Dosage Form Design

Lecture 5

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Chapter 4 \ Dosage Form Design: Pharmaceutical and Formulation Considerations

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- Objectives After reading this chapter, the student will be able to:

1. List reasons for the incorporation of drugs into various dosage forms
2. Compare and contrast the advantages/disadvantages of various drug dosage forms
3. Describe the information needed in preformulation studies to characterize a drug substance for possible inclusion into a dosage form
4. Describe the mechanisms of drug degradation and provide examples of each
5. Describe the five types of drug instability of concern to the practicing pharmacist
6. Describe the purpose and general protocol for accelerated stability studies
7. Summarize approaches employed to stabilize drugs in pharmaceutical dosage forms
8. Calculate rate reactions for various liquid dosage forms
9. Categorize various pharmaceutical ingredients and excipients

Introduction

- Drug substances are seldom administered alone; rather they are given as part of a formulation in combination with one or more nonmedicinal agents (pharmaceutical ingredients or excipients)that serve varied and specialized pharmaceutical functions and formulate different dosage forms.
- The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed **pharmaceutics.**
- The proper design and formulation of a dosage form requires

1. consideration of the physical, chemical, and biologic characteristics of all of the drug substances and pharmaceutical ingredients to be used in fabricating the product.
2. The drug and pharmaceutical materials must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer, and safe.
3. The product should be manufactured with appropriate measures of quality control and packaged in containers that keep the product stable.
4. The product should be labelled to promote correct use and be stored under conditions that contribute to maximum shelf life.

The need for dosage forms

- The potent nature and low dosage of most drugs in use today precludes (not permits) any expectation that general public could safely obtain the appropriate dose of a drug from the bulk material.
- Most drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive prescription or electronic analytical balance.
- When the dose of the drug is minute, solid dosage forms such as tablets and capsules must be prepared with **filler or diluents** so that the dosage unit is large enough to pick up with the fingertips.

Besides providing the mechanism for **the safe and convenient delivery of accurate dosage,** dosage forms are needed for additional reasons:

1. To provide for the safe and convenient delivery of accurate dosage
2. To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampoules)
3. To protect the drug substance from the destructive influence of gastric acid after oral administration (enteric coated tablets)

4- To control the bitter, salty, or offensive taste or odor of a drug substance (capsule, coated tablets, flavored syrups)

5- To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (suspensions)

6- To provide rate-controlled drug action (various controlled-release tablets, capsules, and suspensions)

7- To provide optimal drug action from topical administration sites (ointments, creams, trans-dermal patches, and ophthalmic, ear, and nasal preparations)

8- To provide for insertion of a drug into one of the body's orifices (rectal or vaginal suppositories) or directly in the bloodstream or body tissues (injections)

9- To provide for placement of drugs To provide for optimal drug action through inhalation therapy (inhalation aerosols)

10- In addition, many dosage forms permit ease of drug identification through distinctiveness of color, shape, or identifying markings

GENERAL CONSIDERATIONS IN DOSAGE FORM DESIGN

1. **Drug Consideration In Dosage Form Design**
    - 1.1 Characteristics of Drug Substances
    - 1.2 Drug Stability
    - 1.3 Determining Drug Formulation Stability
    - 1.4 Prevention Against Microbial Contamination
    - 1.5 Appearance and Palatability
2. **Therapeutic Considerations In Dosage Form Design**
    - 2.1 Nature of the disease or illness
    - 2.2 Age of the Patient
3. **Biopharmaceutics Considerations**
    - 3.1 Biopharmaceutics
    - 3.2 Concept of Bioavailability

General considerations in dosage form design

- Before formulating a drug substance into a dosage form, the desired product type must be determined, then various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up.
- The formulation that best meet the goals for the product is selected to be its **master formula**. Each batch of product subsequently prepared must meet the specifications established in the master formula.
- There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease.
- Most commonly, a manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease.

- Before medicinal agent is formulated into one or more dosage forms, among the **factors considered** are such therapeutic matters as

1- The manner in which it is treated (locally or through systemic action)

- If the medication is intended for systemic use and oral administration is desired**, tablets and/or capsules** are usually prepared because they are easily handled by the patient and are most convenient in the self-administration of medication.
- If a drug substance has application in an emergency in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared.

2- The nature of the illness,

- Many other example of therapeutic of therapeutic situations affecting dosage form design could be cited, including motion sickness, nausea, and vomiting, for which tablets and skin patches are used for prevention and suppositories and injections for treatment.

3- the age and anticipated condition of the patient.

- For infant and children younger than 5 years of age, pharmaceutical liquids rather than solid forms preferred for oral administration.
- When a young patient has a productive cough or is vomiting or simple rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instance, injections may be required.
- During childhood and even adulthood, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets, for this reason some medications are formulated as **chewable tablets**.
- **Newly available tablets dissolve in mouth in about 10 to 15 seconds**; this allows the patient to take a tablet but actually swallow a liquid.

Problems and solutions for multiple medication therapy

- Many patients, particularly the elderly, take multiple medications daily.
- ✓ The more distinctive the size, shape, and color of solid dosage forms, the easier is proper identification of the medications.
- Errors in taking medications among the elderly occur frequently because of their multiple drug therapy and impaired eyesight.
- ✓ Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

Performulation Studies

- Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized.
- Drugs can be used therapeutically as solids, liquids, and gases. Liquid drugs are used to a much lesser extent than solid drugs; gases, even less frequently.
- Liquid drugs pose a problem in design of dosage forms and delivery systems.

1- Many liquids are volatile and must be physically sealed from atmosphere to prevent evaporation loss.

2- Inability to formulate in tablet form.

1- Many liquids are volatile and must be physically sealed from atmosphere to prevent evaporation loss.

- **Amyl nitrate**, for example, is clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is kept for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation.
- An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after replacement under the tongue.
- However, because the drug is volatile, it has a tendency to escape from the tablets during storage, and it is critical that the tablets be stored in a tightly sealed glass container.

- Propylhexedrine is another volatile liquid that must be contained in a closed system. This drug is used as a nasal inhalant for its vasoconstrictor action.
- A cylinder roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler.
- The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited time because of the volatility of the drug.

Approaches for liquid drugs

For the most part, when a liquid drug is to be administered orally and a solid form is desired, one of two approaches is used.

First, the liquid substance may be sealed in a soft gelatine capsule.

- Vitamins A, D, and E, cyclosporine and ergoloid mesylates are liquids commercially available in capsule form.

Second, the liquid drug may be developed into a solid ester or salt form that will be suitable for tablets or drug capsules.

- For instance, scopolamine Hydrobromide is a solid salt of the liquid drug scopolamine and is easily pressed into tablets.
- Third approach to formulate liquids into solids is by mixing the drug with a solid or melted semisolid material, such as a high-molecular-weight polyethylene glycol. The melted mixture is poured into hard gelatine capsules to harden and the capsules sealed.

Advantages of liquid drugs

- For certain liquid drugs, especially those taken orally in large doses or applied topically, their liquid nature may have some advantage in the therapy.
- For example, 15-mL doses of mineral oil may be administered conveniently as such.
- Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin,
- However, for the most part, pharmacists prefer solid materials in formulation work because they can easily form them into tablets and capsules.

Why solid dosage forms are preferred ?

- **Formulation and stability difficulties arise less frequently with solid dosage** form than with liquid preparations, and for this reason many new drugs first reach the market as tablet or dry-filled capsules. It is estimated that tablets and capsules constitute the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules

Microscopic Examination

The Phase Rule

Heat of vaporization

Melting point Depression

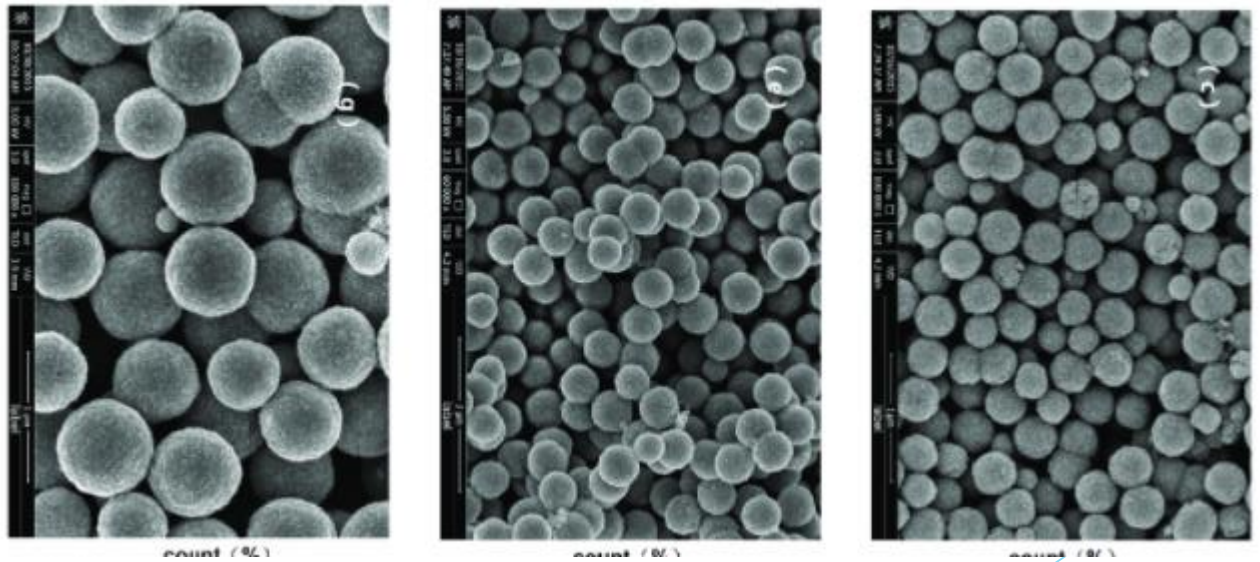
Particle Size

Solubility (solubility and particle size, solubility and pH)

Partition coefficient

Microscopic Examination

- It gives an indication of particle size and size range of the raw material along with the crystal structure.
- Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information in case of problems in formulation processing attributable to changes in particle or crystal characteristics of the drug.



Heat of vaporization

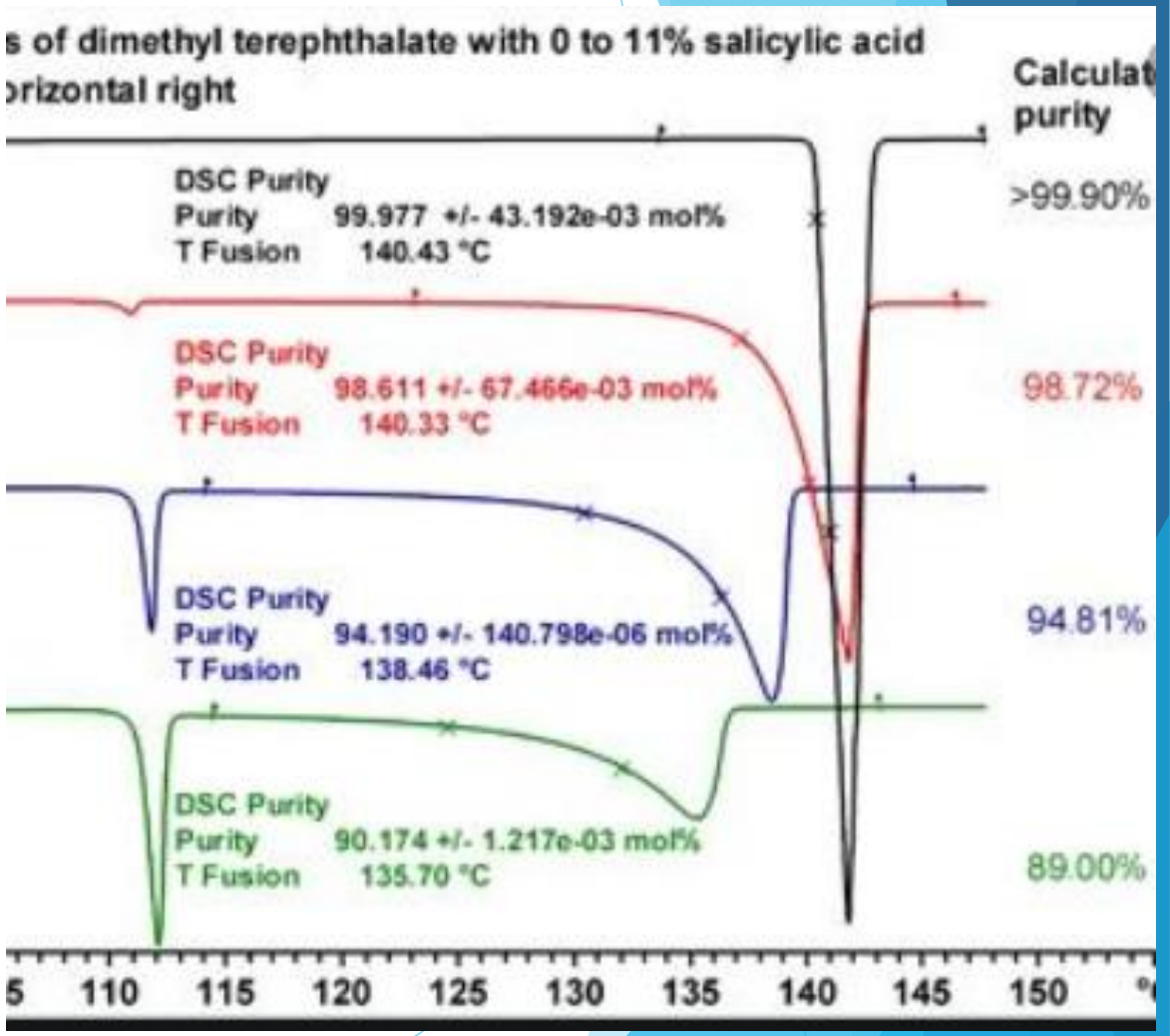
- The use of vapor pressure is important in the following situations:

1. The operation of implantable pumps delivering medication
2. Aerosol dosage forms
3. The use of nasal inhalants (propylhexedrine with menthol and lavender oil-benzedrex) or treating nasal congestion.
4. Some volatile drugs can even migrate within a tablet dosage form so the distribution may not be uniform any longer. This may have an impact in tablet that are scored for dosing where the drug in one portion may be higher or lower than in the other portion.
5. Exposure of personal to hazardous drugs due to handling, spilling, or aerosolizing of the drugs that may vaporize (oncology agents) is another application as the increase in mobility of the hazardous drug molecules may be related to temperature of the environment.
6. Some drugs, such as carmustine, experience greater vapor pressures with increased temperature as compared to cyclophosphamide, etoposide, cisplatin, and 5-fluorouracil).

Note: particle size affects vapor pressure; the smaller the particle size, the greater the vapor pressure.

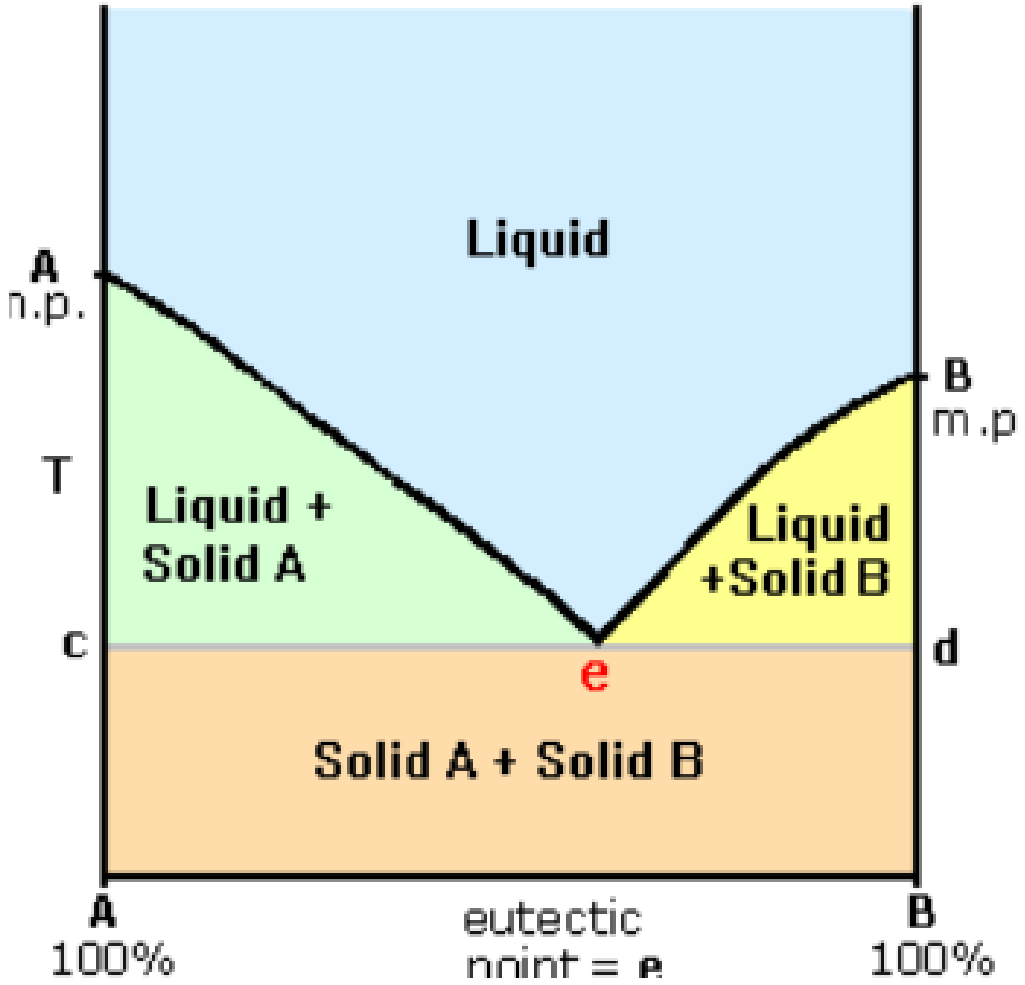
Melting point Depression

- The melting point, or freezing point, of a pure crystalline solid is defined as the temperature at which the pure liquid and solid exist in equilibrium.
- Drugs with a low melting point may soften during a processing step in which heat is generated, such as particle size reduction, compression
- A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a change in melting point. (A pure chemical is ordinarily characterised by a very sharp melting peak).
- This phenomenon is commonly used to determine the purity of a drug substance and in some cases the compatibility of various substances before inclusion in the same dosage form.



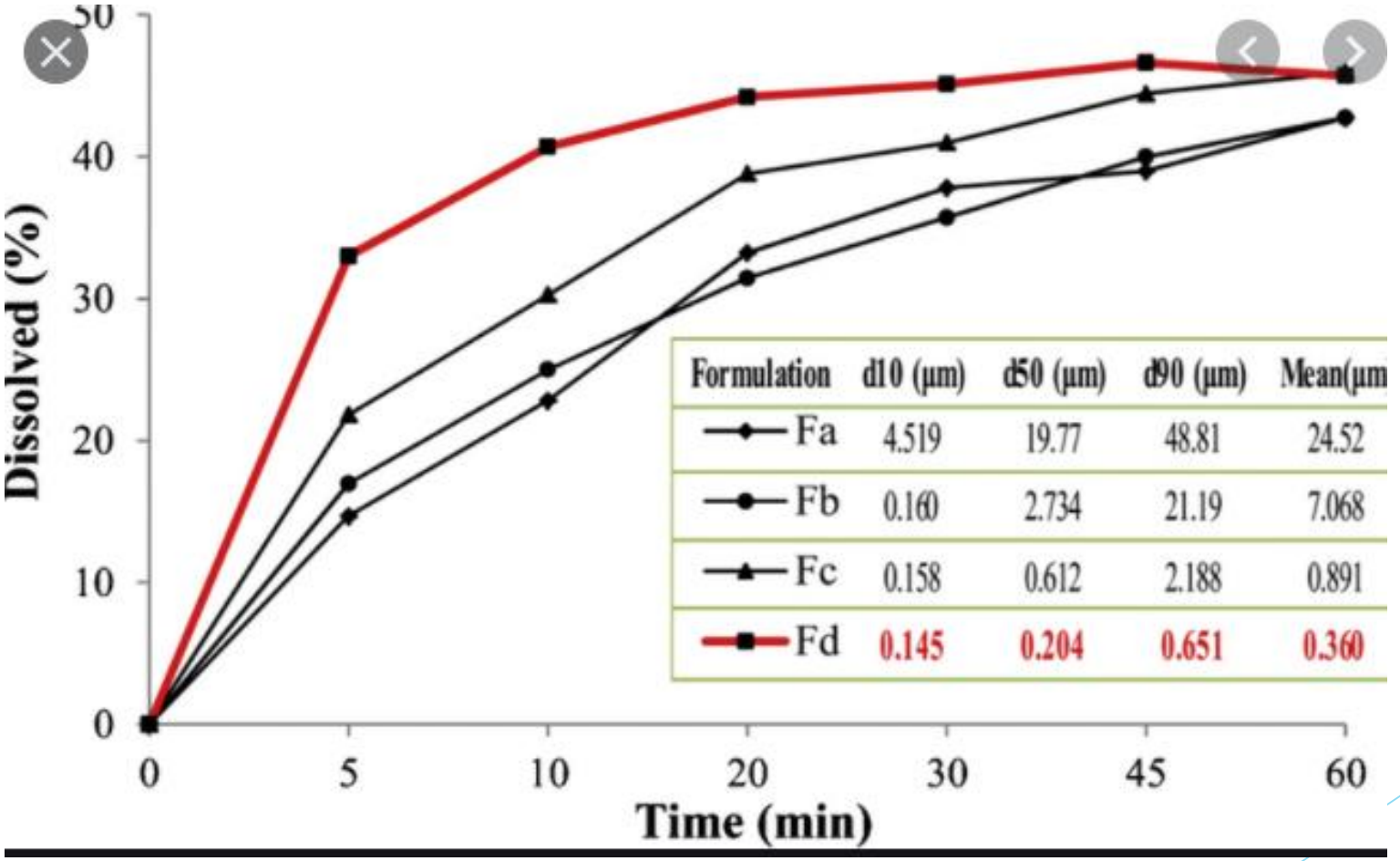
The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound

Phase diagrams are normally two-component (binary) representations, as shown in the following figure



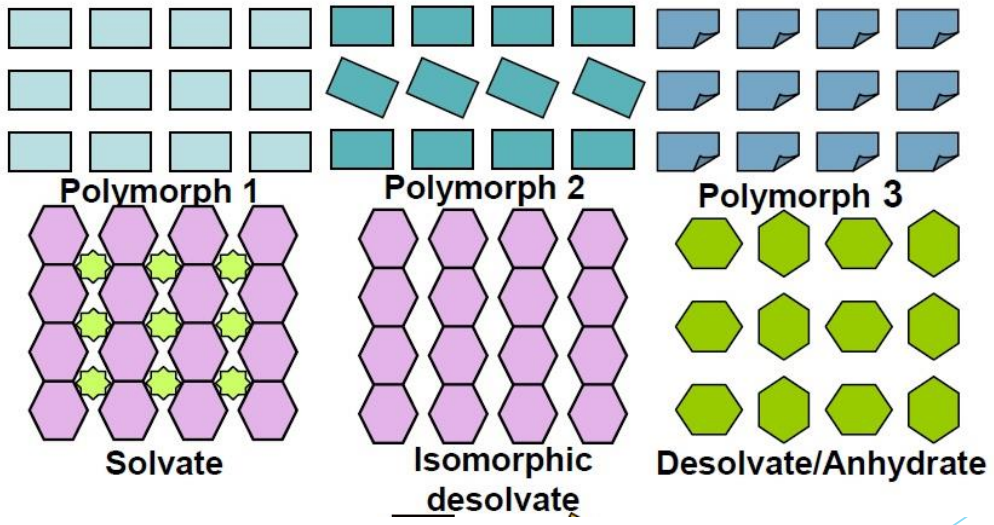
Particle Size

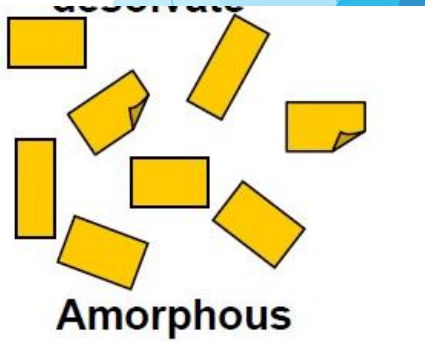
- Certain physical and chemical properties of drug substances, including dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability, are affected by the particle size distribution.
- In addition, flow characteristics and sedimentation rates, among other properties, are important factors related to particle size.
- It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and efficacy of special interest is the effect of particle size on absorption.
- Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.
- Particle size significantly influences the oral absorption profiles of certain drugs, including griseofulvin, nitofurantoin, spironolactone, and procaine penicillin.


Dissolved (%)
0
10
20
30
40
50
0
5
10
20
30
45
60
Time (min)
Formulation d10 (µm) d50 (µm) d90 (µm) Mean(µm
Fa 4.519 19.77 48.81 24.52
Fb 0.160 2.734 21.19 7.068
Fc 0.158 0.612 2.188 0.891
Fd 0.145 0.204 0.651 0.360

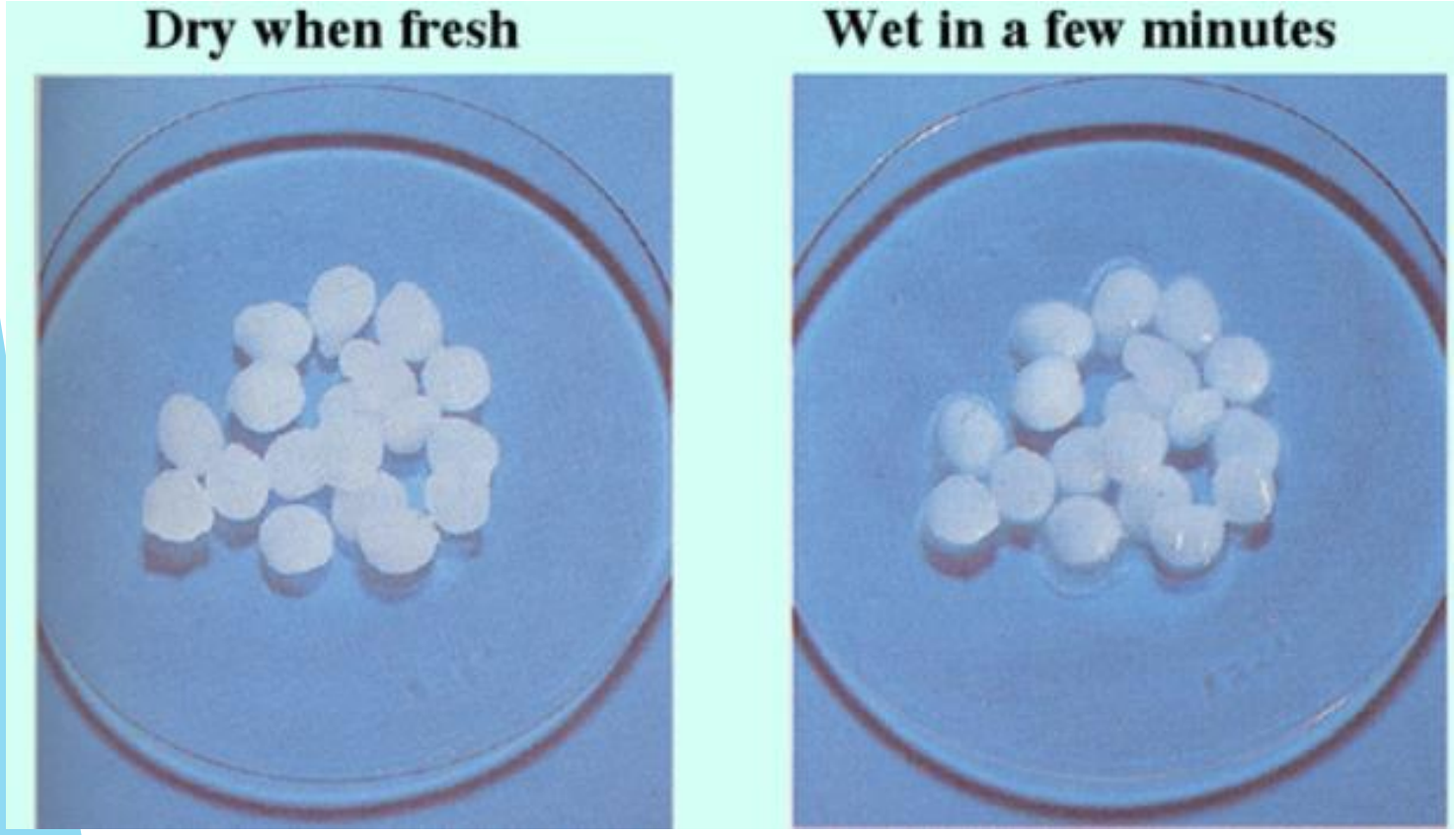
Polymorphism

- An important factor on formulation is the crystal or amorphous form of the drug substance.
- Polymorphic forms usually exhibit different physicochemical properties, including melting point and solubility. Polymorphic forms in drugs are relatively common. It has been estimated that at least one third of all organic compounds exhibit polymorphism.
- In addition to polymorphic forms, compounds may occur in noncrystalline or amorphous forms. The energy required for a molecule of drug to escape from a crystal is much greater than is required to escape from an amorphous powder, therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.
- Evaluation of crystal structure, polymorphism, and solvate form is an important performulation activity. The changes in crystal characteristics can influence bioavailability and chemical and physical stability and can have important implications in dosage form process functions. Many active pharmaceutical agents exist as hydrates or solvates





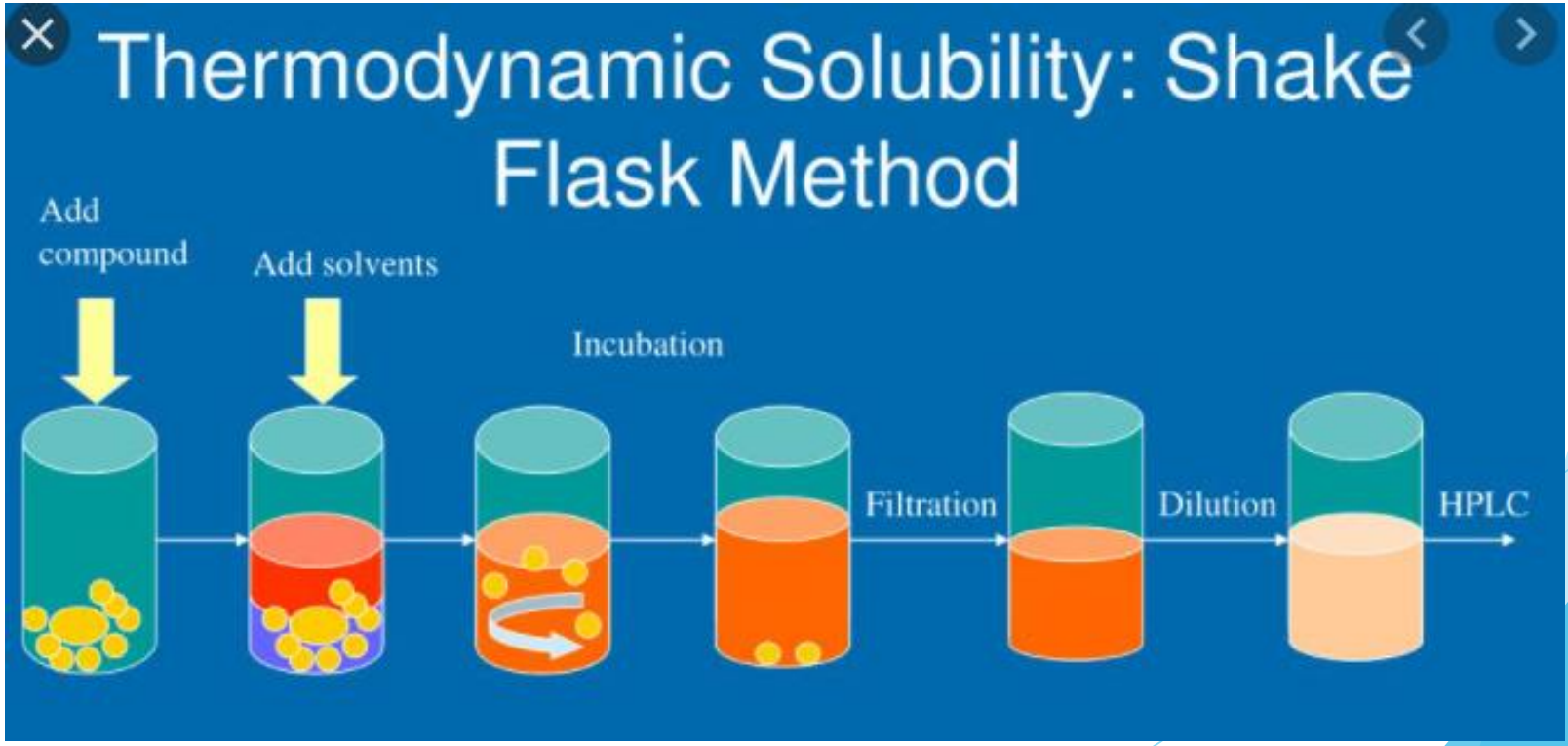
Some are hygroscopic, deliquescent, and/or efflorescent.
Hygroscopic powders are those that will tend to absorb moisture from the air.
Deliquescent powders are those that will absorb moisture from the air and even liquefy.
Efflorescent powders are those that may give up their water of crystallization and may even become damp and pasty.



Solubility

- An important physicochemical property of a drug substance is solubility, especially aqueous system solubility.
- A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation and exert a therapeutic effect, it must first be in solution.
- Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility.
- The methods to accomplish this depend on the chemical nature of the drug and the type of drug product under consideration.
- Chemical modification of the drug into salt or ester forms is frequently used to increase solubility.

- A drug's solubility is usually determined by the **equilibrium solubility method**, by which excess of the drug is placed in a solvent and shaken at a constant temperature over a long period until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.



Solubility and Particle Size

- Although solubility is normally considered a physicochemical constant, small increase in solubility can be accomplished by particle size reduction.

Solubility and pH

- Another technique, if the drug is to be formulated into a liquid product, is adjustment of the pH of the solvent to enhance solubility.
- However, for many drug substances pH adjustment is not an effective means of improving solubility. Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or that may cause stability problems with formulation ingredients. Adjustment of the pH usually has little effect on the solubility of substances other than electrolytes.
- In many cases, it is desirable to use cosolvents or other techniques such as complexation, or solid dispersion to improve aqueous solubility.

Dissolution

- dissolution rate, or time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in absorption.
- when the dissolution rate is the rate-limiting step, anything that affects it will also affect absorption.
- the dissolution rate of drugs may be increased by decreasing the drug's particle size.
- it may also be increased by increasing its solubility in diffusion layer

Means of enhancing the slow dissolution:

1. Particle size reduction (most commonly used).
2. Enhanced surface area by adsorbing the drug on an inert excipient with a high surface area, i.e., fumed silicon dioxide.
3. Co-melting, co-precipitating, or triturating the drug with some excipients.
4. Incorporation of suitable surfactant.
5. the most effective means of obtaining higher dissolution rates is to use a highly-water soluble salt of the parent substance

Dissolution rates of chemical compounds are determined by 2 methods:

1. Constant-surface method – which provides the intrinsic dissolution rate of the agent.
2. Particulate dissolution - in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

Constant-surface method

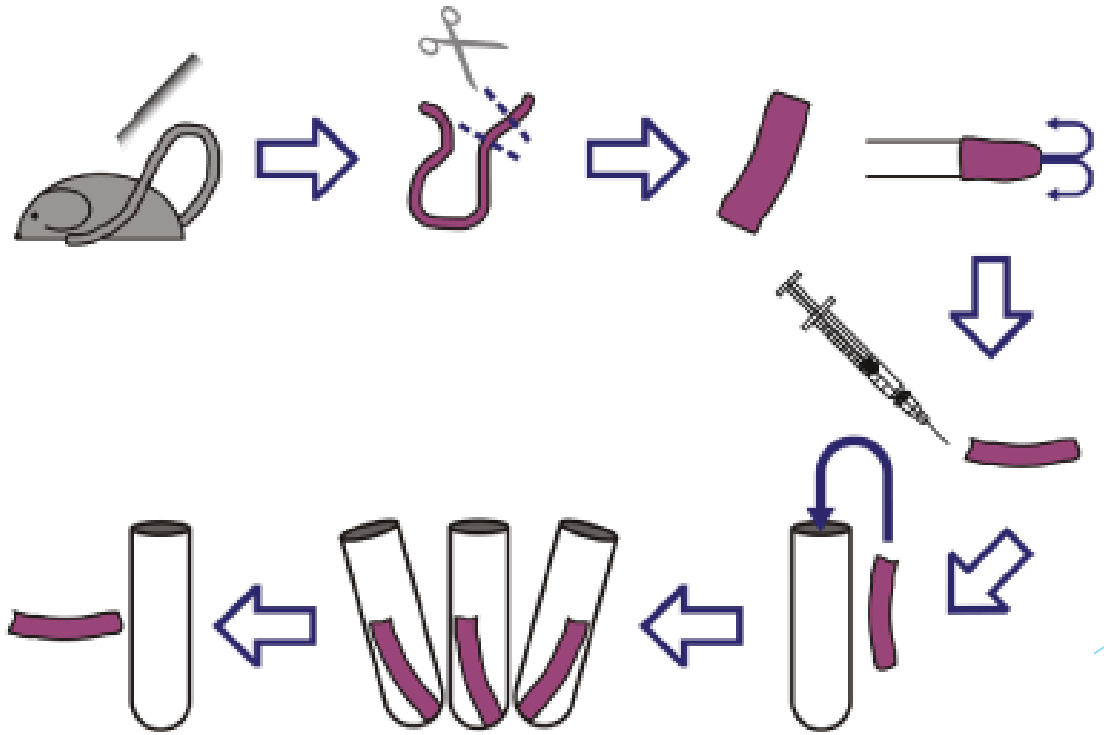
- uses a compressed disc of known area.
- This method eliminates surface area and surface electrical charges as dissolution variables.
- The dissolution rate obtained by this method, the **intrinsic dissolution rate,** is characteristics of each solid compound and a given solvent in the fixed experimental conditions.
- The value is expressed in **milligrams dissolved per minute per centimeters squared.**
- It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate.

Particulate dissolution

- a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system.
- This method is used to study the influence of particle size, surface area, and excipients upon the active agent.

Membrane Permeability

- To produce a biologic response, the drug molecule must first cross a biologic membrane.
- The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of lipid-soluble substances **by passive diffusion,** while lipid insoluble substances can diffuse across the barrier only with considerable difficulty if at all.
- **Everted intestinal sac** may be used to evaluate absorption characteristics of drug substances. A piece of intestine is removed from an intact animal, everted, filled with a solution of the drugs substance, and the degree and rate of passage of the drug through membrane sac is determined.
- This method allows evaluation of **both passive and active transport.**



Excipients

To produce a drug substance in a final dosage form requires pharmaceutical ingredients.

For example, solutions

1. Solvents
2. flavors and sweeteners
3. colorants
4. preservatives
5. Stabilizers

Tablets,

1. diluents or fillers
2. binders
3. antiadherents or lubricants
4. disintegrating agents
5. coatings.

HANDBOOK OF PHARMACEUTICAL EXCIPIENTS AND FOOD AND CHEMICALS CODEX

Flavoring Pharmaceuticals

- The flavoring of pharmaceuticals applies primarily to liquids intended for oral administration, mostly liquids and chewable tablets.

In flavor-formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation.

- With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound.
- **Sucrose**(**8 -**OH), sweeter than **glycerin**(3-OH)
- organic esters, alcohols, and aldehydes are pleasant to the taste
- Many nitrogen-containing compounds, especially the plant alkaloids (e.g., **quinine)** are extremely bitter, but certain other nitrogen-containin compounds (e.g., **aspartame)** are extremely sweet.

The selection of an appropriate flavoring agent depends on several factors, primarily

1. The taste of the drug substance itself.

- cocoa flavored used to mask bitter taste
- Fruit or citrus flavors used to mask sour or acid tasting
- cinnamon, orange, raspberry make preparations of salty drugs

2. The age of the intended patient

- Children prefer sweet candy-like with fruity flavors.
- Adults prefer less sweet with tart flavor.

Flavors can consist of oil- or water-soluble liquids and dry powders; most are diluted in carriers.

- Oil-soluble carriers (soybean and oils)
- water-soluble carriers (include water, ethanol, propylene glycol, glycerin, and emulsifiers.
- Dry carriers (include maltodextrins, corn syrup, modified starches, gum, salt, sugars, and whey protein).

Sweetening Pharmaceuticals

In addition to sucrose, a number of artificial sweetening agents have been used in foods and pharmaceuticals over the years.

- Some of these, including aspartame, saccharin, and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale
- saccharin is excreted by the kidneys virtually unchanged.
- Cyclamate is metabolized in GIT and excreted by kidneys
- Aspartame breaks down in the body into three basic components: **the amino acids phenylalanine and aspartic acid, and methanol.** are metabolized through regular pathways in the body
- use of aspartame by persons with **phenylketonuria** (PKU) is discouraged. They cannot metabolize phenylalanine adequately, so they undergo an increase in the serum levels of the amino acid (hyperphenylalaninemia). result in **mental retardation** and can affect the fetus of a pregnant woman who has PKU.
- **Acesulfame potassium**, a non nutritive sweetener Structurally similar to saccharin, it is 130 times as sweet as sucrose and is excreted unchanged in urine.
- Stevia powder30 times as sweet as sucrose or cane sugar. Used in both hot and cold preparations. It is natural, nontoxic, safe

Coloring Pharmaceuticals

- Coloring agents are used in pharmaceutical preparations for esthetics.
- Although most pharmaceutical colorants in use today are synthetic, a few are obtained from natural mineral and plant sources.
- riboflavin (yellow), cupric sulfate (blue), cyanocobalamin (red), and red mercuric iodide (vivid red).
- **ferric oxide mixed with zinc oxide to give calamine pink color.**
- Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored.
- The dye also must be chemically stable
- must be protected from oxidizing agents, reducing agents (especially metals, including iron, aluminum, zinc, and tin), strong acids and alkalis, and excessive heating.
- Dyes must also be reasonably photostable;
- **dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders.**

PRESERVATIVES

Although some types of pharmaceutical products, for example, ophthalmic and injectable preparations, are sterilized by physical methods (autoclaving for 20 minutes at 15 lb pressure and 121°C, dry heat at 180°C for 1 hour, or bacterial filtration) during manufacture, many of them also require an antimicrobial preservative to maintain their aseptic condition throughout storage and use

Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients are protected by the addition of an antimicrobial preservative.

Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative

- 15% V/V alcohol will prevent microbial growth in acid media
- 18% V/V in alkaline media.

Most alcohol-containing pharmaceuticals, are self-sterilizing and do not require additional preservation (elixirs, spirits, and tinctures)

General Preservative Considerations

- Intravenous preparations given in large volumes as blood replenishers or nutrients not contain bacteriostatic additives.
- Aqueous preparations are within favorable pH range must be protected against microbial growth. Preservative must **dissolve in sufficient concentration** in **aqueous phase** of preparation.
- only **undissociated fraction** of preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism.
- Acidic preservatives **benzoic**, **boric, and sorbic acids** more **undissociated** more effective as the medium is made more **acid.** Conversely, **alkaline preservatives** are less effective in acid or neutral media and more effective in **alkaline media**.
- if formula interfere with solubility or availability of preservative t, its chemical conc may **misleading**, because it may not be a true measure of the effective concentration. tragacanth, **attract and hold preservative**, such as the **parabens and phenolic** rendering them unavailable for preservative function.
- preservative **must not interact with container**, such as a metal ointment tube or a plastic medication bottle, or closure, such as a rubber or plastic cap or liner.

Reference

Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition