

DOSAGE FORM DESIGN

Abstract

Dosage form design plays a crucial part in the formation of medicaments that associate combination of active pharmaceutical ingredient plus excipients. The drug and pharmaceutical material must be accordant with one another to form a medicament that is balanced, appealing, easy to distribute and dispense.

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

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I. INTRODUCTION

Dosage forms are as old as 1500 BC where primitive age men formulated medicaments with medicinal herbs and other plants to survive in the forests. But in the present times there has been numerous developments in the dosage form design, to make it easy to manufacture or dispense suitable medicaments. Drug substances are seldom dispensed alone, but they are manufactured by the unique combination of active ingredients and non- medical agents. The objective of dosage form design is to acquire necessary or predictable therapeutic action in suitable site of action. This also overcomes the challenges that pharmacists or physicians face during dispensing or prescribing of medicaments

- Efficacious
- Biocompatible
- Maintain shelf life
- Economical to the patient
- Bioavailability
- Physically and chemically stable
- Easy to manufacture and reproduce

II. NEED FOR DOSAGE FORM.

The potent nature and low dosage of most of the drug prevents trouble free administration. 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
Albuterol sulfate	4.00	Bronchodilator
Felodipine	2.50	Vasodilator
Clonazepam	1.00	Anticonvulsant

Drug substances are never taken without 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 a balanced dosage form such as tablets, capsules, creams, emulsion, pastes, syrups etc.

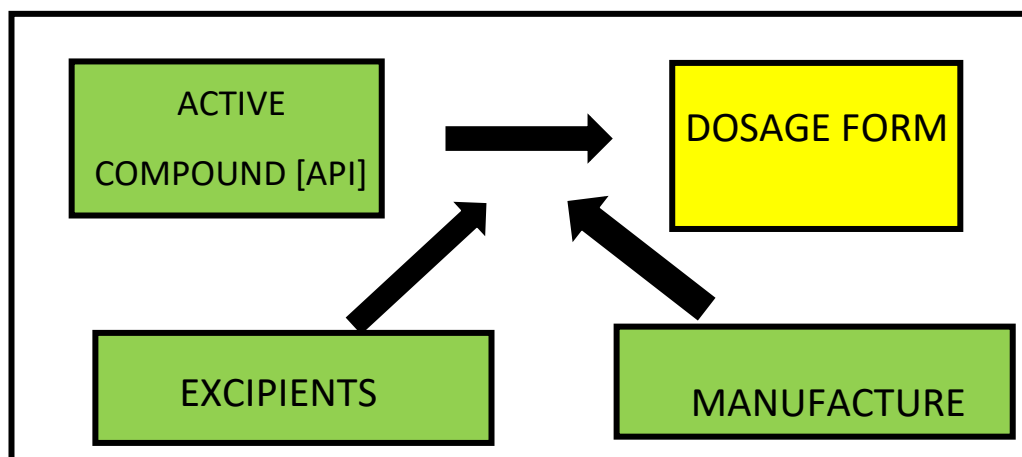


Figure 1: API to dosage form

III. WHY DO WE NEED DOSAGE FORM?

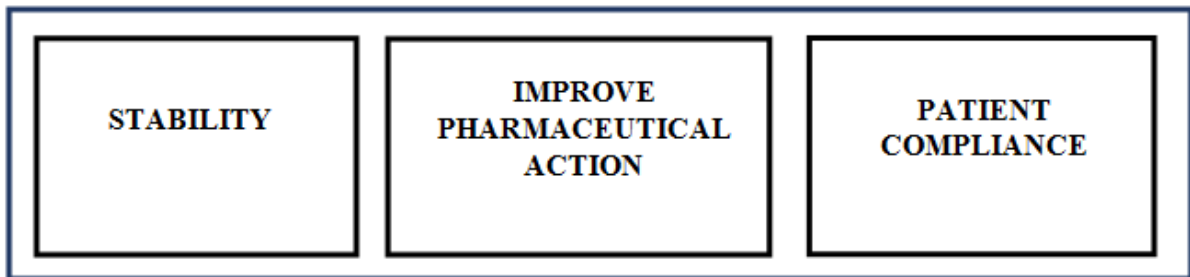


Figure 2: Need for pharmaceutical products

1. Stability

- Safeguard the drug from atmospheric condition such as destructive influence of atmospheric pressure
- Safeguard acid labile drug from the corrosive gastric acids produced by GIT

2. Improve Pharmaceutical Action

- By contributing desired drug action to appropriate site
- Contribution of desired medicament directly into blood stream or body tissue
- By insertion of drugs into one of body orifices

3. Patient Compliance

- Accuracy of dose by providing unit dose
- To conceal or mask the bitter, salty, or offensive taste or odor of a drug substances.
- Ease of handling and administration
Reduction in frequency of dose

IV. TYPES OF DOSAGE FORM

Dosage form can be classified based on:

- Physical form
- Route of administration

1. 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.

2. Based on Route of Administration

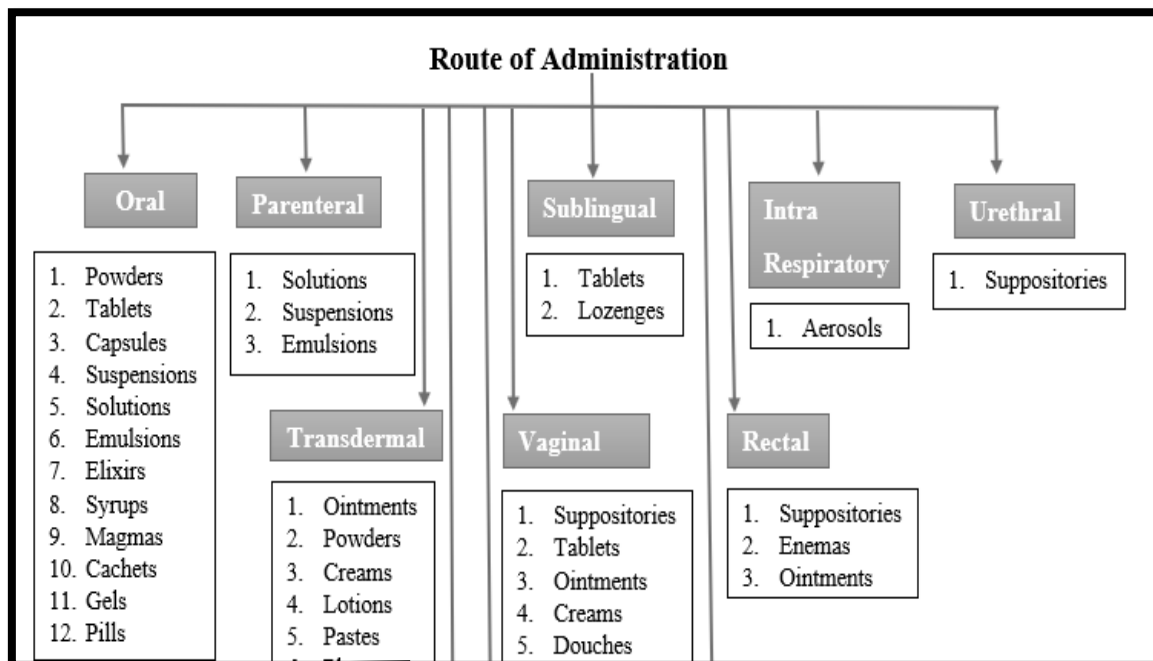


Figure 3: Route of administration

V. CONSIDERATIONS IN DOSAGE FORM DESIGN

1. 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.

2. Goals of preformulation studies are:

- Choosing of unerring drug substance based on type of dosage form development
- Understand biopharmaceutical properties of drug
- Reduce drug development, time and cost

3. Preformulation study plays an important role to

- Establish the new drug molecule's identity
- API and excipient compatibility
- Characterize physiochemical properties of new drug molecules
- Produce safe cost efficient and stable dosage form
- Minimize problems in various phases of drug development
- Provide necessary data for development of calibration method

4. Preformulation drug characterization

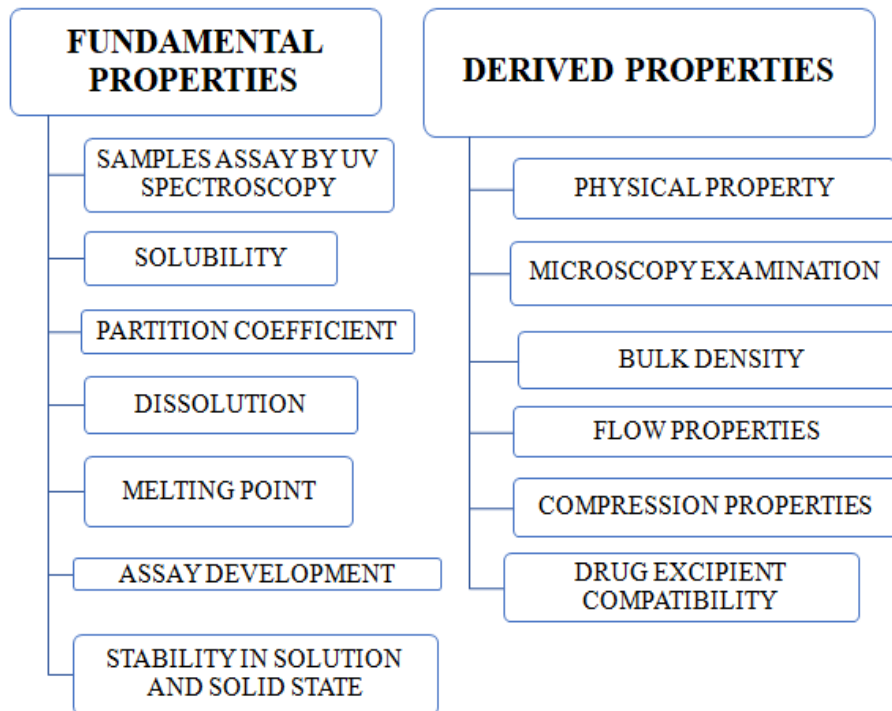


Figure 4: Preformulation properties

VI. BULK CHARACTERIZATION

- Physical properties
- Polymorphism
- Hygroscopicity
- Melting point depression
- Flowability

1. **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.

2. Microscopic examination



Figure 4: Microscope

3. **Polymorphism:** Crystal or amorphous form of the drug is an crucial factor on formulation of medicament . Polymorphic forms usually exhibit different physiochemical properties, including melting point and solubility. It has been estimed that atleast one third of all organic compunds shows polymorphism.

Polymorphism can be measured by:

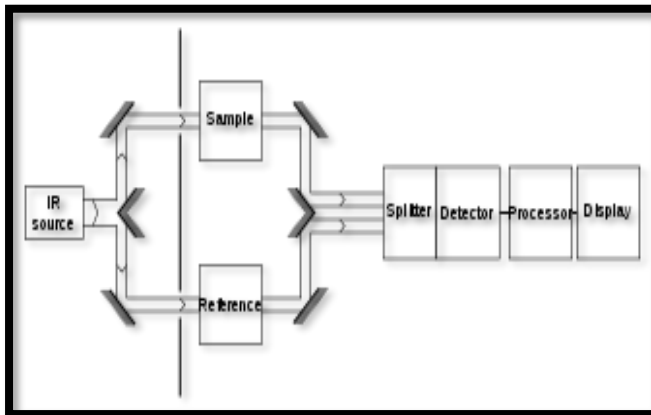


Figure 5: Infrared Spectrophotometry

Figure 6: Differential Scanning Calorimetry [DSC]

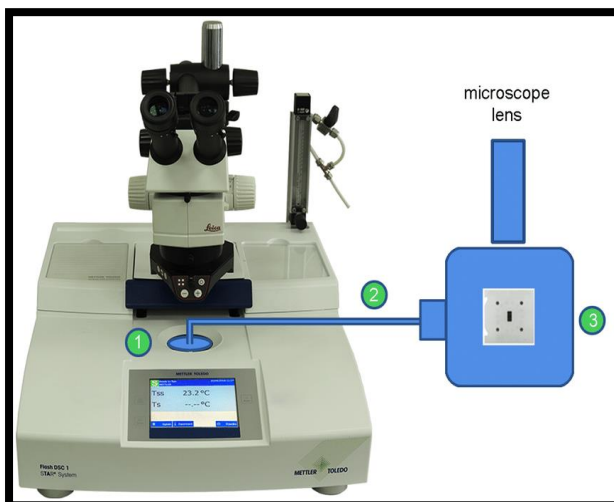


Figure 7: Hot Stage Microscopy [HSM] Figure 8: X- Ray Powder Diffraction [XRD]

4. Hygroscopicity

- Water soluble salt form of drug that has the tendency to absorb moisture. Such material can be classified as:
 - Efflorescent substance: substance that posses the tendency to lose water molecule and become anhydrous in nature.
 - Hygroscopic substance: substance that posses the tendency to absorb water molecules and get in equilibrium with water molecules present in the atmosphere
- 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.
- Hygroscopicity can be measured by:

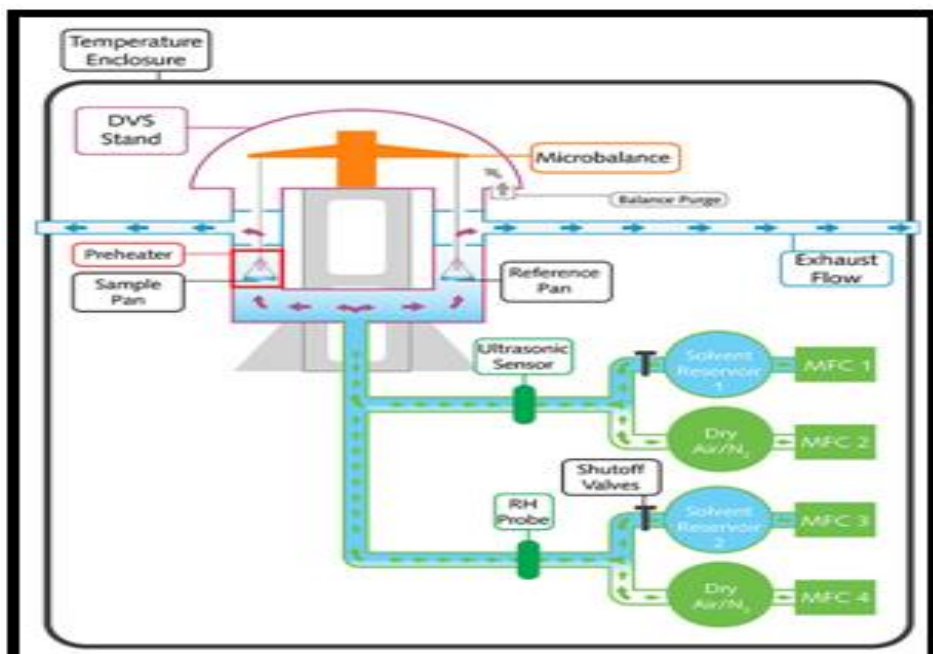


Figure 9: Dynamic vapor sorption method

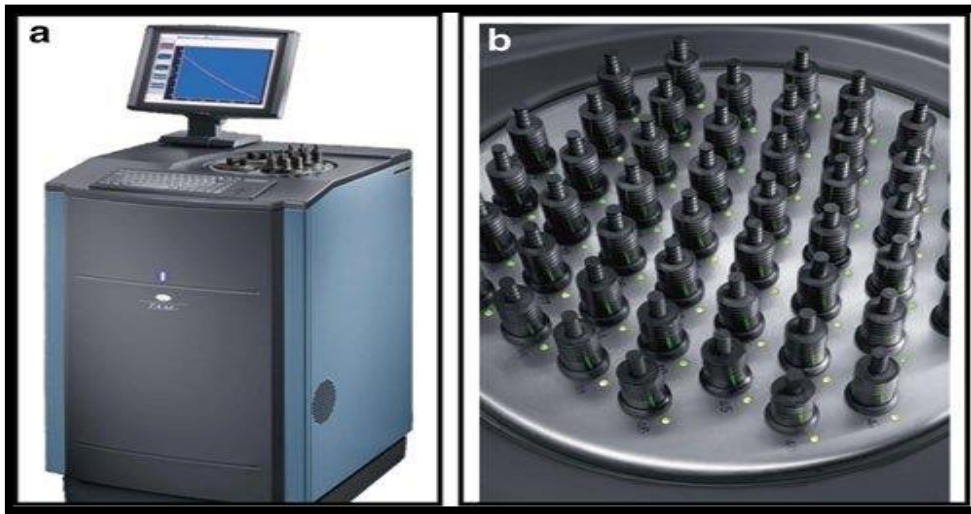


Figure 10: Isothermal Microcalorimetry

5. Melting Point: Melting point plays a crucial part in the purity of the substance; if the given substance is not pure the substance will exhibit a difference in melting point. This concept is mainly used to find whether a substance is pure.

- **Melting point can be measured by:**

- Capillary melting
- Hot stage microscopy

6. Flowability: Flowability of powder plays a crucial part in pharmaceutical preparation of dosage form.

- **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

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

- **Carr's compressibility index and Hausner ratio**

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

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

7. Solubility: A medicament must possess 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.

8. 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.

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

C_{oil} = Concentration of oil
 C_{water} = concentration of water

- **Methods to esteem partition coefficient**
 - Shake flask method
 - HPLC

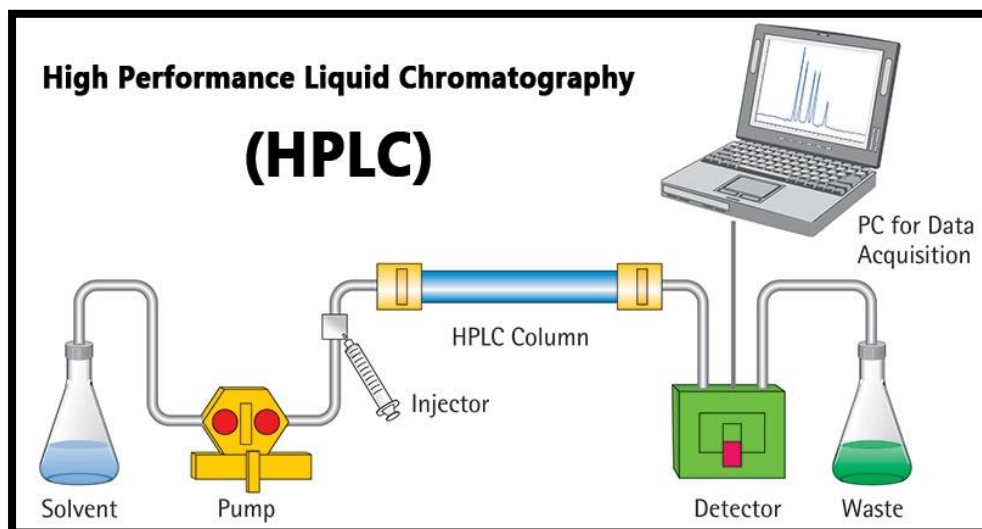


Figure 11: High Performance Liquid Chromatography

1. Counter current and Filter Probe method

- 9. 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.

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

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

- **Estimation of dissolution**
 - Rotating disk method
 - Particulate dissolution

- 10. Ionization constant (pKa):** When we administer a weak 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 weakly acidic or basic drug in a solution at a given pH can be acquired by Henderson-Hassel batch equation.

- **Estimation of pKa**
 - Potentiometric method
 - Conductivity method
 - Liquid-liquid partition method
 - Dissolution rate method
 - Spectrophotometric method

11. Stability studies: All medicaments possess inherent stability, it is a crucial part in preformulation studies. Stability of drug implies that a drug product maintains same properties and attributes throughout its shelf life. Various processing stages influence the stability of drug substance such as milling, drying, compression, storage condition etc. Stability studies help to choose processing conditions, environment conditions and packaging systems. Chemical degradation or oxidation may lead to reduced therapeutic action or formation of toxic substances.

- Solid state stability
- Solution phase stability

VII. METHODS FOR CHARACTERIZING PHARMACEUTICAL SOLIDS

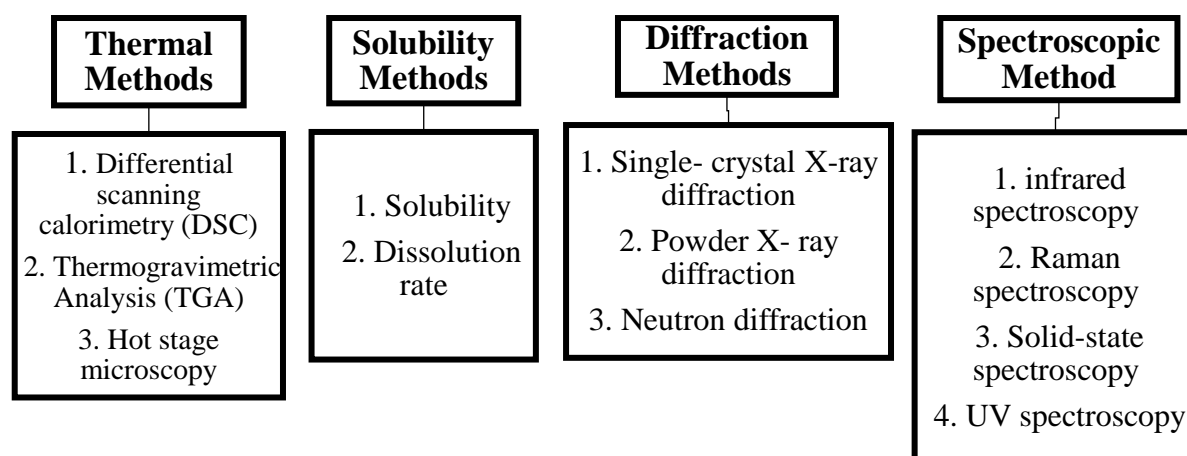


Figure 12: methods to characterize pharmaceutical solids

VIII. PHARMACEUTICAL EXCIPIENTS

To formulate active pharmaceutical ingredients into stable medicaments, it requires excipients, for instance one or more additives are added to the API 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.

- 1. 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, but in cases of chewable tablets such as antacids 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

- 2. 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 2. Sucrose
Non- nutritive	Sugar alcohol	Intermediate sweetness onset with short duration	1. Erythritol 2. Maltitol 3. Mannitol 4. Sorbitol 5. Xylitol
	High intensity	Variable sweetness onset with long duration	1. Acesulfane Potassium 2. Advantame 3. Aspartame 4. Neotame 5. Saccharin 6. sodium saccharin 7. sucralose

- 3. Coloring Agents:** Coloring agents are used in medicament formulation for appealing form 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

4. **Preservatives:** Preservatives are added pharmaceutical formulation to prevent and stabilize against chemical and physical degradation due to change in atmospheric condition. Certain pharmaceutical preparation must be preserved.

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%)