (plastic) from glassy state.

***Application of glass transition temperature*:**

1. *Glass transition temperature* can be brought down by addition of plasticizers where they either disturb or deform the molecular arrangements, thus they reduce the *Tg.*

2. During the unit operation like milling, all the solids must remain below *Tg*.

3. Amorphous novobiocin is more soluble and has higher bioavailability than its crystalline form.

Difference between crystalline and amorphous form

Crystalline forms	Amorphous forms
(i) Crystalline forms have defined internal structure (ii) These forms are more stable than amorphous forms. (iii)These forms of active principles have lesser solubility than their amorphous form. (iv)Crystalline form has lesser inclination to change its form during storage.	(i) Amorphous forms do not have any defined internal structure (ii) Amorphous forms have higher thermodynamic energy than crystalline counter parts. (iii) These forms are less stable than crystalline forms. (iv) Amorphous forms have greater solubility than its crystalline forms. (v) Amorphous substance have a tendency to return back to more stable forms during storage.

Table -1:Highlights of difference between crystals and amorphous substance

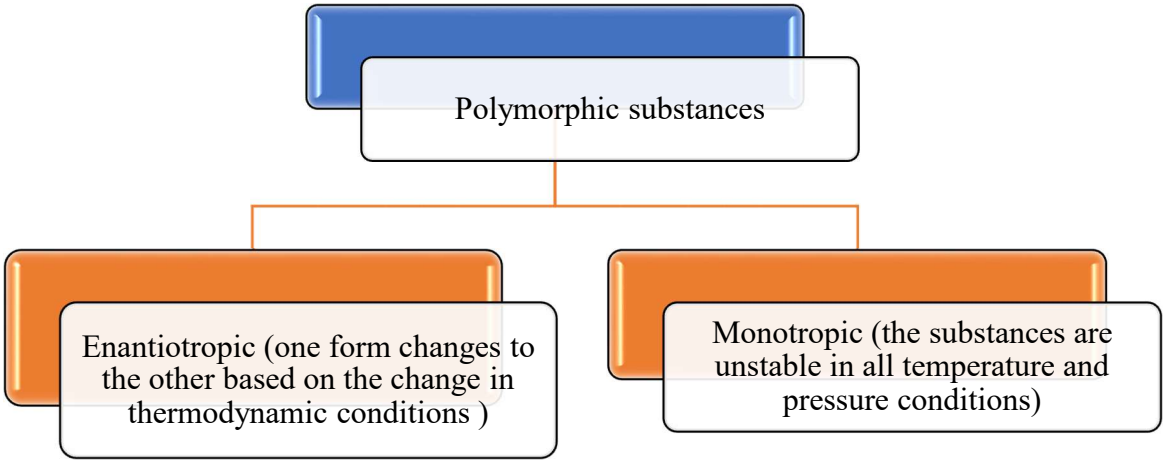
Polymorphism*:* As described earlier when crystals exhibits more than one physical form in accordance to its internal structure (i.e. packing pattern) the various crystalline forms are called *polymorphs* and the phenomenon is known as *polymorphism*. Based on thermodynamic stability, the polymorphs are categorised in to stable, metastable and unstable forms. Unstable form has a inclination to convert into stable form. Metastable forms in dry state will remain stable, but if melted or dissolved will form stable polymorph.

Features of polymorphs:

Features of polymorphs	***Stable form***	***Metastable form***	***Unstable form***
Packed arrangement of molecules in crystal lattice	Tightly packed	Less tightly packed	Loosely packed
Melting point	Highest	Moderate	Lowest
Rate of dissolution	Lowest	Moderate	Highest

Table-2: Representation of the features of the polymorphs

***Classification of polymorphs**:* The polymorphic substances can be categorised as follows:

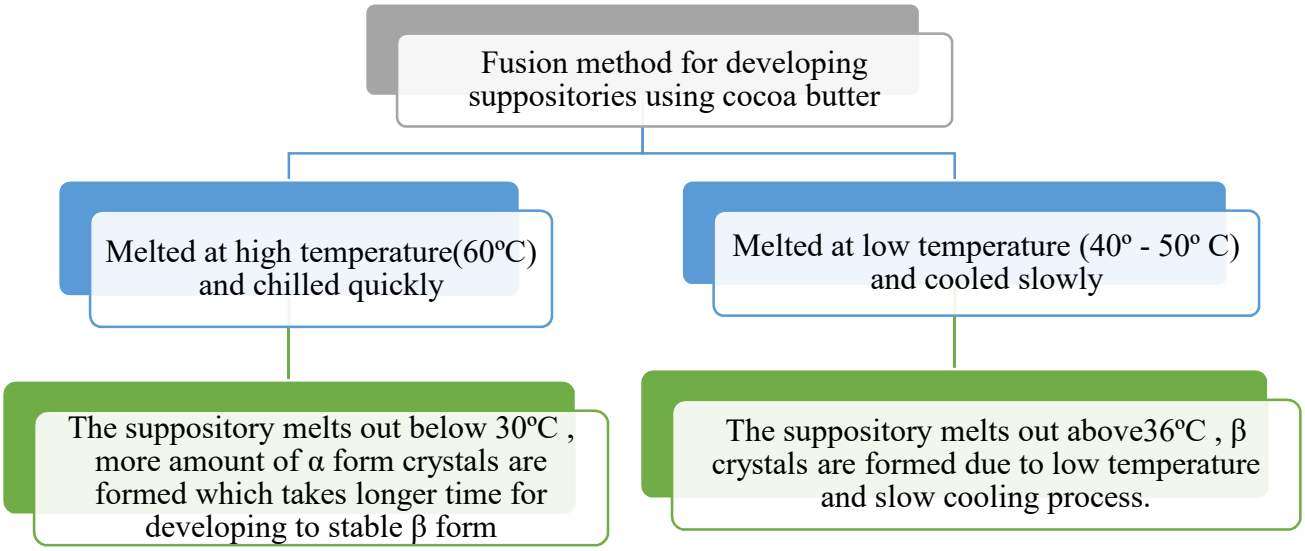


Effects of polymorphism in bioavailability of drugs:

Quite a large number of drugs are hydrophobic by nature; this implies that they have low aqueous solubility. That means these substances in their most stable form will produce the slowest rate of dissolution followed by low bioavailability. While in case of a highly aqueous soluble drugs dissolution does not get hindered. For example: Chloramphenicol palmitate exhibits three polymorphs (stable- α), (metastable- β) and (unstable- γ). Similarly aspirin demonstrates polymorphic forms when isolated from 95% ethanol and n-hexane. Where the n- hexane isolated aspirin has high solubility in aqueous medium compared to the one isolated from 95% ethanol.

Effects of polymorphism on melting point:

Polymorphic forms are found in case of Cocoa Butter or Theobroma oil, it's a base used for preparation of suppositories. Theobroma oil demonstrates 3 polymorphic forms with respect to melting points α - 20º C (meta stable), β - 36º C (stable), γ - 15º C (unstable). Below is depicted few descriptions about how fusion process of developing suppositories gets influenced under the influence of temperature using cocoa butter base.



Effect of polymorphism and cake formation in suppositories:

Basically in suspensions the suspended particles tend to settle down as a result they get closer to each other and proximity distance decreases. Other than this a suspension formulation experiences various range of temperature during storage. The rise in thermal factors tend to dissolve the metastable polymorph in the stagnant layer and during reduction of thermal value the particles may bridge out among themselves along with stable forms leading to irreversible caking. As a result redispersion becomes difficult.

Molecular Adducts

During the process of crystallization, some substances tend to entrap the solvent molecules within the lattice being formed. These defined as molecular adducts and can be classified as follows:

1. Non-Stoichiometric inclusion compounds (or adducts)

In these crystals mother liquor molecules are trapped within the crystal lattice and the number of solvent molecules are not included in stoichiometric number. Based on the shape they are of three types:

(1) *Channel:*

Where the crystal contains continuous channels in which the mother liqour molecule can be included. For example: Urea forms channel.

(2) *Layers*: Here solvent is trapped between layers of crystals.

(3) ***Clathrates (Cage)****:* Solvent molecules are entrapped within the cavity of the crystal from all sides.

2. Stoichiometric inclusion compounds (or stoichiometric adducts):

These molecular complexes entrap the mother liquor molecules into specific sites within the crystal lattice and have stoichiometric number of solvent molecules complexed.

If the incorporated solvent is water, then the complex is called hydrates while if the solvent is other than aqueous system, then complex is defined as solvates. Depending on the ratio of water molecules within a complex these can be categorized as follows:

(i) ***Anhydrous*** : 1 mole compound + 0 mole water

(ii) ***Semi hydrate***: 1 mole compound + ½ mole water

(iii) ***Monohydrate****:* 1 mole compound + 1 mole water

(iv) ***Dihydrate*** : 1 mole compound + 2 moles water

Properties of solvates / hydrates:

(i) Very commonly, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is due the fact that the hydrates are in equilibrium with water and therefore have less necessity for water. For example; anhydrous forms of theophyline and ampicillin have higher aqueous solubility than their hydrates.

(ii) On the other hand the non aqueous solvates have greater tendency for aqueous solubility than the non-solvents. For example; chloroform solvates of griseofulvin are more water soluble.

Polymeric materials:

Polymers are very large molecules and are flexible thus are not aligned perfectly to form crystals. They have two regions one ordered region within their structure and the other is the disordered one that surrounds the ordered region. Thus polymers are said to be semi crystalline substance and their degree of crystallinity depends on their synthesis process and experimental conditions there off.

Equipments used to characterise a solid substance (for its various nature like crystal, amorphic forms, and polymorph): there are few analytical instruments that help us to determine the nature of the solid drug substances like:

1. Optical microscopy

2. Scanning Electron Micorscopy (SEM)

3. Hot stage microscopy

4. Differential Thermal Analysis

5. Differential Scanning Calorimetry

6. Thermogravimetric Analysis (TGA)

7. X-ray powder diffraction

8. IR-Spectroscopy

Detailed study on Instruments used for characterising the solid substances:

Microscopy: The instrument works on principle of passing light through cross-polarizing filters. As a result any substance that is super cooled or has crystal lattice will demonstrate refractive index while amorphous systems will not exhibit this behavior.

Differential Scanning Calorimetry *(DSC):* In this method the difference of energy inputs i.e. ΔH values of test sample and that of reference sample is determined based on controlled temperature programming. Mostly samples that are studied under this are powders, fibers, crystals, polymers etc. the study finds its application in various sections like determination of purity of sample, number of polymorphic forms of a substance, heat of salvation, compatibility of drug and excipients, glass transition phase of a given polymeric sample. Similar to DSC there is yet another technique that assists in determination of physical nature of solids i.e. *Thermogravimetric Analysis (TGA):* this method uses the variation in sample weight with respect to change in time or temperature. It's basically used to study the desolvation and decomposition processes.

X-Ray Powder Diffraction*:* This study is based on Bragg's law of diffraction; it's mostly exhibited by crystalline powders. Amorphous systems do not demonstrate this property under diffraction study. The diffraction pattern is specific based on the lattice arrangement of the given crystal. It's also called finger print pattern of a crystal.

Hygroscopicity*:* Active ingredients basically aqueous soluble salt forms having pharmaceutical importance usually take up moisture from atmosphere and are defined as hygroscopic materials.

There are yet another category of materials called *Deliquescent substances* that absorb moisture from environment and dissolve out completely.

How to determine hygroscopic materials*:* there are few analytical instruments that can help us out to identify hygroscopic material to name a few of them are Gravimetry, Thermogravimetric analysis (TGA), Karl-Fischer titration (KF-titration), Gas chromatography (GC). These substances need at most care while they are to be formulated to a dosage form.

Significance of Hygroscopicity determination*:* The determination of hygroscopic materials in a given pharmaceutical bulk system plays vital role like it helps to decide about the method of storage to be adopted for such substances, helps to determine condition of storage with respect to temperature and humidity. It also enables to decide upon the packaging material needed for packing the material, it also helps us to determine the effect of moisture level in the compound and how it will affect flow behavior, consolidation or compaction stages during tabletting or filling of capsules. The study also enables the formulation chemist with the idea that in case there is formation of hydrates then how this is going to influence the dissolution of the drug or how presence of moisture is going to degrade an active principle.

Fine particle characterization and powder flow behavior properties: The study includes analysis of powder based on particle size and size-distribution, shape of the particle, surface topography study etc. even few instrumental methods also help us to characterize particles nature like sieve analysis, optical micrometer, light microscope techniques, coulter counting techniques, etc.

Fine particle characterization

Sieve Analysis: The study is based on IP method of determination of particles using sieve of standard sizes. In this study the given powder sample is passed through a standard sieve set as per the procedure mentioned in IP. The particle size is plotted against % weight retained on each sieve. The method finds utility to measure the particle size mostly when our powder sample is course natured.

Size and size distribution of the given active ingredient can be determined by sieve analysis method[5]. In this method the given sample is separated in to various size fractions by sieving those using standard sieves of different aperture size. For example 12, 14, 16, 18 and 22 (mesh apertures i.e. 1.4 mm, 1.18 mm, 1.0 mm, 0.85 mm and 0.71 mm respectively) for 5 min. After 5 min sample that is retained on each sieve are collected separately and weighed.

The study is usually conducted in triplicate and mean particle size of powder samples are calculated using the following formula,

$$Mean\ particle\ size = \sum(mean\ particle\ size\ of\ the\ fraction\ X\ weight\ fraction \Big/ \sum weight\ fraction$$

Stream Scanning method or coulter counter method: There are few instrumental methods that work out on the principle of stream counting for determining the particle size of a sample. Some of the instruments are:

a) Coulter counter or Anderson pipette method works based on electrical sensing

b) HIAC counter works on the principle of optical sensing

c) Malvern particle and droplet sizer works based on laser diffraction technique

Procedure:

In this method the sample under study is suspended in a conducting medium (vehicle) and a few drops of surface active agents are also used to distribute the particles uniformly in the medium. A known volume approximately 0.5 to 2 ml of this suspension is pipetted into a tube through a small opening of 0.4 to 800 μm diameter over which a voltage is applied. As the particle pass through the opening, the particle is counted and size is determined based on the electrical resistance the particle displays while forcing out the particle volume from the medium. The obtained size distribution is determined from the graph obtained from the software. Unlike other methods this method also has its own disadvantage i.e. it too much time consuming.

Surface topography study: Scanning electron microscopy helps us to determine the surface characteristic of a given powder sample in black and white image form. In this study we get a magnified image of the particle using electron wave instead of photons.

Procedure:

The sample under study is dried with precaution to prevent it from shrinkage, and then the sample is coated using gold by help of sputter-coater. Post this process the sample is placed in the vacuum chamber of the microscope unit and exposed to high beam of electrons through a series of magnetic lenses system focused on to a fine zone. Thus, capturing the image and helping to know about surface texture whether it is rough or smooth or whichever texture feel we can note.

Powder characteristics: the powder can be characterized by the following parameters. Bulk density, tapped density, true density, flow behavior etc.

Bulk density: It's also called the apparent bulk density of a powder and is expressed in terms of g/cm^3. It is calculated by the formula:

$$Apparent\ Bulk\ Density = {}^{Weight\ of\ the\ powder}/_{Bulk\ volume}$$

Why do we measure Bulk density: Bulk density is a required parameter when compaction or filling of capsule with high dose active ingredient is an operation in manufacturing process. If at all the drug has low bulk then it has to be aided with excipients. Even in case of low dose drugs a large difference between drug and excipient is a challenge in manufacturing unit.

Similarly, the *Tapped Density* also expressed in terms of g/cm^3 is expressed by the equation

$$Tapped\ Density = {}^{Weight\ of\ the\ powder}/_{Tapped\ volume}$$

Why do we measure Tapped density: as bulk density tapped density helps us to know the compactability of the powder bed when formulating tablet and in case of capsule helps to select the size of capsule for filling the active principle based on dose.

True Density (g/cm^3): It's defined as the density of a powder bed excluding the volume of its pores either (open or closed). True density usually explains about packability and behavior of the powder when used in binary mixtures at various proportions. It's basically determined by displacement method utilizing either an insoluble solvent or through gas displacement using helium gas.

Apparent density: Unlike true density this parameter measures the density of powder bed taking the volume of closed pores in to account. This is useful study about the behavior of powder bed when under the influence of die filling and compaction

Porosity: its synonym is void fraction and its measurement of void spaces or empty spaces of a powder bed. It is calculated as ratio of volume of voids: total volume. It lies between 0 and 1. This parameter plays a significant role in deciding the powder behavior, selection of composition of final formulation, the selection of various unit operations that may be needed for developing the final product. The porosity also decides upon various parameters like selection of granulation method, hardness of formulate tablets, disintegration of tablets, dissolution rate, thereof.

How to determine void volume and porosity: the following formula can be used to determine porosity,

$$Porosity = \frac{Void\ volume}{Bulk\ volume} = m^{\left(\frac{1}{\rho bulk} - \frac{1}{\rho true}\right)} \Big/ \frac{m}{\rho bulk} = 1 - \frac{\rho bulk}{\rho true}$$

Flow behavior: this parameter is characterized by various sub parameters like particle size, density, shape, charge of powder bed, moisture content etc. powder being used for formulation basically tablet may demonstrate few problem like developing cohesive nature due some factors. This issue that may arise needs to be solved by adapting to few techniques like: enhancing densification of powder through slug preparations, granulating the sample, changing to a suitable formulation instead of the one selected previously. Flowability of powder and chemical stability depends on the habit and internal structure of a drug.

Angle of repose: it is the simplest of all parameters but plays a predominate role in describing the inter-particle cohesion. If the cohesive force is dominant in a powder sample then its flow will be poor while it's reversed true when cohesive forces are less.

Why inter-particle cohesion is found: it may be due to existence of non-specific Vanderwaal's force or may be due to high moisture content of the sample; it may also be resultant of surface tension between the sample and media absorbed by it. It may also be attributed to the forces experienced due to contact or friction that the powder sample experiences while in contact with the equipment[6,7,8].

Sl. No.	***Method of determination adopted***	***Angle value obtained in terms of***	***How to interpret angle of repose***

1	Fixed height	Angle of repose	*$\theta < 25^o$ implies very good flow behaviour*
2	Fixed base cone	Angle of repose	
3	Tilting surface	Angle of repose	*$25^o < \theta < 50^o$ implies satisfactory flow*
4	Rotating cylinder	Dynamic Angle of repose	
5	Ledge	Drained Angle of repose	
6	Crater	Drained Angle of repose	*$\theta > 50^o$ implies unsatisfactory flow behaviour*
7	Platform	Drained Angle of repose	

Table-3: Methods to determine angle of repose and interpretation of angle of repose

Compression behavior study: The compression properties (basically the parameters like elasticity, plasticity, fragment ability) for minor amount of a new drug or existing drug candidate can be established. This property is used in proper selection of the formulation ingredients. It is characterized by Carr's index and Hausner ratio.

Compressibility index or Carr's index: It is expressed in terms of ratio between tapped bulk density and fluffy bulk density of a given powder sample.

$$\%\ Compressibility = \frac{\rho t - \rho 0}{\rho t}\ X\ 100$$

Where the terms are ρ_t = tapped bulk density and ρ_0 = fluffy bulk density.

Similarly another parameter i.e. Hausner ratio also helps out in determining the compressibility ability of a given sample of solid system. It is the ration between tapped density and pre tapped density. It is expressed by the following formula;

$$Hausner\ ratio = {}^{Df}/_{Do}$$

Where *Df* is the tapped density while *Do* is the pre tapped density.

How to interpret the datas of compressibility index and Hausner's ratio: it is said that if the value of *Hausner's ratio* is higher it indicates that the sample is cohesive natured due to which the sample will exhibit poor flow behavior. Similarly, *Compressibility index* with a

higher range value implies more cohesiveness and poor flow. The table below depicts the type of flow behavior with respect to compressibility index:

Compressibility index (%)	***Flow behavior exhibited***	***Illustrations about the Samples that depict the mentioned flow***
>40	Extremely poor	Cohesive powders have very poor flow
35-38	Very poor	Cohesive powders but fluidised
28-35	Poor	Cohesive powders natured but fluidised
23-28	Poor	Demonstrates fluidised behaviour
18-23	Fair	Granules of powdered nature exhibit this flow
12-18	Good	Exhibited by free flowing powdered granules
5-15	Excellent	Free flowing granules

Table-4: Various Compressibility index (%) values and flow behavior exhibited by the samples

Solubility profile (pKa, pH, Partition coefficient) and its significance

One vital aspect of the preformulation study is to design a suitable method for obtaining a solution form of the drug in a suitable media. This is a need because to have a good therapeutic efficacy of a drug it has to enter in to the systemic circulation and the very first media it encounters is aqueous natured so, it should possess aqueous solubility. It has been demonstrated by insoluble compounds that they get poorly absorbed. Thus, focus of study mainly lies on solubility parameter and the inter molecular forces of attraction within the substance and force of attraction between solute and solvent. This implies there is need overcome the solute-solute interaction forces, the solvent-solvent interaction forces and attain the solute-solvent attraction (drug-body fluid interaction). For example: if we want to understand about the solubility of an orally administered drug then we need to study about its solubility in simulated gastric fluid (SGF). A new drug entity is always evaluated for its solubility profile. For example if a drug has low aqueous solubility there is a fair chance of it to suffer from absorption problems in bio fluids.

Factors on which the solubility of a drug depends:

Solubility is influenced by temperature, physicochemical properties of a drug, nature of vehicle or solvent in with which it has to interact, the pressure above it, acidity and basicity of the solution, the rate of agitation to which it is subjected while being dissolved in the solvent.

Methods adopted for solubility analysis:

a) Determination of solubility profile

b) Determination of pKa value

c) Common ion effect

d) Partition coefficient

e) Membrane permeability

Methods adopted to improve the drug solubility profile:

Few of the adopted measures for improving drug solubility are: Chemical modification of the drug into salt or its ester forms by use of a suitable solubilising agent, by usage of co-solvents, by adopting to micronization or nanonization techniques, developing solid dispersion system of the drug or by adjusting the pH of the solvent in which the drug can be dissolved[9].

a) Intrinsic Solubility determination: it is definite that all factors that influence solubility and dissolution of a drug must be fixed. While determining the intrinsic solubility the first step is to disperse a slight excess amount of drug in the vehicle at constant temperature, agitation and with respect to time withdraw a small amount of the solution and either filtrate it out or centrifuge it. Then assay of collected sample for drug content is determined using UV, HPLC, GC or other analytical instruments and the value estimated is recorded.

b) pKa and pH determination: there exist unique relation between dissociation constant, lipid solubility and pH at site of absorption which is based on the principle of pH-partition theory. As described earlier quite a large number of drugs are either weak acids or bases. The ionisation and dissociation features of a drug molecule often are governed by degree of ionization which is dependent on pH of a solution and pKa value. The individual information about a drug on pH and pKa is always a need as it govern the absorption of drug to systemic circulation. The pKa and pH values can be determined over by using Henderson-Hasselbach equation.

For acidic drug compounds

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

pH = pKa + log [ionized] / [unionized] = pKa + log $[A^-]$ / [HA] = pka + log [base] / [acid]

For Basic drug compounds

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

$$pH = pKb + \log [\text{Unionized}] / [\text{ionized}] = \text{pKa} + \log [B] / [BH+]$$
$$= \text{pKa} + \log [\text{base}]/[\text{acid}]$$

Significance

a) the determination of pH as a solution basically is needed to design ophthalmic and parenteral products as these dosage forms need through consideration of pH since below pH value of 3 the patient to whom the product is administered may feel pain while above the pH of 9 the person may exhibit tissue damage so these dosage should be buffered suitably.
b) With the knowledge of solubility profile and pKa, pH of a solution can be determined.
c) The pH equation can helps to determine solubility profile of the salt.
d) Helps in determining suitable media from which the drug will be absorbed. For example, acidic drugs will be absorbed from acidic region while basic drugs will be absorbed from basic environment.

Partition coefficient-This is the oil/water partition coefficient that measures drug molecules lipophilic characters that is, whether the drug has affinity for hydrophilic or lipophilic solvent. This parameter decides upon the development of dosage form. The distribution of the solute between two immiscible solvents i.e. it is defined as ratio of unionized drug in organic layer versus ionized drug in aqueous layer at equilibrium.

$$K_{o/w} = \{C_{oil} / C_{water}\} \text{ at equilibrium}$$

Drug molecules with higher $K_{O/W}$ will cross the lipid bio-membrane.

Dissolution studies: Dissolution rate is defined as the rate at which the active ingredient dissolves with the media. Dissolution mostly depends on the parameters like drug's solubility, dissociation constant and partition coefficient. These factors can be used as indicative measure to know about the potential and efficacy of drug post administration. Noyes-Whitney equation helps to determine the dissolution constant of a drug and also explains how surface area or particle size influences dissolution. Less is particle size of the sample higher will be dissolution profile.

Noyes-Whitney equation:

$$\frac{dc}{dt} = \frac{DA}{hV}(C_S - C)$$

where, D = diffusion coefficient of the drug in the dissolution medium, h = thickness of the diffusion layer at the solid/liquid interface, A= surface area of drug exposed to dissolution medium, V = volume of the medium, C_S = Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature, C=Concentration of drug in solution at time t.

Significances:

a) Determination of dissolution study helps in finding any potential problems that may affect bioavailability in future.

b) It is assists in anticipating probable problems that may lead to poor absorption

c) This study aids in determining the effects of various factors like particle size, surface area, and excipients on release rate of the active agent.

Solubilization: for any drug candidate that has a poor solubility profile a study on how to enhance its solubility must be studied.

Methods to enhance solubility:

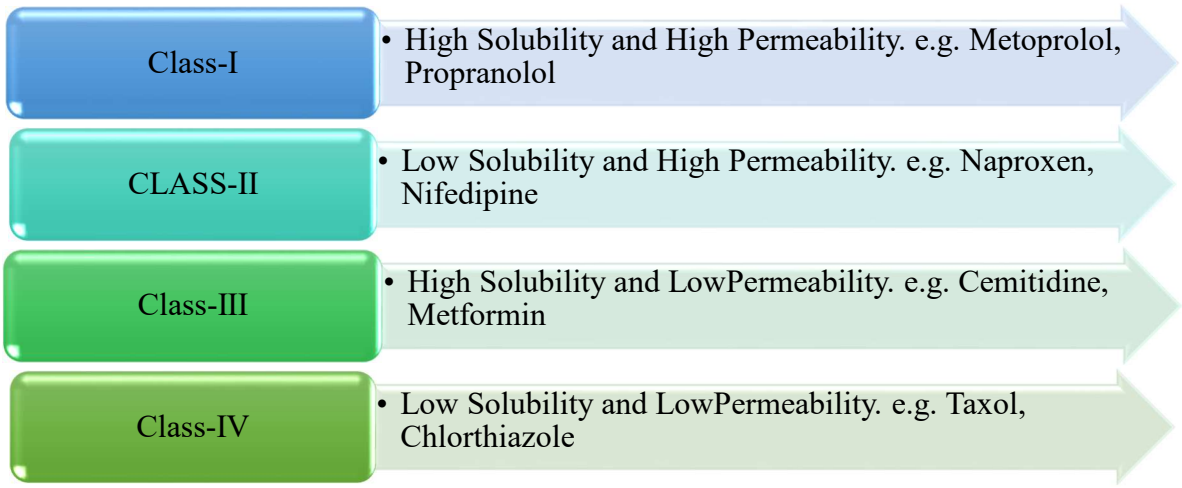
- Addition of a co-solvent to the aqueous system e.g. ethanol, propylene glycol and glycerin.
- Solubilization in micellar solutions such as surface active agent solution.
- Solubilization by forming molecular complexes e.g. para amino benzoic acid and caffeine complex.

- Solubilization by developing solid dispersion.
- By changing the pH of the solution
- By changing the polymorphs

Approaches of decreasing the solubility of drugs: like enhancing solubility of a sample there are methods to suppress solubility of a drug molecule, to name a few of them are esterification, coating with polymers of opposite natured, changing the polymorphic form of the molecule which has better solubility in a given media, or by using hydrate forms instead of anhydrous ones.

BCS classification of drugs & its significant:

The Biopharmaceutical Classification System was first developed in the year 1995, by a group of scientists (Amidon and his team). The Biopharmaceutical Classification System can be defined as a scientific model for categorizing the active principle (drug molecule) to different categories or classes based on its aqueous solubility and intestinal permeability.



Applications of BCS Classification: Helps to predict the *in-vivo* functioning of the drug base on solubility and permeability, assists in various stages of drug discovery, assists in identification of suitable drug delivery system, helps in scaling up a batch and bio equivalence data generation, can also help in bio-waiver analysis of drug.

Significance: it acts as predicting tool for bio equivalence study design through accurate in-vivo study. It also aids in *in-vitro in-vivo correlation study* (IVIVC) study[10].

Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization:

Hydrolysis: Most of the drug molecules follow this common degradation path, thus water plays a huge role not only in solution but also solid dosage forms also even in its slightest value. Hydrolysis takes place due to nucleophilic attack of the water molecule on the hydrolytic bonds. Demonstrating a decrease in value in the order series of lactam > ester > amide > imine. The process is also influenced by pH. If the solvent is not water, solvolysis may take place in case there is incompatible reaction.

Oxidation: The phenomenon is influenced by environmental stresses like load of oxygen (or an oxidizing agent), light, and trace metals presences that are able to provoke the catalyzing process. The reaction is usually faster in case the process takes place due to molecular oxygen and is called as auto-oxidation. These responses usually involve free radical chain reactions. The reaction continues till an anti-oxidant stops it. These reactions generally produce high intensity coloured degradation products, which can be visually detected.

Photolysis: certain compounds have the tendency to absorb light which initiates the cleavage of bonds leading to photodegradation. This reaction is based on wave length and intensity of light. Maximum degradation occurs through UV light, of sunlight in the range of 290–1750 nm and sometimes due to artificial lighting such as fluorescent tubes of range 320–380 nm. Prevention of photodegradation is accomplished packing in suitable light resistive systems like foil wraps or amber glass.

Stability analysis:

The chemical stability of any new molecule can be quantified by preformulation study. The study design includes: stability study in toxicology formulation, stability study in solution state and finally stability study in solid state.

In toxicology formulations: The analyses help out in evaluating a toxicological formulation for stability and potential problems associated with the homogeneity. Usually an active principle is fed to the animals in their food, or by oral feeding of a solution or suspension of drug in an aqueous vehicle forcefully. Agents like water, essential vitamins, minerals, which can affect the shelf life of a drug and decrease stability thereof are fed to the animal along with the feed. The animal is kept under observation and any instability is detected and reported.

Solution stability: the study aims in establishing conditions that affect the stability of drug.

Factors on which stability depends: Stability of a new drug may depend on quite a few parameters like pH, ionic strength, co-solvent, light, temperature, moisture and oxygen levels to which the drug is exposed.

pH stability study: in order to study the effect of extreme pH and temperature condition that affects the stability of the drug a study is designed as follows keeping temperature constant: a) Set-1(extreme acidic): 0.1N HCl solution at 90^0C. b) Set-2(neutral): Solution in water at 90^0C. c) Set-3(extreme basic): 0.1 N NaOH solution at 90^0C. this study assists in studying about rate of degradation of a sample in different environment.

Ionic strength: the pH of most of the pharmaceutical formulations should be compatible with body fluids as described earlier as basically when choice of route for their administration is parenteral. The ionic strength (μ) of the solution plays a vital role here for example ionic strength of an isotonic 0.9%w/v sodium chloride solution is 0.15. the ionic strength is calculated from the formula

$$\mu = \frac{1}{2}\sum m_i Z_i^2$$

Where m_i = molar concentration of the ion and Z_i = valency of the ion

Effect of temperature on stability: thermodynamic principles also play a vital role in stability of a drug molecule. Heat of solution, ΔHs may give idea about either release of heat or energy or amount of heat absorbed during a process(when a mole of solute is dissolved in a large quantity of solvent).

Significance

- In most of the cases, the solubility process is an endothermic reaction. For instance if ΔH is positive then it implies that solubility increases with enhancement in temperature.
- Similarly in case of an exothermic process ΔH_S is negative implies solubility is lowered

Light: exposure of a drug to photons is very crucial basically during its storage period as any wrong exposure to photons may lead to instability. For example drugs like Naproxane is instable in all forms stray light, it needs to be store in dark room. Thus in order to preserve the nature of a drug the stability of the drug under influence of light should be carried out. For this study design sample are subjected to light exposure by storing in various container such as clear glass, amber coloured glass, yellow-green colour glass which are intended to be

used in future to store the drug and these systems are studied over a period of time to identify the problems.

Temperature: The degradation rate constant (k) of a chemical reaction for a drug molecule will vary with change in temperature according to Arrhenius equation.

$$k = Ae^{-Ea/RT}$$

$$\text{Or,} \quad Ln = Ln\,A - {}^{Ea}/_{R}\,({}^{1}/_{T})$$

Where, k is the rate constant, A is defined as frequency factor, E_a is the energy of activation, R is gas constant, while T is absolute temperature. The above equation is used to study and estimate the shelf life of the drug.

Solid state stability

Objectives: this analysis is performed in order to understand and find a suitable storage conditions for active principle in its solid state and also identify the drug- excipients compatibility for a given formulation.

Characteristics: The rate of decay of the drug in its solid state is much more gradual, so the rate of appearance of the decay process is determined instead of determining the amount of drug remaining unchanged. In order to carry this analysis few analytical equipments are taken in to due considerations like TLC supported by UV/Visible spectroscopy, Differential Scanning Calorimeter, Infra-Red spectroscopy, reflectance equipments(to determine any change in colour intensity that take places on the surface of the sample due to oxygen stress.

Drug-excipient stability profile: in this study experimental dosage forms are prepared with various additives, at various concentrations and are exposed to various experimental conditions to study the interactions of drug and excipients.

Conclusions:

After carrying out the preformulation evaluation of new drug candidates, a complete report of it is prepared where the pharmaceutical problems associated with molecules are brought in to notice, this helps to develop the first phase of formulation and also assists in subsequent modifications if needed in order to develop a stable dosage form.

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