# DOSAGE FORM DESIGN


## ABSTRACT

Dosage form design plays a vital role in the preparation of pharmaceutical products that involve combination of active pharmaceutical ingredient and excipients, along with other non- recoverable materials. The drug and pharmaceutical material must be compatible with one another to form a drug product that is stable, attractive, easy to administer and safe.



## KEYWORD

Dosage form design, palatability, excipients, active pharmaceutical ingredients, types of dosage forms, preformulations, coloring agents, preservatives


## INTRODUCTION

Each type of dosage form is unique in it physical, chemical and pharmaceutical characteristics, these varied preparations bring manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and delivery system to prescribe. The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in a dosage form. Many factors are combined to form an ideal dosage form. Ideal dosage form should be:

- Easy and safe to administer
- Easy to handle
- Efficacious
- Biocompatible
- Maintain shelf life
- Economical to the patient

- Bioavailability
- Physically and chemically stable
- Easy to manufacture and reproduce

The product should be manufactured with calibrated measures of quality control and packaged in containers that keep the product stable, the product should be labeled appropriately and be stored to contribute maximum shelf life.

## NEED FOR DOSAGE FORM.

The potent nature and low dosage of most of the drug prevents any expectation that general public could carefully obtain that appropriate dose of a drug from bulk material. Most drug substances are administered in milligram quantities, which is much too small to be weighed on anything but a sensitive analytical balance. For example, how can patient accurately obtain 325mg of aspirin from a bulk supply usually found in a common tablet? Which is not possible, or a dose of ethinyl estradiol is 0.05mg, which is too small to be weighed, this may lead to inconvenience for the patients

| DRUG | USUAL DOSE (MG) | CATEGORY |
|---|---|---|
| Betaxolol HCL | 10.00 | Antianginal |
| Clotrimoxazole | 10.00 | Antifungal |
| Methylphenidate HCL | 10.00 | CNC stimulant |
| Chlorazepate dipotassium | 7.50 | Tranquilizer |
| Buspirone HCL | 5.00 | Antianxiety |
| Albuterol sulfate | 4.00 | Bronchodilator |
| Felodipine | 2.50 | Vasodilator |
| Clonazepam | 1.00 | Anticonvulsant |

Drug substances hardly ever taken without adding additives, as it is difficult to maintain the accuracy, if not maintained it will not provide the desired therapeutic action. The active pharmaceutical ingredient and excipients are suitably compounded to convert them into suitable dosage form such as tablets, capsules,

creams, emulsion, ointments, pastes, syrups etc. The selection and processing of excipients such as coloring agents, flavoring agents etc. plays a major role as it may alter the therapeutic properties of the drug.

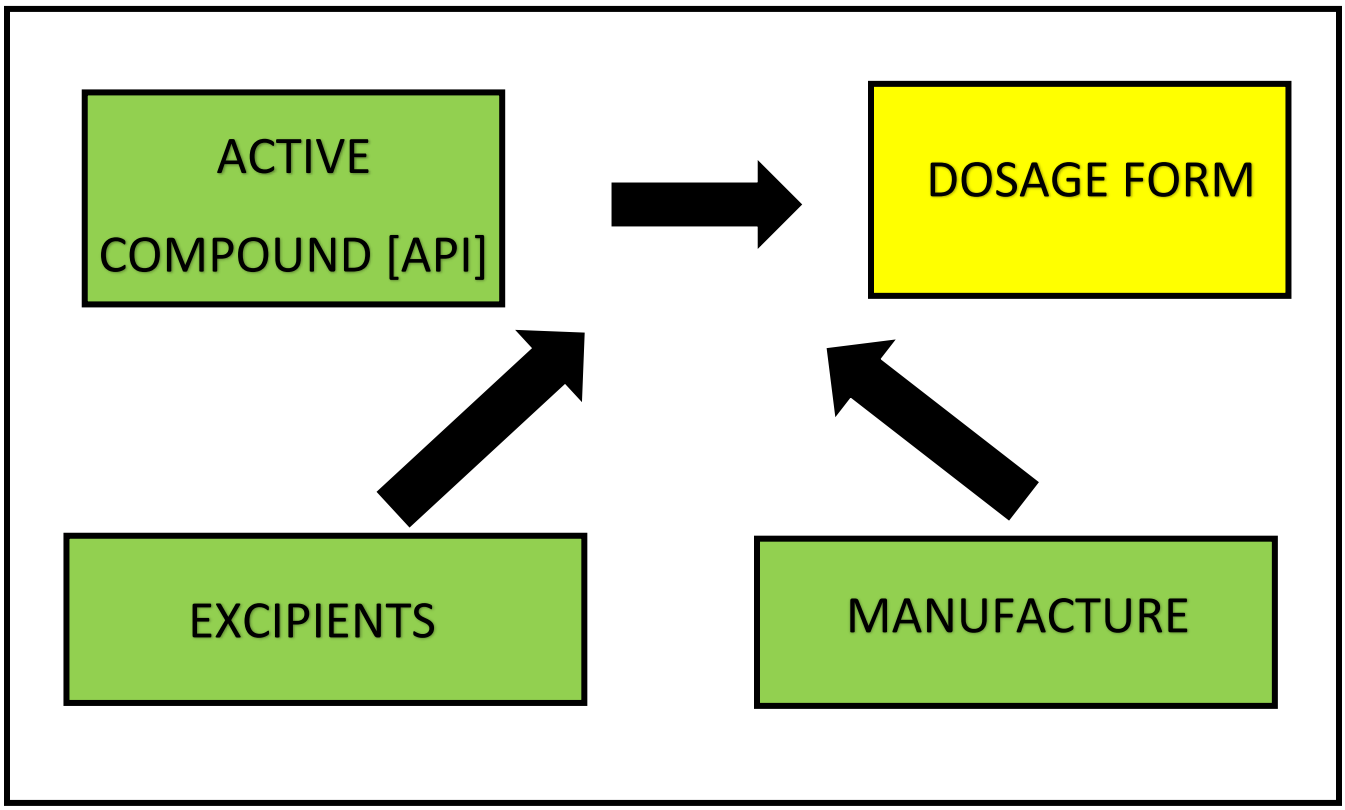


**Fig 1**: API to dosage form

## WHY DO WE NEED DOSAGE FORM?


**Fig 2**: Need for dosage form

## PROTECTION

To protect the drug from external environmental condition such as destructive influence of atmospheric oxygen

To prevent degradation of acid labile drug from the corrosive gastric acids produced by stomach

## IMPROVE PHARMACEUTICAL ACTION

1 To provide desired drug action to appropriate site

[ointments, creams, ear and nasal preparation]

2 To provide desired drug action directly in the blood stream or body tissue

[injections, inhalants, inhalation aerosol]

3 To provide rate-controlled drug action

[controlled-release tablets, suspension]

4 To provide for insertion of drugs into one of body orifices

[suppositories, pessaries]

## PATIENT COMPLIANCE

Accuracy of dose by providing unit dose

[tablets, pills, capsules]

To conceal or mask the bitter, salty, or offensive taste or odor of a drug substances.

[coated tablets, flavored syrups]

Ease of handling and administration

[chewable table]

Reduction in frequency of dose

[prolonged and controlled release delivery]

## TYPES OF DOSAGE FORM

Dosage form can be classified based on:

Physical form

Route of administration

A. On the basis of Physical Form
   Dosage form is classified as

   Solid dosage form.

      Example: capsules, lozenges, chewing gum, pills, pellets, controlled release tablets, powder etc.

   Liquid dosage form

      Example: Syrups, elixirs, spirit, tincture, injection, mouthwash, suspension, emulsion etc.

   Semisolid dosage form

   Example: ointment, cream, gel, suppositories, pessaries, jellies etc.

   Gaseous dosage form

   Example: aerosol, inhaler, nebulizer etc.

Based on Route of administration

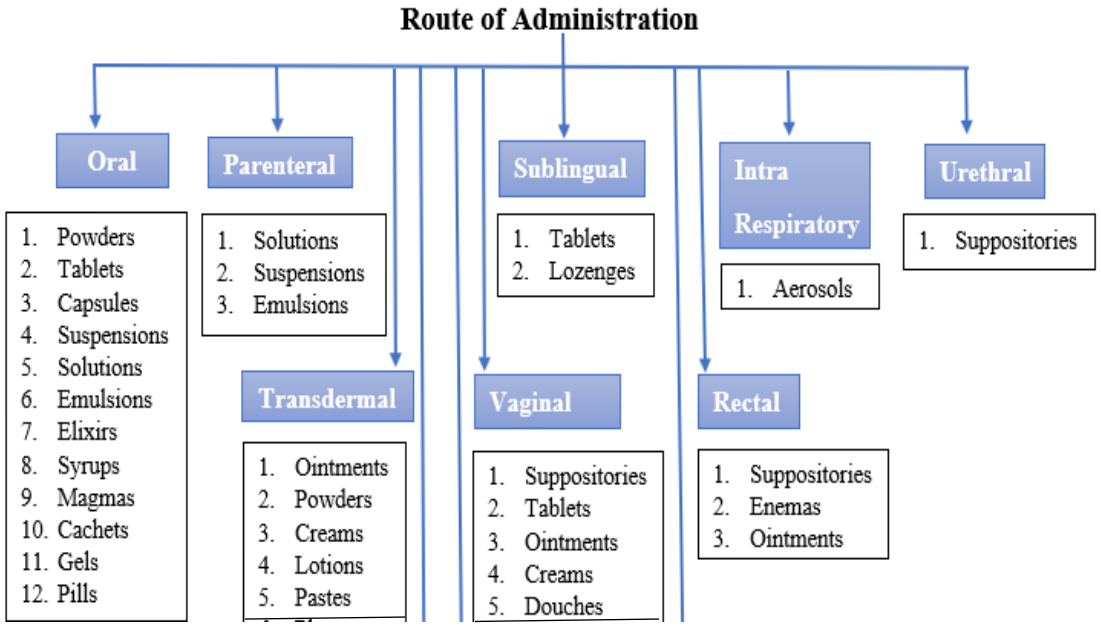


**Fig 3**: Route of administration

## CONSIDERATIONS IN DOSAGE FORM DESIGN

### Preformulation studies

Drug and drug product stability

Preformulation is a primary development step used to characterize the properties of drug substance and also to understand the properties that a particular compound may possess during formulation.

Preformulation Concept

Before the formulation of a drug substance into a dosage form, it is important that it should be chemically and physically characterized. Preformulation studies provide information needed to define the nature of the drug substance and all the activities carried out at and before formulation stage of dosage form. It includes all studies performed on a newly identified drug substance in order to produce a stable and therapeutically effective drug dosage form. It also involves the application of pharmacokinetic and biopharmaceutical principles.

## Goals of preformulation studies are:

1. Selection of correct form of drug substance based on type of dosage form development
2. Understand biopharmaceutical properties of drug
3. Evaluation of physical and chemical properties of drug substance
4. To produce safe effective reproducible drug delivery system
5. Reduce drug development, time and cost

## Significance of Preformulation Studies

It is a process of designing the drug delivery thorough determination of physical and chemical properties of newly synthesized drug molecule, it provides useful information for formulation of a physiochemically stable suitable dosage form

Preformulation study plays an important role to

1. Establish the new drug molecule's identity
2. Determine API and excipient compatibility
3. Establish kinetic rate profile of new drug
4. Combine pharmacokinetics and biopharmaceutical properties
5. Characterize physiochemical properties of new drug molecules
6. Produce safe cost efficient and stable dosage form
7. Minimize problems in various phases of drug development
8. Provide necessary data for development of calibration method

**PREFORMULATION DRUG CHARACTERIZATION PROPERTIES**

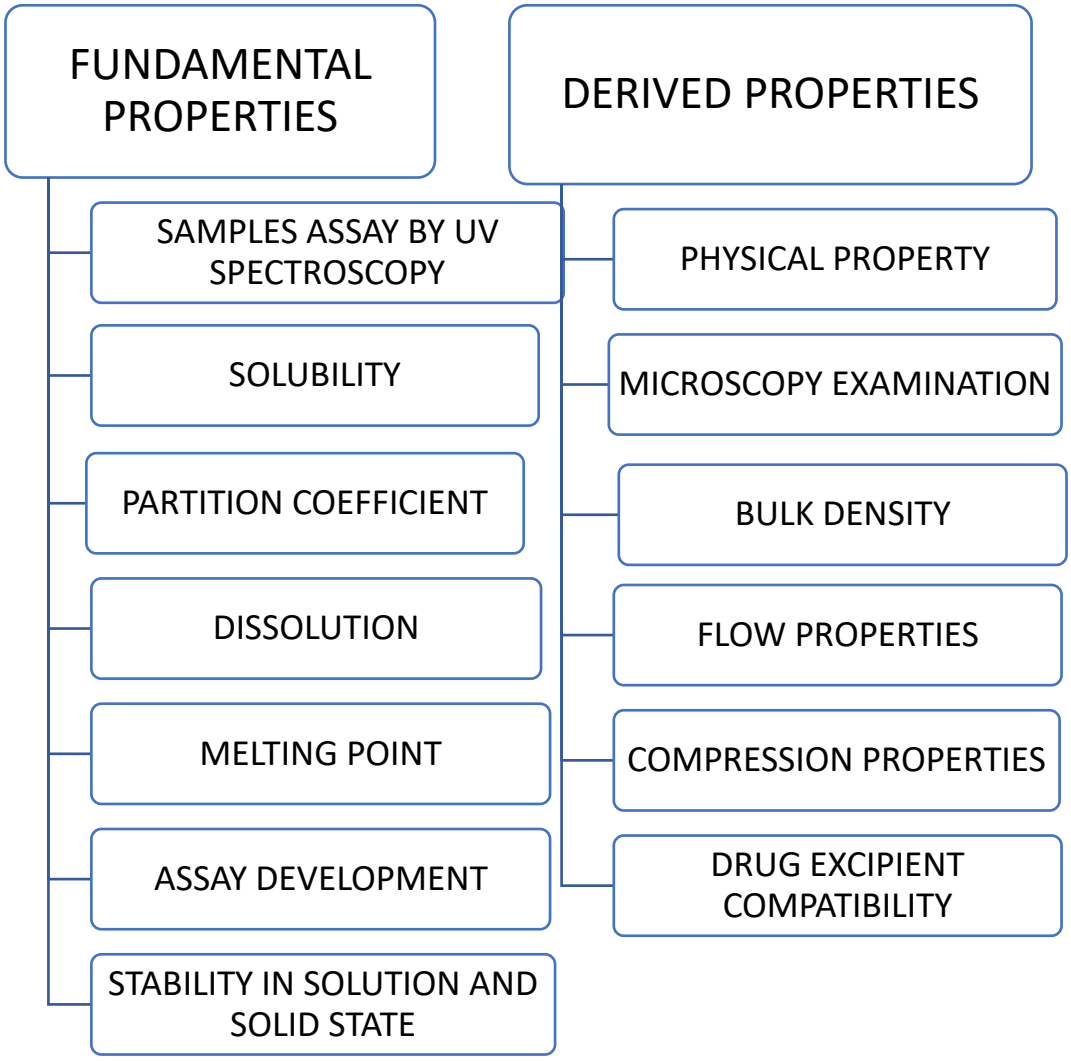


**Fig 4:** Preformulation properties

## Bulk characterization

In the process of development of dosage form the bulk properties of drug substance such as particle size, crystallinity, powder flow, compaction case and other physical properties highly influence in preformulation process.

a. Physical properties
b. Polymorphism
c. Hygroscopicity
d. Melting point depression

e. Flowability

## Physical properties

It is crucial to understand the physical properties of a drug substance before formulating to dosage form. Most drug substances used presently are solid materials, pure chemical compounds of either crystalline or amorphous constituent. Physical properties include characteristics such as physical description, particle size, crystalline structure, melting point, and solubility. These properties relate to its ability to get a site of action and suitable biological response.

There are many different methods available for particle size analysis such as:

1. Sieving
2. Sedimentation
3. Optical microscopy
4. Electron microscopy
5. Coulter counter
6. Laser diffractometer

## Microscopic examination

Microscopic examination of raw substance plays a main role in preformulation work. It indicates the particle size and size range of raw material along with the crystal structure. In some procedures the solid drug powders must flow freely and not form clumps.

**Fig 4:** Microscope

## Polymorphism

Crystal or amorphous form of the drug substance is an important factor on formulation of dosage form. Polymorphic forms usually exhibit different physiochemical properties, including melting point and solubility. It has been estimed that atleast one third of all organic compunds exhibit polymorphism.

Polymorphism are of two types

1. Enantiotropic: one polymorph reversibly changes into another form by change in temperature and pressure.
2. Monotropic: one polymorphic form is unstable at all temperatures and pressure.

## Parameters to be considered during polymorphism

1. Number and type of polymorphs
2. Solubility parameters
3. Degree of stability
4. Stability of metastable form
5. Temperature etc,

## Polymorphism can be measured by:

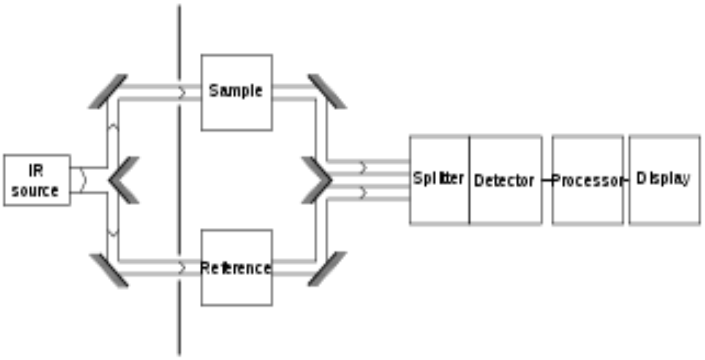


**Fig 5:** Infrared Spectrophotometry

**Fig 6:** Differential Scanning Calorimetry [DSC]

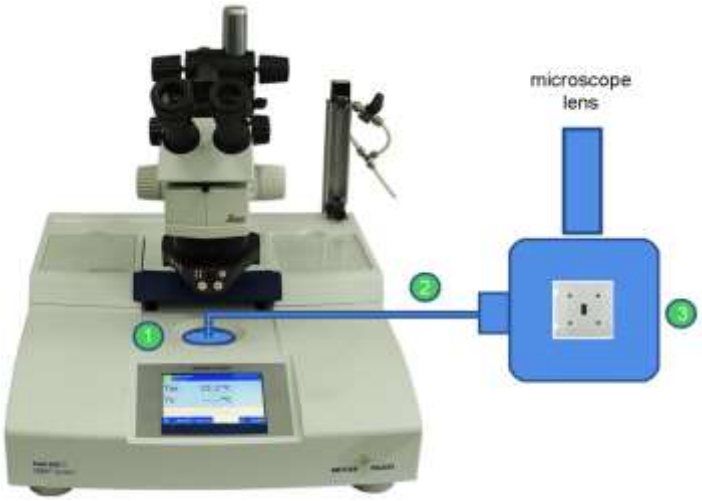


**Fig 7:** Hot Stage Microscopy [HSM]

**Fig 8:** X- Ray Powder Diffraction [XRD]

## Hygroscopicity

1. Water soluble salt form of drug that has the tendency to absorb moisture. Such material can be classified as:
   a. Efflorescent substance: substance that posses the tendency to lose water molecule and become anhydrous in nature.
   b. Hygroscopic substance: substance that posses the tendency to absorb water molecules and get in equilibrium with water molecules present in the atmosphere
   c. Deliquescent substance: substance that partially or wholly liquifies after absorbing moisture from atmosphere.
2. It is necessary to consider hygroscopicity because high absorption of moisture may lead to many stability issues such as poor flow, weight variation, cracking, picking, cake formation etc.
3. Hygroscopicity can be measured by:

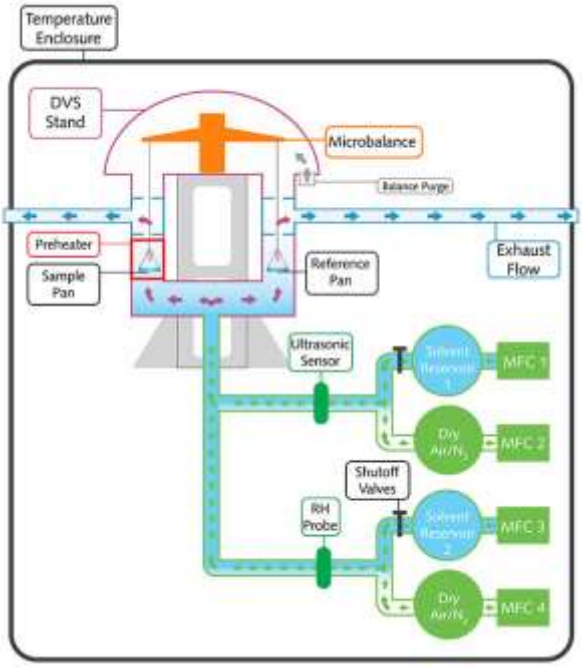


**Fig 9:** Dynamic vapor sorption method

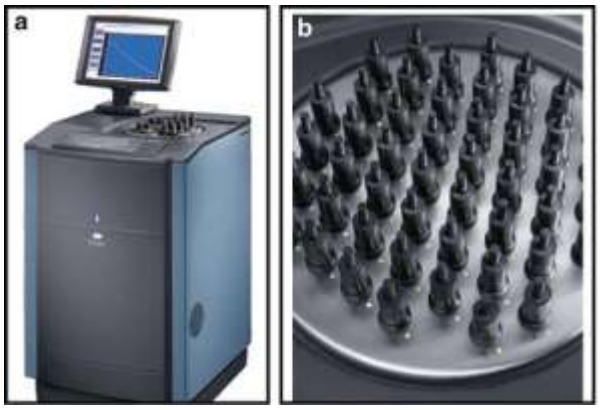


**Fig 10:** Isothermal microcalorimetry

## Melting Point

Melting point plays an important role in the purity of the substance, if the given substance is not pure the substance will exhibit a change in melting point. This phenomenon is mainly used to determine the purity of drug substance.

## Melting point can be measured by:

A. Capillary melting: Drug substance is placed in a thin-walled capillary tube that was closed at one end and heated slowly and evenly. The temperature at which the substance melts is taken as the melting point. This method determines the melting range of the given substance
B. Hot stage microscopy: the melting process is observed with help of a microscope equipped with heated and wrapped stage. This method enables to study and characterize material physically based on temperature and time

## Flowability

Flowability of powder plays an important role in pharmaceutical formulation of dosage form. Flow properties of the powder is affected by small variations on particle size, shape, density electro static charge, moisture level.

## A. Angle of repose:

Angle of repose is the maximum angle which is formed between the horizontal base of the surface and the pile of powder.

Angle of repose θ

$$\tan\theta = \frac{h}{r}$$

where, h= height of the pile

r= radius of base of pile

## B. Carr's compressibility index and Hausner ratio

Carr's compressibility index and Hausner ratio are determined by the formula:

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

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

## Solubility

A drug must posses' aqueous solubility to initiate its therapeutic action, that is when a drug substance enters the systemic circulation and exerts therapeutic action it must be in solution. When the drug is relatively insoluble substance often exhibit incomplete and erratic absorption. If the solubility of drug substance is less than required, measures must be taken to improve or increase solubility. Hence, it's a very important physiochemical property as it deals with dissolution, rate of drug delivery and pharmaceutical action. For desired pharmaceutical action the solubility in physiological pH range of 1-8 at $37^0$C.

## Method to determine solubility

A. Equilibrium solubility method
B. Neplometric solubility method
C. Ultrafiltration LC/MS solubility method

D. Direct solubility method

## Partition coefficient

Partition coefficient is measure of drug's lipophilicity; it indicates the ability of drugs to cross cell membranes. It is the ratio of drug distributed between the organic and aqueous phase at equilibrium.

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

$C_{oil}$ = Concentration of oil

$C_{water}$ = concentration of water

The biological membranes are lipoidal in nature hence, the rate of drug transfer or absorption of drugs is directly related to lipophilicity of the drug substance. The partition coefficient is commonly determined using an oil phase of octanol or chloroform in water.

## Methods to esteem partition coefficient

1. Shake flask method
2. Chromatographic method (HPLC- High Profile Liquid Chromatography)

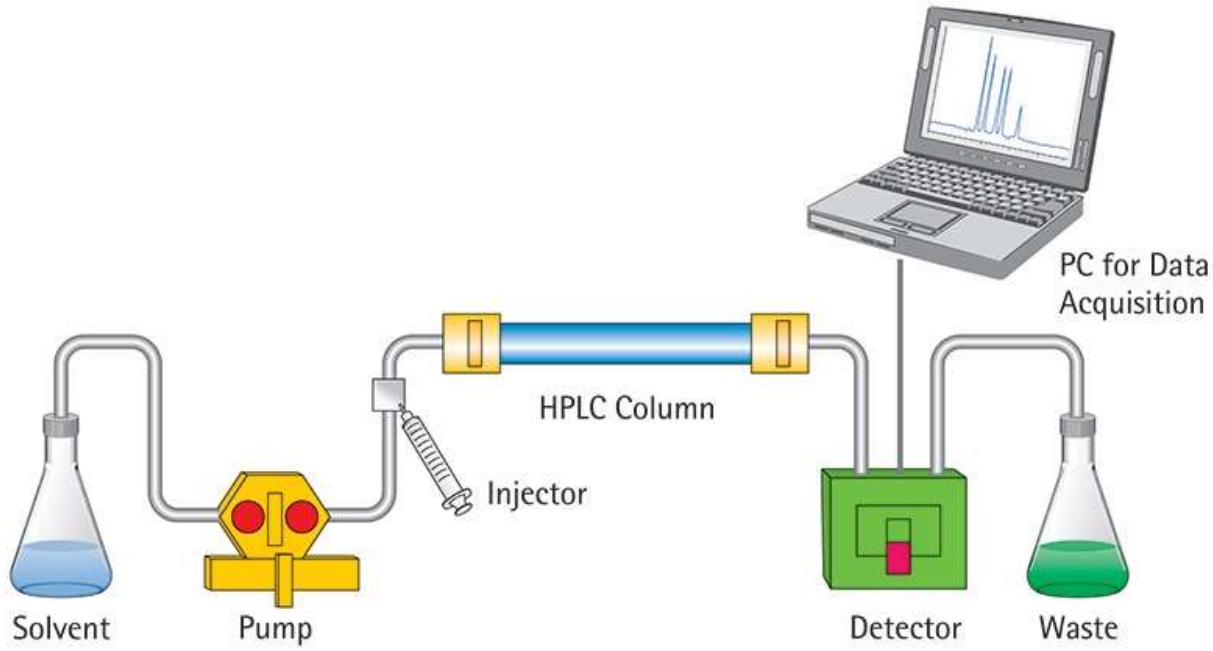


**Fig 11**: High performance liquid chromatography

3. Counter current and Filter Probe method

## Dissolution

Dissolution rate is the time taken for the drug to dissolve in the fluids at the absorption site, it is the rate limiting step in absorption.it can affect the onset, intensity and duration of response and control the overall therapeutic action and bioavailability of the drug.

## Dissolution rate can be increased by:

a. Decreasing the drug's particle size
b. Increasing solubility in diffusion layer
c. Using highly water-soluble salt of parent substance

Dissolution of drug is widely influenced by chemical form, crystal habit, particle size, surface area, wetting and solubility.

Dissolution rate of the drug substance are represented by modified Noyes- Whitney equation.

$$\frac{dC}{dt} = \frac{DA}{hV}(C_5 - C)$$

Where, D = diffusion of coefficient in the dissolution medium

h= thickness

A= surface volume

V=volume

$C_5$=concentration of drug in saturated solution

C=concentration at particular time

## Estimation of dissolution

a. Rotating disk method
b. Particulate dissolution

## Ionization constant (pKa)

When we administer a week basic or acidic drug, it will undergo ionization in gastrointestinal fluids. Determination of dissociation constant for a drug constant for a drug capable of ionization under pH range 1 to 10 plays an important role in solubility and absorption, which can be altered by changing pH. The concentration of unionized and ionized form of weekly acidic or basic drug in a solution at a given pH can be acquired by Henderson-Hassel batch equation.

pH=pKa + log [unionized form]/ [ionized form] for week bases

pH=pKa + log [unionized form]/ [ionized form] for week acids

## Estimation of pKa

a. Potentiometric method
b. Conductivity method
c. Liquid-liquid partition method
d. Dissolution rate method
e. Spectrophotometric method

## Stability studies

All drug substance possesses inherit stability, it is a crucial factor in preformulation studies and plays vital role in development of drug product. Stability of drug implies that a drug product maintains same properties and attributes throughout its shelf life. Various processing stage influence the stability of drug substance such as milling, drying, compression, storage condition etc. Stability studies help to choose processing condition, environment condition and packaging system. Chemical degradation or oxidation may lead to loss of potency or formation of degraded product which may lead to toxic drugs.

a. **Solid state stability**
   Solid state degradation is due to hydrolysis, oxidation, photolysis and pyrolysis depending on chemical structure of drug substances. Solid state stability generally comprises of effect of temperature, humidity condition, light etc. Instable may cause adverse effects, change in dissolution or changes in physical properties of dosage form.
b. **Solution phase stability**
   Solution state stability plays vital role in drug development process. The degradation rate is much rapid in solution form when compared to solid

drugs. Major source of degradation is residual moisture, content from wet granulation, low melting point excipients etc.

## Factors affecting drug stability

1. pH
2. Elevated temperature studies
3. Stability under high humidity condition
4. Photolytic stability
5. Stability upon oxidation

c. Compatibility studies: Drug and excipients compatibility plays a crucial role in formulation to select the appropriate excipients. In preformulation screening of drug excipient compatibility requires only 5mg of drug in 50% excipients to maximize the palatability of the interaction.

## Methods for characterizing pharmaceutical solids

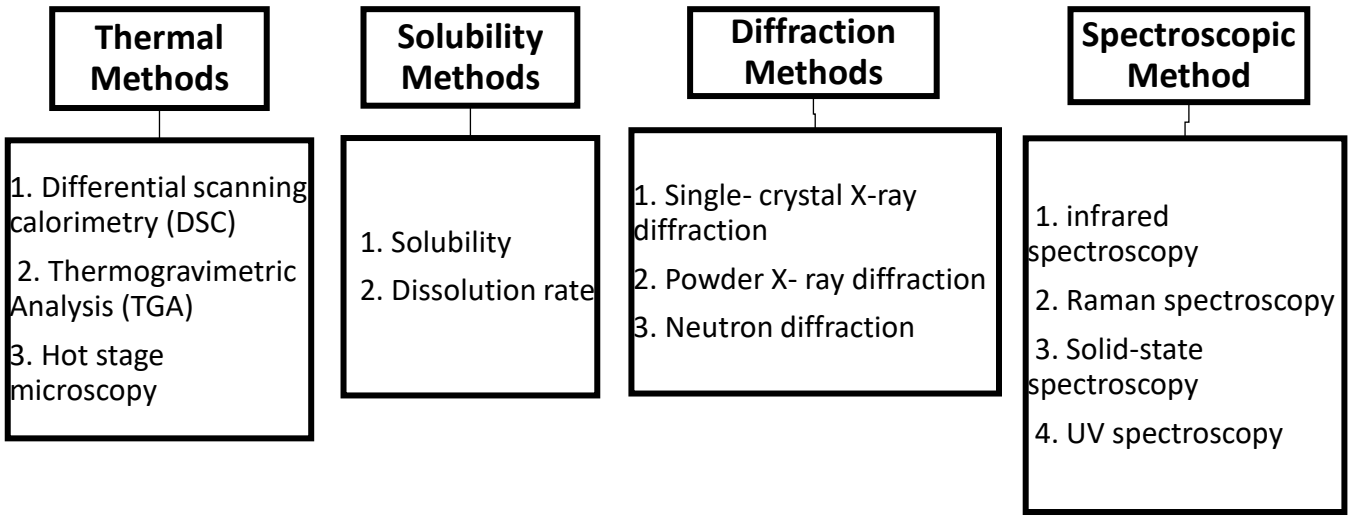


**Fig 12:** methods to characterize pharmaceutical solids

## Pharmaceutical Excipients

To formulate drug substance into final dosage form requires pharmaceutical excipients, for instance one or more solvents are added to the drug substance such

as coloring agents that enhance the appealing nature of the dosage form and flavoring agents or sweeteners that enhance the palatable nature of the dosage form. Preservatives are added to prevent microbial growth that prevents the degradation of the drug substance, many other stabilizers such as chelating agents, antioxidants, anticoagulating agents etc.

## Flavoring Agents

The flavoring of pharmaceutical formulation is primarily intended for liquid oral preparation. Liquid pharmaceutical preparations require flavoring agents to mask the unpleasant or bitter test. Tablets or other solid preparations are mostly uncoated or unflavored, swallowing them with water is sufficient to mask the unpleasant taste. But in cases of chewable tablets such as antacids or vitamin products usually has sweetening and flavoring agents to improve palatability.

| Flavour Natural | Synthetic Flavours | Basis of Choosing a Flavor |
|---|---|---|
| Juices – Raspberry | Alcoholic solutions | Complementary to existing flavor of the drug |
| Extracts – Liquorice | Aqueous solutions | Known popularity of particular flavors |
| Spirits - Lemon & Orange | Powders | Age of patients |
| Aromatic Oils – Peppermint & Lemon. | ---------- | Allergy |

## Sweetening Agents

In pharmaceutical formulations, addition of sucrose and other artificial sweetening agents have been used for decades, these ingredients mask the unpleasant bitter taste of active pharmaceutical ingredients

| Sweetener Type | | Sweetness Profile | Examples |
|---|---|---|---|
| Nutritive | | Rapid sweetness onset with short duration | 1. Dextrose<br>2. Fructose<br>3. High fructose corn syrup<br>4. Sucrose |
| Non- nutritive | Sugar alcohol | Intermediate sweetness onset with short duration | 1. Erythritol<br>2. Maltitol<br>3. Mannitol<br>4. Sorbitol<br>5. Xylitol |
| | High intensity | Variable sweetness onset with long duration | 1. Acesulfane Potassium<br>2. Advantame<br>3. Aspartame<br>4. Neotame<br>5. Saccharin<br>6. sodium saccharin<br>7. sucralose |

## Coloring Agents

Coloring agents are used in pharmaceutical formulation for esthetics and to enhance the appearance. These days most of pharmaceutical colorants are synthetic and few are obtained from natural mineral and plant sources, for instance zinc oxide liberate pale pink color in calamine lotion

| FD&C Colors | Common Name | Type of Chemical | Shade |
|---|---|---|---|
| Blue #1[b] | Brilliant Blue | Triphenylmethane | Blue |
| Blue #2 | Indigotine | Sulfonated indigo | Dark blue |
| Green #3 | Fast Green | Triphenylmethane | Blue-green |
| Yellow #5 | Tartrazine | Azo | Yellow |
| Yellow #6 | Sunset Yellow | Azo | Orange |
| Red #3 | Erythrosine | Xanthene | Pink |
| Red #40 | Allura Red | Azo | Red |
| Citrus Red #2[c] | Citrus Red | Azo | Orange |
| Orange B[d] | Orange B | Pyrazolone | Orange-red |

## Preservatives

Preservatives are added pharmaceutical formulation to prevent and stabilize against chemical and physical degradation due to change in environmental condition. Certain pharmaceutical preparation must be preserved against microbial contamination.

| Preservatives | # of formulations (%) |
|---|---|
| Methylparaben | 33 (45,2%) |
| Propylparaben | 26 (35,6%) |
| Sodium benzoate | 24 (32,8%) |
| Sodium metabisulfite | 8 (11%) |
| Benzoic acid | 4 (5,4%) |
| Hydroxyparabenzoate | 4 (5,4%) |
| Potassium sorbate | 2 (2,7%) |
| hydroxyparabenzoic acid | 1 (1,3%) |