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Preformulation Studies of Pharmaceutical New Drug Molecule & Products: An Overview.

Kailash Vilegave[1]*, Gali Vidyasagar[2], Pratibha Chandankar[3],
1.School of Pharmaceutical sciences JJT University Chudela Jhunjhunu Rajsthan.
2. Veerayatan Institute Jhakhaniya Bhuj Gujrat 370460
3. S.S.Jondhle College of Polytechnic Ambarnath M.S - 421501.

ABSTRACT

Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drug's combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of Preformulation study is to develop the elegant (stable, effective, and safe) dosage form by establishing kinetic rate profile, compatibility with the other ingredients & establish Physico-Chemical parameter of new drug substance. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in Preformulation study. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule. So the for study of crystal properties some techniques are mentioned in this article. And also stability of drug and product how they affected and prevention is mentioned. Preformulation study is a step in time saves nine that is disastrous effect after formulation is prevented in advance.

Keywords: Preformulation, Stability testing, Physic-Chemical properties, Polymorphism.

*Corresponding Author Email: vilegavekailash@gmail.com
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INTRODUCTION

Preformulation studies was evolved in 1950 & early 1960 and it is defined as an investigation of physical & chemical properties of drug substance alone and when combined with excipient. Preformulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system. In this prior studies taken before the formulations of various dosage forms. A step in time saves nine, so the Preformulation studies of the new product can away the disaster that is disasters are prevented in advance [1]. Many people take various dosage forms without any hesitation about its safety, why? because they trust on us & our formulations so we (Pharmaceutical scientist & formulation pharmacist) have also responsibility to go true to their expectations .that is development of a final product submitted to the FDA for marketing approval is promising one (withstand in chemical & physical properties)

Need of Dosage forms[1, 2.]

- To provide mechanism for the safe & convenient delivery of accurate dose.
- To protect from environment i.e. destructive effect of oxygen or humidity.
- To protect from the destructive effect of gastric acid after oral administration Ex. Enteric coated tablet.
- To conceal the bitter, salty, nauseous odor of drug substance. Ex. Capsule, Coated tablet.
- To provide liquid preparation which are unstable or insoluble in vehicle. Ex. Suspension
- To provide clear dosage forms of substance. Ex. Syrups , Solutions
- To provide rate controlled drug action. Ex. Sustained Release & Controlled release Tablets
- To provide optimal drug action from topical administration. Ex. Ointments, Creams, Patches.

Objectives[1, 2]:

- To develop the elegant dosage forms (stable, effective & safe)
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is 1st step in rational development of a dosage form of a drug subt before dosage form development.
- It generates useful information to the formulator to design an optimum drug delivery system.

Goals[1]:

1. To establish the physico-chemical parameters of new drug substance.
2. To establish the physical characteristics.
3. To establish the kinetic rate profile.
4. To establish the compatibility with the common excipient.

In figure 1 show how drug formulation goes in to market stepwise representation is mentioned in it.

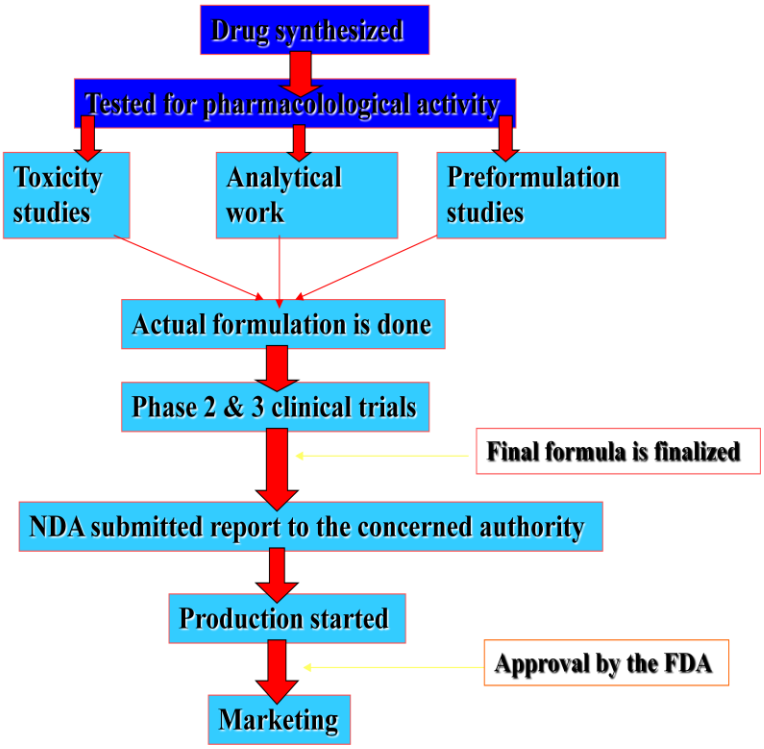

Figure. 1: Drug formulation and its entry in to market stepwise representation.

MAJOR AREA OF PREFORMULATION RESEARCH [2, 3, 4]

Bulk characterization:

1. Crystallinity & polymorphism,
2. Hygroscopicity,
3. Fine particle characterization,
4. Powder flow properties.

Solubility analysis:

1. Ionization constant –Pka
2. pH solubility profile,
3. Common ion effect-Ksp ,
4. Solubilization ,

5. Dissolution,
6. Partition co-efficient

Stability analysis:

1. Solution stability,
2. pH rate profile,
3. Solid state stability,
4. Bulk stability,
5. Stability in toxicology formulation.

Crystallinity & Polymorphism

Crystal habit & internal structure of drug can affect physico-chemical properties which range from flow ability to chemical stability. Habit means the description of outer appearance of a crystal. While internal structure describes the molecular arrangement within the solid, changes in internal structure usually alter crystal habit.

Ex. 1: Conversion of sodium salt to its free acid form produce both a change in internal structure & crystal habit.

Ex. 2: Conversion of Sod. Benzoate to Benzoic acid.

Figure 2 and 3 gives chemical compound classification. And the idea about salts, solvates, hydrates and co-crystals respectively. Depending upon internal structure of a compound can be classified as

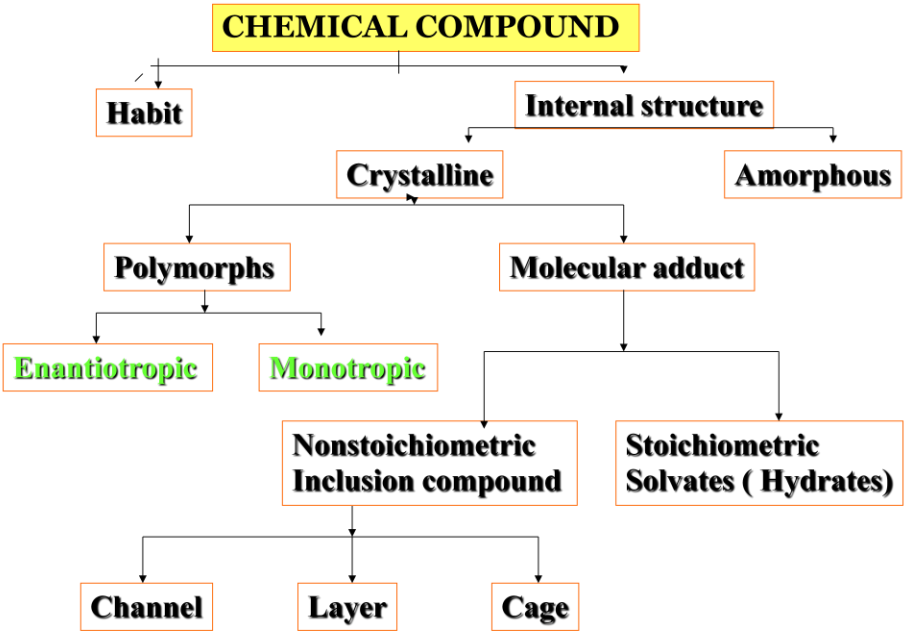

Figure. 2: chemical compound and its classification according to crystal habit and internal structure.

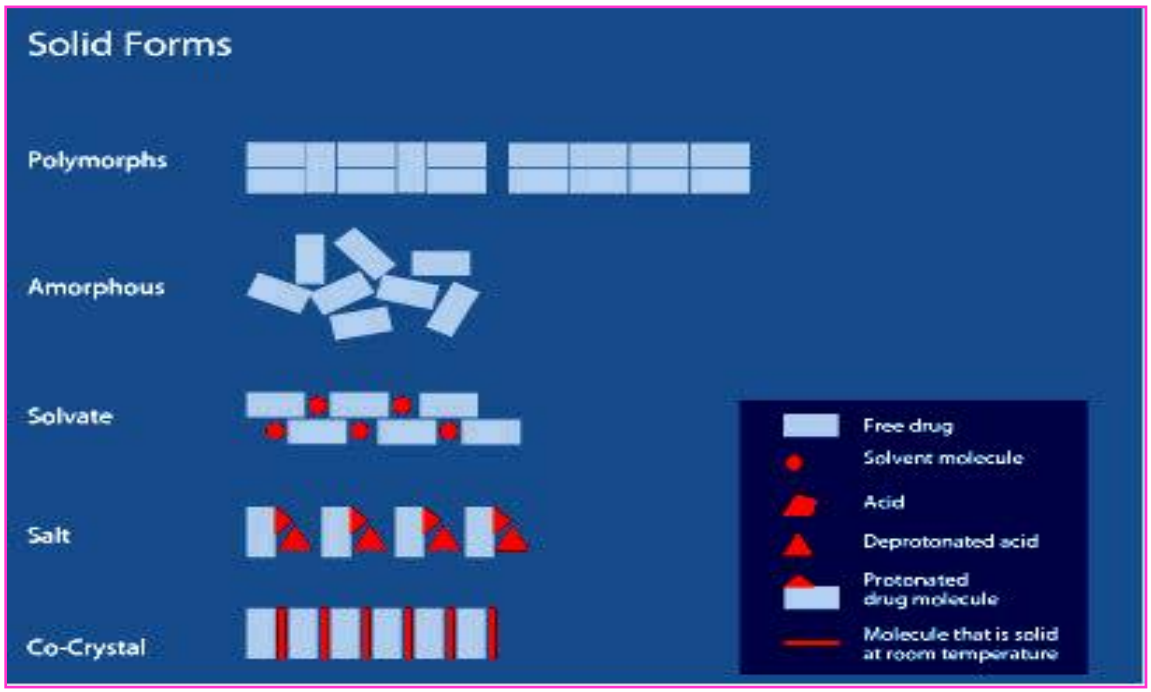

Figure. 3: General idea about polymorphs, amorphous, solvates, salts, and co-crystals.

A. Crystalline; and B. Amorphous / non crystalline.

A. Crystalline: Crystals are characterized by repetitious spacing of constituent atoms or molecule in a dimensional array. Evaluation of crystal structure, polymorphism, & solvate form is an important Preformulation activity. The changes in crystal characteristics can influence bioavailability, chemical and physical stability, & can have implication in dosage form process functions. Ex. It can be a significance factor relating to tablet formulation because of flow and compaction behavior among other.

B. Amorphous / non crystalline: In this form atoms or molecule are randomly placed as liquid.

Polymorphism (Crystal forms)

An important factor affect on formulation is the crystalline or amorphous form of the drug. Polymorphic form exhibits different physico-chemical properties including MP and solubility.

Polymorphic form in drug are relatively common, it has been estimated that at least 1/3 of all organic compounds exhibit polymorphism. Polymorphism is defined as The property of drug that exist in more than one crystalline form that different forms are designated as polymorphs and its phenomenon is known as 'Polymorphism'

Types:

1) Enantiotrophic polymorphs,

2) Monotrophic polymorphs.

1) Enantiotrophic polymorphs: is the one which can be reversibly changed into another form by altering the temperature or pressure. Ex: Sulfur. Carbon. Nitrogen .Oxygen

2) Monotrophic polymorphs: The transition take place in only one direction is called as monotrophic polymorphs. Or is one which is unstable at all tempt & pressure. Ex: glyceryl sterates.

The polymorphs differ from each other with respect to their physical properties, such as solubility, MP, density, hardness, dissolution, compression characteristics.

Crystal morphology:

Repetition of atom or molecule in regular three dimensional arrays (structure) there are six crystalline systems,

1) Cubic

2) Tetragonal

3) Orthorhombic

4) Monoclinic

5) Triclinic

6) Hexagonal, Which have different internal structure & spatial arrangements is shown in figure 4

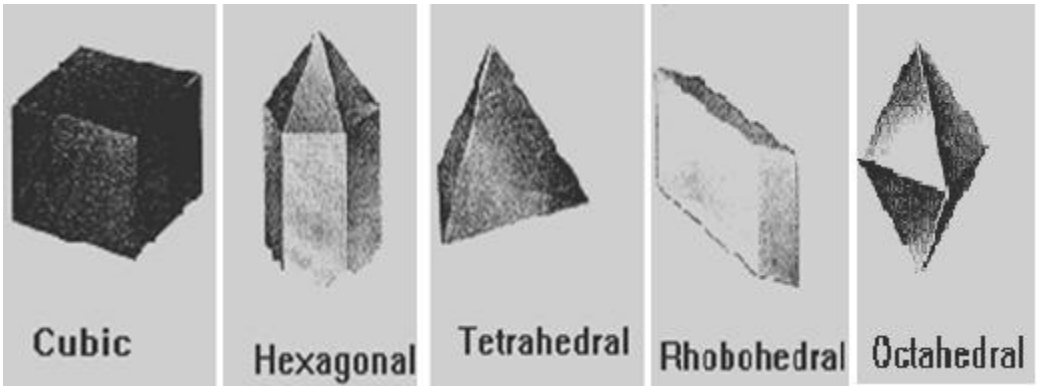

Figure. 4: Different crystal morphology of molecules present in universe.

As the change in internal structure there may be change in external structure that is crystal habit of which five types are recognized

1) Tabular: moderate expansion of two parallel faces

2) Platy: plates

3) Prismatic: columns

4) Acicular: needle like

5) Bladed: flat acicular shown in figure 5.

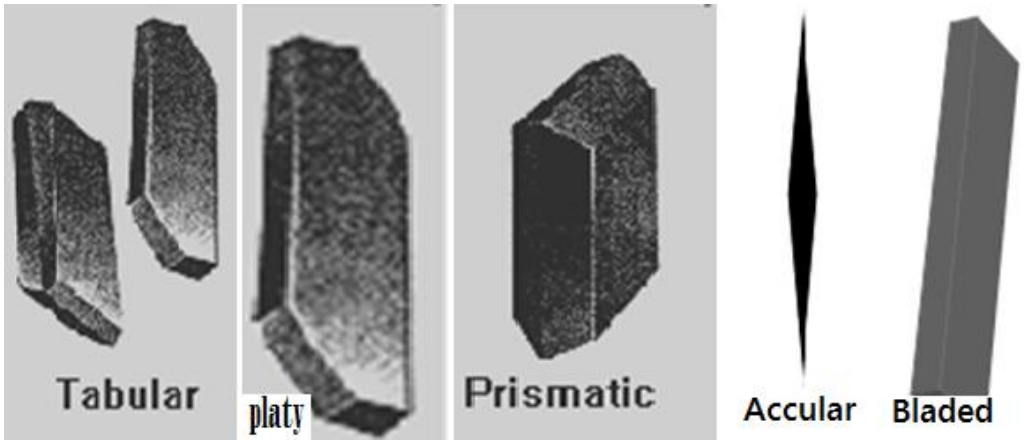

Figure. 5: Crystal habit (internal structure) of a molecule

Crystal habit can be modified by 1. Excessive super saturation which tends to transform a prism to needle shape. And 2. Cooling rate & agitation which changes habit, it changes the degree of super saturation Ex. Naphthalene gives thin plates when rapidly recristallized in cold ethanol or Methanol

3. The addition of co-solvent or other solutes & ions which change habit by poisoning crystal growth in one or more direction. Ex. Sod. Chloride is cubic but Urea produces an octahedral habit.

Polymorphs (Drugs and There Polymorphic forms) [1,3]

1) Steroids like Progesterone has 5 polymorphs.
2) Barbiturates like Barbitone have 2, & Pentabarbitone has 3.
3) A sulphonamide like Sulphabenzamide has 4 polymorphs & 3 solvates.
4) Caffeine has 2 polymorphs.
5) Chlorpropamide has 3 polymorphs.
6) Clenbuterol has 2 polymorphs.
7) Dipyridamol has 2 polymorphs.
8) Mebendazole has 4 polymorphs.
9) Nadoxidine has 4 polymorphs.
10) Sulphabenzamide has 2 polymorphs.
11) Phenobarbitone has 2 polymorphs.
12) Sorbotol has 5 polymorphs.

Effects of polymorphs [3, 4]

Depending upon their chemical stability,& solubility changes due to polymorphism can impact on bioavailability Such form are a) Stable polymorphs. & b) Metastable polymorphs

a) Stable Polymorphs

One of the several polymorphic forms will be physically more stable than the other. Such a stable polymorphs represents lowest energy state, has highest MP,& least aqueous solubility

b) Metastable polymorphs[4]

The remaining polymorphs are called as Meta stable forms which represents the highest energy state, low MP, highest aqueous solubility In detail Since the Meta stable form have greater aqueous solubility they show better bioavailability and preferred in formulation

Ex 1. Chloramphenicol palmitate : This exists in 4 polymorphs in that 3 are crystalline (A B & C) & one is amorphous one. A B & C, the B form shows best bioavailability due to metastable form , yielded a higher blood concentration compared to other forms upon oral administration of 1.5gm of dose.

Ex 2. Riboflavin : The polymorphic form III of riboflavin is 20 times more water soluble than the for I.

Ex 3 . Sulphameter : It exist as 6 polymorphs, crystalline form II is about twice as soluble as crystalline form III . The rate and extent of absorption of sulphameter is 40% greater after administration of II than of III. As Metastable are more soluble in the aqueous so they have greater bioavailability , but only 10% of pharmaceuticals are present in their Metastable forms due to their poor thermodynamic stability The aging of dosage forms containing Metastable forms usually results in formation of less soluble stable polymorph.

Ex: The more stable crystalline form II of Cortisone acetate converts to less soluble form V in an aqueous suspension resulting in caking of solid

Inhibition to transformation of Meta stable to stable form[4]

- By dehydrating the molecule environment.
- By adding viscosity building macromolecules such as PVP, CMC, Pectin, Gelatin. gelatin that prevent such a conversion by adsorbing onto the surface of the crystals

Crystal properties: Polymorphism[4]

Practically all the substance is handled in powdered form at some stage during manufacture in to dosage forms. Crystalline form varies in physical properties dissolution and solid state stability & also process behaviors Polymorphic transition can also occurs during milling, granulating, drying, compression, operations. E.g.:1) Transition during milling for digoxine & Spironolactone , 2) Granulation can result in solvate formation. 3) Metastable to stable after aging.

A. Crystal characteristics and Bioavailability

B. Crystal characteristics and Chemical Stability.

C. Crystal characteristics and Tableting Behavior

D. Crystal characteristics and Physical stability.

A)Crystal characteristics and Bioavailability:

Different polymorphic forms of a given drug shows difference in the dissolution rate & solubility .When absorption of drug is dissolution rate limited, as more soluble and faster dissolving form may be utilized to improve the rate and extent of bioavailability.

Ex .Chloramphenicol palmitate Comparative blood level data obtained in human after oral administration of 1.5gm of pure A & pure B forms of Chloramphenicol palmitate & their mixtures.

These data shows that the pure form B is more soluble so was most bioavailable. Where as pure form A is less soluble so least bioavailable.

B) Crystal characteristics and Chemical Stability:

For drugs prone to degradation in the solid state, the physical form of drug influence the rate of degradation. Ex. Aztreonam (monobactam antibiotic) Exist in needle like α and spherical β-crystalline forms. In the presence of high humidity (37 C / 75% RH), the α-form undergoes β -lactum hydrolysis more readily with a half life of about 6 months Where as the β -form under identical condition is stable for several years . In as much as two crystal forms of labile drugs could exhibit widely different solid state stabilities. So the Preformulation scientist might have consider changing the crystal form for eliminate a stability problem. Under the stress condition, anhydrous crystalline form of the experimental drug degraded rapidly with a half life of 18 weeks. Solvate form of the drug under some condition was essentially stable. The dissolved form degraded most rapidly.

C) Crystal characteristics and Tableting Behavior:

In a typical tableting operation flow and compaction behaviors of the powder mass to be tabled are important. These properties among other are related to morphology, tensile strength, and density, of the powder bed . Two polymorphic forms of same drug could differ significantly respect to these properties. The morphology of crystal also depends on crystal habit in which environment changes external shape of a crystal without altering their internal structure, then a different habit results. Crystal habit is influenced by presence of an impurity, concentration, rate of crystallization, and hydrodynamics in crystallizer.

D) Crystal characteristics and Physical stability:

One form of the polymorphic form is thermodynamically stable at given tempt. & pressure. The other form converts to the stable form that time. This transformation may be rapid or slow. When

the transformation is not stable the thermodynamically is unstable form is referred to as metastable form. The stable polymorph exhibit highest melting point, the lowest solubility and maximum physical and chemical stability under safe condition to justify its use for reason of better dissolution or ease of tableting.

Whenever metastable form is remanded a Preformulation scientist must assure its integrity under a variety of processing conditions. Polymorphic transformation can occur during grinding, granulation, drying, and compressing operation. Ex. Digoxine, Spironolacton, and estradiol are reported to undergo, polymorphic transformation during the size reduction. Ex. Phenylbutazone under goes polyphormic transformation as a result of grinding and compression.

- Granulation since it make use of a solvent molecule, can lead to solvate, formation

A solvate molecule changes to anhydrous crystalline form or amorphic form in drying step.

- Polymorphic stability is also needed to predict long term physical stability of dosage form.

Ex. Capping like cracking in tablets of anhydrous crystalline carbocromen hydrochloride upon storage under high humidity condition

This was determined due to transformation of the anhydrous form into a dehydrate form.

TECHNIQUS FOR THE STUDY OF CRYSTAL PROPERTIES [4, 5]

1. Microscopy
2. Hot stage microscopy
3. Differential Thermal Analysis (DTA)
4. Differential Scanning Colorimetry (DSC)
5. Single crystal X-ray diffraction technique
6. Powder X-ray diffraction technique
7. I.R. Spectroscopy
8. Dilatometry
9. Thermo Gravimetric Analysis (TGA)
10. Other methods.

Microscopy:

Isotropic only one refractive index E.g. NaCl (cubic crystalline form) . They do not transmit light, and they appear black. Material with more than one refractive index is anisotropic and appears bright with brilliant colors (bifringes)_against the black polarized background. The interference colures depends on the crystal thickness and the differences in refractive indices

Most drugs are either uniaxialy having two refractive indices Most drugs are biaxial corresponding to either an orthorhombic, monoclinic, Or triclinic crystal system. Proper orientation of the crystal along its crystallographic axes is required to describe the crystalline form completely. A protein crystal seen under a microscope. Crystals used in X-ray crystallography are generally smaller than a millimeter across

Hot stage microscopy:

Polarizing microscope fitted with hot stage is useful instrument for investigating polymorphism. In this Sample size required is only 1 mg. This is visual observation of melting point under a microscope equipped with a heated and lagged sample stage. The heating rate is controlled and up to three transitions can be registered. It is most precise since the phase transition (1st melt, 50% melt, & completion) can be resister on the recorder as the melting proceeds. And by virtue of high magnification. The values are more accurate. Hot stage microscope is shown in figure 6.

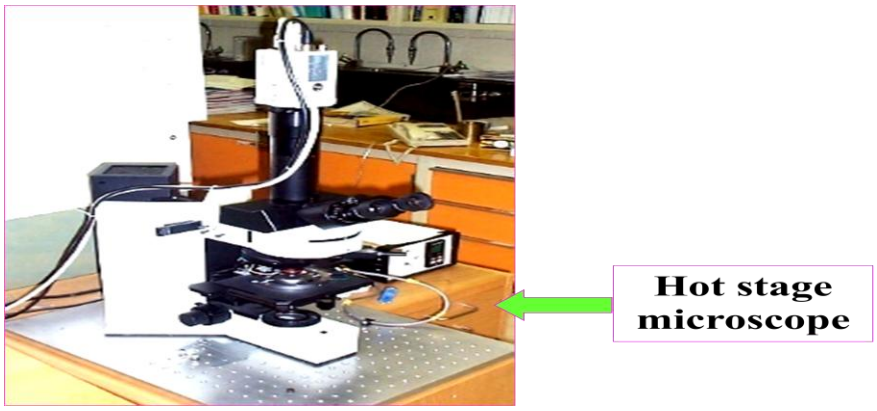

Figure. 6: Hot stage microscope

Differential Thermal Analysis (DTA):

The advantage is that the sample size required is only 2-5mg. DTA measures the tempt difference between sample and reference as a function of temperature or time when heating at constant rate it is Shown in figure 7. The crystal used in this experiment is lithium fluoride. Assuming that the large flat face will be perpendicular to a particular crystallographic direction, this is set parallel to the line containing the source and detector at $\theta = 0$. The gearing of the counter arm is such that, once set, the $\theta - 2\theta$ relationship between the incident, transmitted and diffracted beams is maintained. Using the 2θ value observed at a peak of intensity, the known wavelength λ for Cu Ka, = 1.54Å and the Bragg equation, a value for the plane spacing (d spacing) can be determined. If the peaks can be indexed, i.e. assigned to scattering from certain planes, then from simple geometry lattice parameters can be calculated. This is shown later in the TLP.

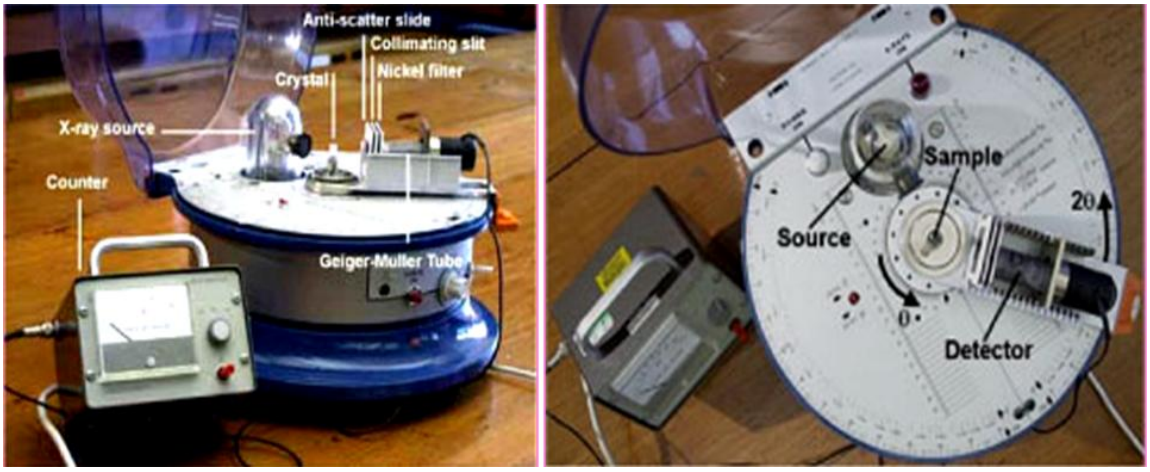

Figure.7: a) side view and b) view from upper side of Differential thermal analysis instrument

Differential Scanning Colorimetry (DSC):

DST is also like to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e. it measures the enthalpy of transition. When no physical or chemical changes are occurring within the sample then there is neither a temperature change nor the need to input energy to maintain an isotherm. However when phase change occurs then latent heat suppresses the tempt increases or fall and the change in tempt required resisters on a recorder as a result of an electrical signal generated by thermocouple. Figure 8 shows the DSC instrument and typical graph obtained by DSC.

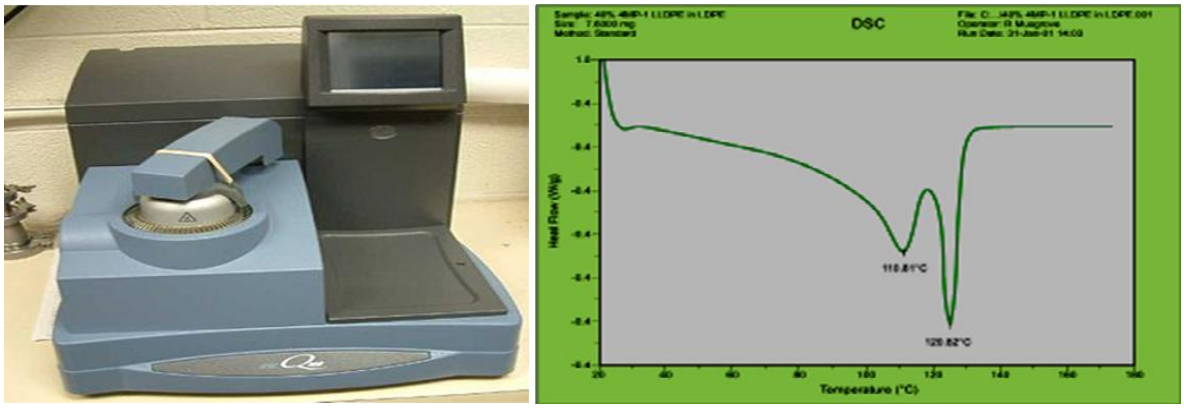

Figure. 8: The DSC instrument and typical graph obtained by DSC shows the accurate melting point of few milligrams of sample and sample containing two and more ingredients.

Single crystal X-ray diffraction technique:

It provide the most complete information about solid state (identification & description). This method is based on the scattering of x-ray by crystals

• By this method one can identify the unit cell dimensions & conclusively establish the

crystalline lattice system & provide specific differences between crystalline forms of given compound.

- It is tedious time consuming so it is not used or unsuitable for routine use. (Shown in figure 9).

Powder X-ray diffraction technique:

Important technique for establishing the batch to batch reproducibility of crystalline form. Random orientation of crystal lattice in a powder sample causes x-ray to scatter in a reproducible pattern of peak intensities at distinct angle Θ relative to the incident beam. Each diffraction pattern is characteristics of a specific crystalline lattice for a given compound. An amorphous form dose not produces a pattern. In this mixture of different crystalline forms can be analyzed by using normalized intensities at specific angle which are unique for each crystalline form (Figure 9).

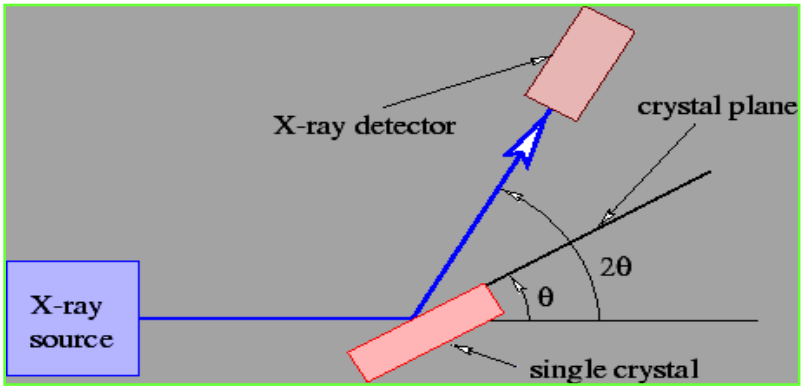

Figure. 9: X- ray diffraction technique

I.R. Spectroscopy:

Different packing arrangement will affect energy of the molecular bond thus altering the I.R. Spectra. Solid samples must be used since polymorphs of a compound have identical spectra in solution.

Dilatometry:

Dilatometry measures the change in volume caused by thermal or chemical effects. It has been used to follow the melting behavior of theobroma oil by measuring the specific volume of both rapidly and slowly cooled theobroma oil as a function of increasing tempt . This technique is extremely accurate, however it is extremely tedious and time consuming. It is widely used.

Thermo Gravimetric Analysis (TGA):

TGA is a type of testing that is performed on samples to determine changes in weight in relation to change in temperature. Such analysis relies on a high degree of precision in three measurements (weight, temperature, and temperature change). As many weight loss curves look

similar, the weight loss curve may require transformation before results may be interpreted. A derivative weight loss curve can be used to tell the point at which weight loss is most apparent. Again, interpretation is limited without further modifications and deconvolution of the overlapping peaks may be required.

TGA is commonly employed in research and testing to determine characteristics of materials such as polymers, to determine degradation temperatures, absorbed moisture content of materials, the level of inorganic and organic components in materials, decomposition points of explosives, and solvent residues. It is also often used to estimate the corrosion kinetics in high temperature oxidation. Instrument Shown in Figure 10.

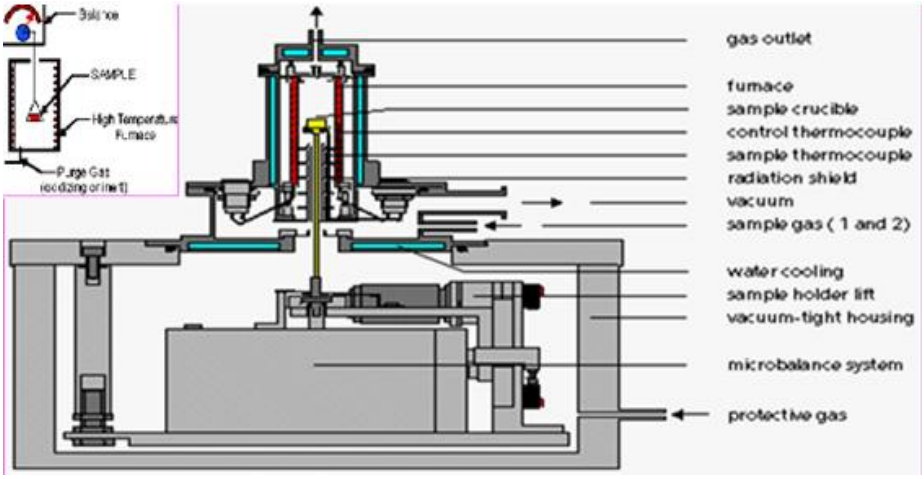

Figure. 10: Thermogravimetric analyzer (TG 209)

Other methods

- PMR -- Proton Magnetic Resonance,
- NMR – Nuclear Magnetic Resonance,
- SEM -- Scanning electron microscopy Have additional application for studding polymorphism.

Physical Degradation of Pharmaceutical Products[4, 6, 7, 8]

- Loss of Volatile Constituents

Ex: - Iodine, Camphor, Menthol, Nitroglycerine tablets.

- Loss of Water

Ex: - Borax, Caffeine, Emulsions exhibit cracking.

- Absorption of Water

Ex: - Gelatin capsules, calcium chloride.

- Color Changes

Ex: - Aspirin tablets – Pink

Ascorbic tablets – Yellowish brown

The drug product must be stable chemically, physically, toxicologically, and therapeutically.

Drug degradation can occur by.

1. Temperature
2. Hydrolysis
3. Oxidation
4. Photolysis
5. Presence of metal ions
6. pH
7. Hygroscopicity
8. Solvolysis

Temperature:

The general procedure involves Storing the product/drug samples at different temperatures. They are withdrawn at different time period intervals & observe for physical, chemical, microbiological changes, level of impurities, degradation products. If significant changes are observed at the accelerated condition. It is advisable to analyze the same sample at normal temperatures conditions. In case degradation product are observed change the packaging material.

Hydrolysis:

Most likely cause of drug instability is hydrolysis. Water plays a dominant role & in many cases it is implicated passively as a solvent vector between two reacting species in solution Hydrolytic reaction involves nucleophilic attack of labile bonds. Ex. lactum > ester > amide > imides. By water on the drug in solution. When the attack is by the solvent other than water is called as 'Solvolysis'

A no. of condition catalyses the break down

- The presence of OH group
- The presence of H_3O
- The presence of divalent metal ions
- Ionic hydrolysis
- Heat
- Light
- Solution polarity & ionic strength
- High drug concentration

Prevention of Hydrolysis:

- By passing an insoluble salt form
- By preparing solid dosage form
- By replacement of water by some other solvents.

  Ex.: such as Alcohols or Polyhydroxy solvents

Aspirin suspensions showed improved stability on addition of high concentration of sorbitol, Ampicilline also showed good stability on addition of alcohol

Oxidation:

All oxidative products are toxic. Heavy metal such as cupric ions or ferric ions accelerates the oxidation of ascorbic acid and phenothiazines. During storage of formulation undergo oxidation by atmospheric oxygen. Sometimes oxidation can be occurs due to the secretion of enzymes produced by microorganism so in this case problem is avoided by adding a suitable antimicrobial preservative. Studies should be initiate to establish the oxidative route and steps taken to determine what additives can be added to formulation to minimize the degradation. Oxidative degradation is common with drugs as Ascorbic acid, Epinephrine, Vitamin A, Chlorpromazine, Morphine, Unsaturated oils and fats. Sometimes pH is critical, since a greater number of oxidation-reduction processes depends on the concentration of hydrogen and hydroxyl ions.

Light usually accelerate degradation, thus storage of products in ambered colored container can prevent this problem. Auto oxidation can occurs when material such as fats and oils are stored in the presence of air. Ex. Phenolic compounds like Epinephrine and Isoproterenol

Prevention of oxidation

1. The oxygen concentration in solution is a factor in many cases and often depends on the temperature of storage or solvent employed. Oxygen is more soluble in water at lower temp
2. Ascorbic acid is more stable in 90% propylene glycol or in syrup than in water because of lower oxygen concentration in the vehicle.
3. Preparation sensitive to oxidation are sometimes stabilized by effectively removing the oxygen and by addition of suitable antioxidants
4. Use of Antioxidants like Ascorbic acid, Sodium bisulfate, Sodium metabisulfite, Butylated hydroxy toluene, Tocopherols , Citric acid, and Chelating agent.

Photolysis: Oxidation and to some extent Hydrolysis is often catalyzed by light. The energy associated with the reaction increases, as the wave length decreases, so that the energy of UV visible is greater than that of IR. And it is independent of temperature. When molecule are exposed to E M Radiation they absorb light at characteristics wavelengths which cause an

increase in energy, which can

- cause decomposition
- be retained or transferred
- be converted to heat
- result in emission of light at a new wavelength(Fluorescence & Phosphorescence)
- Natural sunlight lies in the wave length range 290-790nm of which only the energy UV range 190-320nm causes photo degradation of drug and sunburn

Prevention of photolysis:

Use Packaging material like: Low actinic amber glass bottles, Card board outers, Aluminum foil, over wrappers and blisters, Plastic containers

Presence of metal ions: Chelating agents are complexes, unlike simple ligands. Ex- Ferrocinide which forms complex salts by a single bond provided by a lone electron pair

Chelating agents are capable for forming more than one bond Ex. Ethylene Diamine, Tripyridine, EDTA.

pH:

The degradation of most drug is catalyzed by the extreme of ph i.e. high [H_3O] and[OH] many drugs are most stable between pH 4 to 8. Injections should have low buffer capacity to prevent un necessary challenges to the homeostatic pH of the blood.

The increase of water miscible solvents in the formulation will be increase stability by

- Suppressing ionization
- Reducing the extreme of pH required to achieve solubility.
- Reducing water activity by reducing the polarity of the solvent

Ex. 20% propylene glycol in Chlordiazepoxide injection

7) Hygroscopicity: A substance which absorbs sufficient moisture from the atmosphere is called hygroscopic. Most pharmaceutical compounds lose or gain water from the atmosphere depending on the relative humidity (RH). Materials unaffected by RH are termed as non hygroscopic.

Why do we care about Hygroscopicity?

- Amorphous compounds may take up water and re-crystallize & or degrade Anhydrous material may hydrate and become less soluble.
- The weight change with sorption may cause errors in potency.
- The volume changes associated with water gain and loss may compromise dosage form integrity.

- Changing the solid state form in the dosage form requires regulatory approval.
- Different forms may have different compaction, flow and charging characteristics.

Prevention of Hygroscopicity

- Good packaging (air tight)
- Use of foil blisters
- Use of desiccants.

Solvolysis:

Where the reacting solvent is not water then break down is termed as solvolysis. Or any change in solvent polarity (usually measures as dielectric constant) as result of increase ionic strength .If the compound produce degradation product which are polar than itself then the addition of less polar solvent will stabilize the formulation and vice versa. With the hydrolysis of neutral non polar drugs such as steroids the transition state will be non polar and with no net charge. In this case solvent will not affect the rate of decomposition and can be used to increase stability.

Solution stability[4, 6, 7, 8]

These studies include the effect of

- pH ,
- Ionic strength,
- Co solvent,
- Light ,
- Temperature, and
- Oxygen

Solid stability[4, 6, 7, 8]

"The primary objective of this study is investigation and identification of stable storage condition for drug in the solid state and identification of compatible excipient for a formulation."

In all solid dosage formulation there will be some free moisture (contributed by excipient as well as the drug). And certainly in tablets a significant percentage typically 2% w/w is required to facillate good compression. This free water has ability to act as a vector for chemical reaction between drug and excipients and the absorbed moisture films are saturated with drug compared to the dilute solutions encountered in injectables.

Stability Testing of Pharmaceutical Products [8]

It is first quantitative assessment of chemical stability of new drug. And it is defined as "The capability of a particular formulation in a specific container/ closer system, to remain within its physical chemical, microbiological, therapeutic, and toxicological specifications throughout its

self life"

Stability is officially defined as "the time lapse during which the drug product retains the same properties & characters that is processed at the time of manufacture.

The stability of a product is expressed as the expiry period or technically shelf life.

Stability studies are important for the following reasons

1. Assurance to the patient
2. Legal Requirement
3. Economic Repercussions

Types of stability and the condition maintained during the shelf life of the product are maintained in table 1.

Table 1: Types of Stability and the Condition Maintained During the Shelf Life of the Product

Types of stability	Conditions maintained during the shelf life of the product
Chemical	Retains its chemical integrity & labeled potency
Physical	Appearance; palatability; uniformity; dissolution, and suspendability are to be retained
Microbiological	Retains sterility; effectiveness of antimicrobial agents
Therapeutic	Drug action remains unchanged
Toxicological	No significant increase in toxicity

Purpose of stability study [8,11,13,18].

- To ensure the efficacy.
- To ensure the safety.
- To ensure the quality of active drug substance and dosage forms.
- To establish shelf life or expiration period and to support label claims.
- To gain information about its packaging.
- Assess the condition of the product on storage on prolong period of time.
- To determine compatibility of drug with excipient and other additives.
- To determine the dosage form in which the drug is most suitable.

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