DOSAGE FORM DESIGN

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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

INTRODUCTION

Dosage form 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

[1] 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
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.

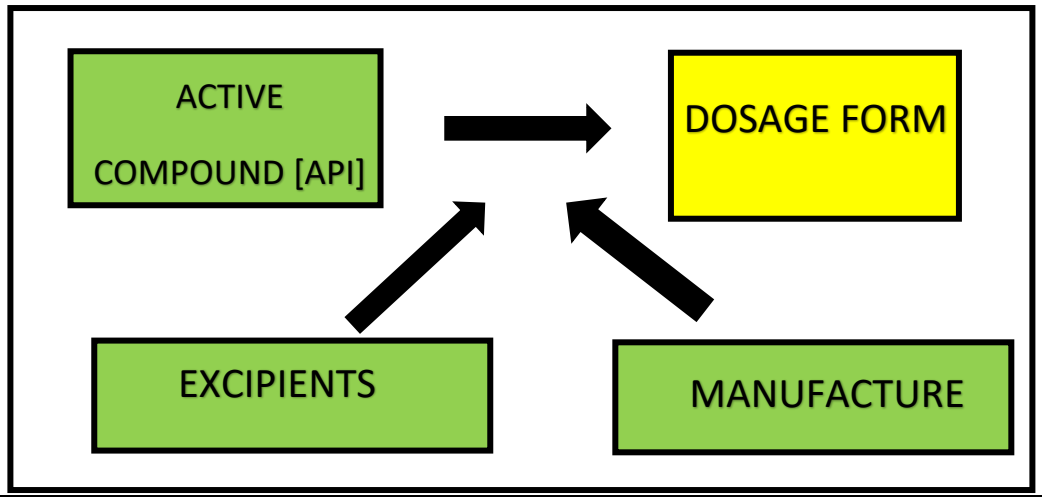

Fig 1: API to dosage form

[2] WHY DO WE NEED DOSAGE FORM?

Fig 2: Need for pharmaceutical products

2.1 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

2.2 IMPROVE PHARMACEUTICAL ACTION

1 by contributing desired drug action to appropriate site

2 Contribution of desired medicament directly into blood stream or body tissue

4 By insertion of drugs into one of body orifices

2.3 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

[3] TYPES OF DOSAGE FORM

Dosage form can be classified based on:

- Physical form
- Route of administration

3.1 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.

3.2 BASED ON ROUTE OF ADMINISTRATION

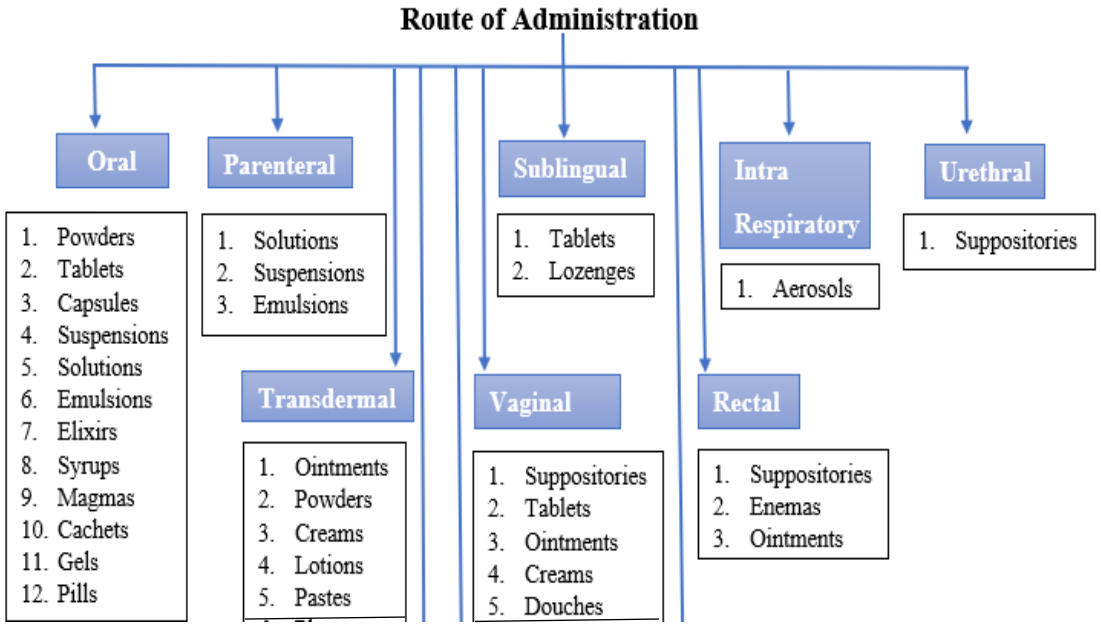

Fig 3: Route of administration

[4] CONSIDERATIONS IN DOSAGE FORM DESIGN

4.1 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.

4.2 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.

4.3 Goals of preformulation studies are:

- Choosing of correct form of drug substance based on type of dosage form development
- Understand biopharmaceutical properties of drug
- To produce safe effective reproducible drug delivery system
- Reduce drug development, time and cost

Preformulation study plays an important role to

- Establish the new drug molecule's identity
- Determine API and excipient compatibility
- Combine pharmacokinetics and biopharmaceutical properties
- 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

4.4 PREFORMULATION DRUG CHARACTERIZATION

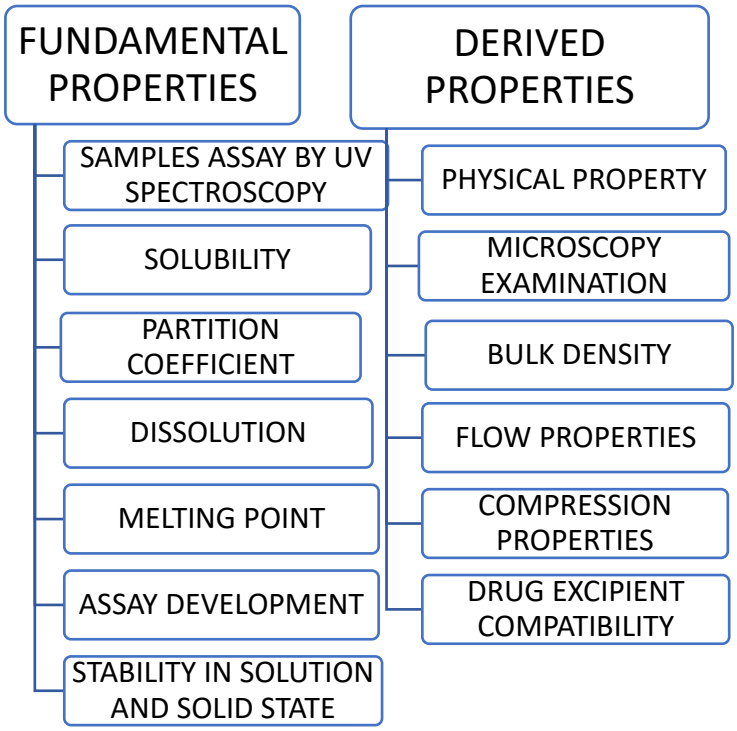

Fig 4: Preformulation properties

Bulk characterization.

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

5.1 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. 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.

Microscopic examination

Fig 4: Microscope

5.3 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 exhibit polymorphism.

Polymorphism can be measured by:

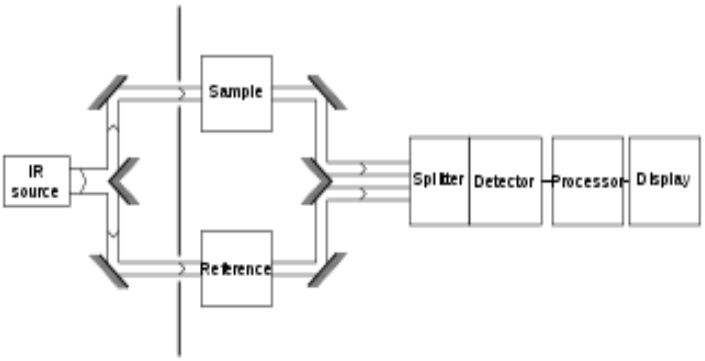

Fig 5: Infrared Spectrophotometry

Fig 6: Differential Scanning Calorimetry [DSC]

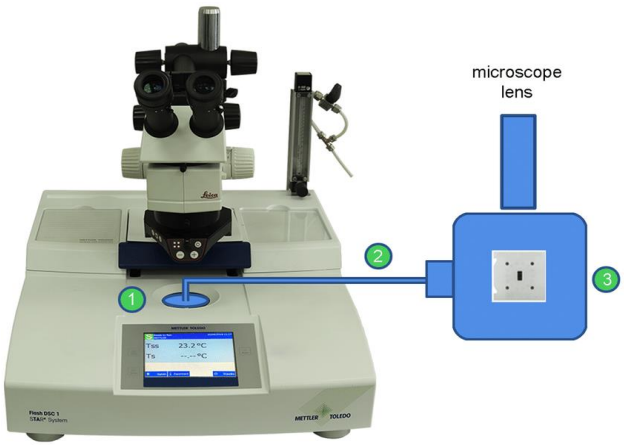

Fig 7: Hot Stage Microscopy [HSM]

Fig 8: X- Ray Powder Diffraction [XRD]

5.4 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:

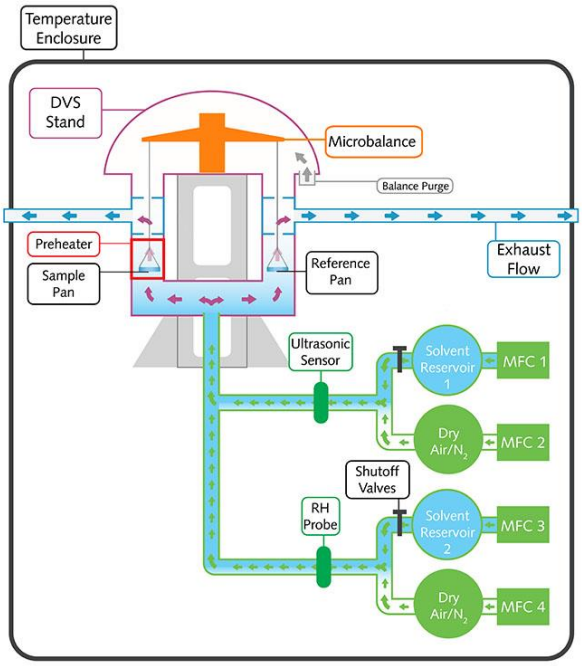

Fig 9: Dynamic vapor sorption method

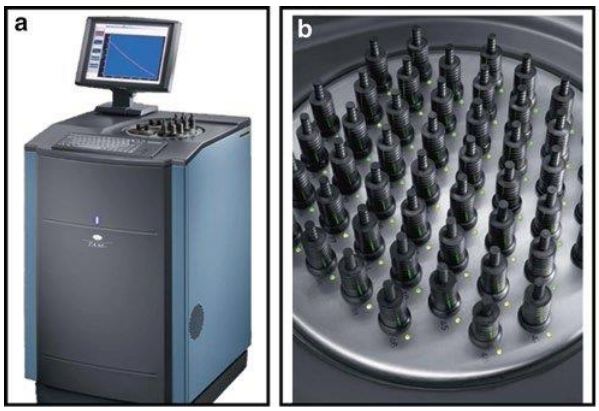

Fig 10: Isothermal microcalorimetry

5.5 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 determine the purity of drug substance.

Melting point can be measured by:

A. Capillary melting
B. Hot stage microscopy

5.6 Flowability

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

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

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

B. Carr's compressibility index and Hausner ratio

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

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

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

5.7 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.

Method to determine solubility

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

5.7 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

Methods to esteem partition coefficient

1. Shake flask method
2.

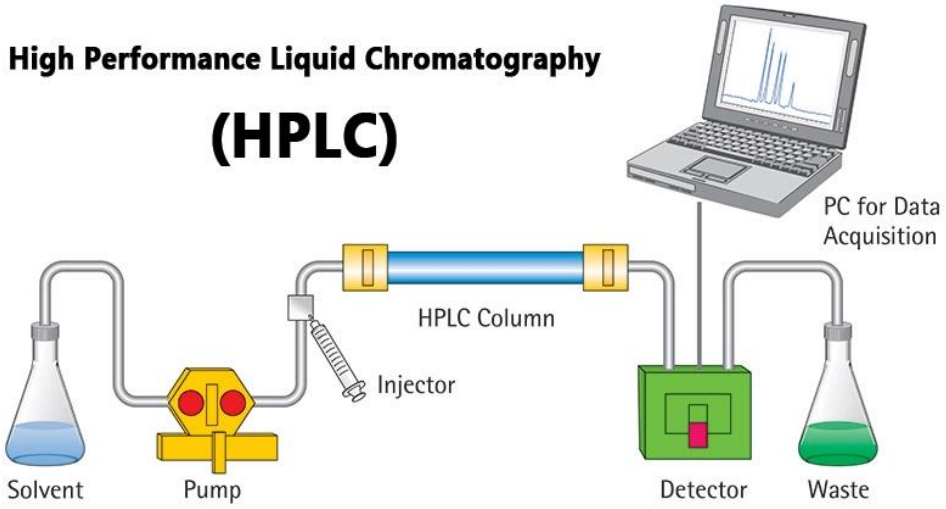

Fig 11: High performance liquid chromatography

3. Counter current and Filter Probe method

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

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

Estimation of dissolution

a. Rotating disk method
b. Particulate dissolution

5.9 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.

Estimation of pKa

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

5.10 Stability studies

All medicament possesses inherit 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 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 reduced therapeutic action or formation of toxic substances.

a. Solid state stability
b. Solution phase stability

Factors affecting drug stability

- pH
- Elevated temperature studies
- Stability under high humidity condition
- Photolytic stability
- Stability upon oxidation

[6] Methods for characterizing pharmaceutical solids

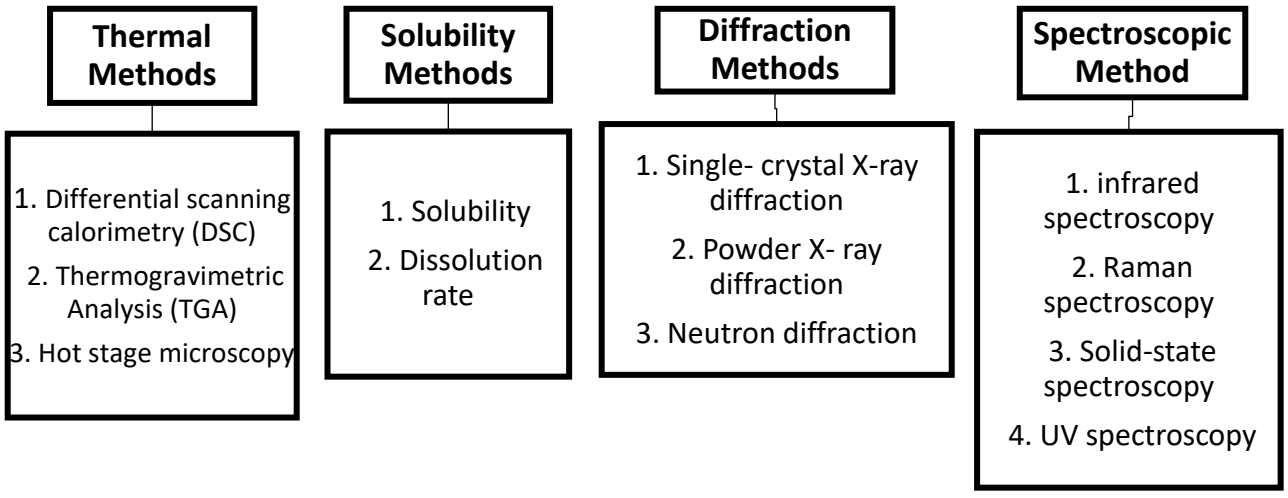

Fig 12: methods to characterize pharmaceutical solids

[7] Pharmaceutical Excipients

To formulate active pharmaceutical ingredient into stable medicament, 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.

7.1 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

7.2 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. Fructose 3. High fructose corn syrup 4. 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

7.3Coloring 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

7.4 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%)