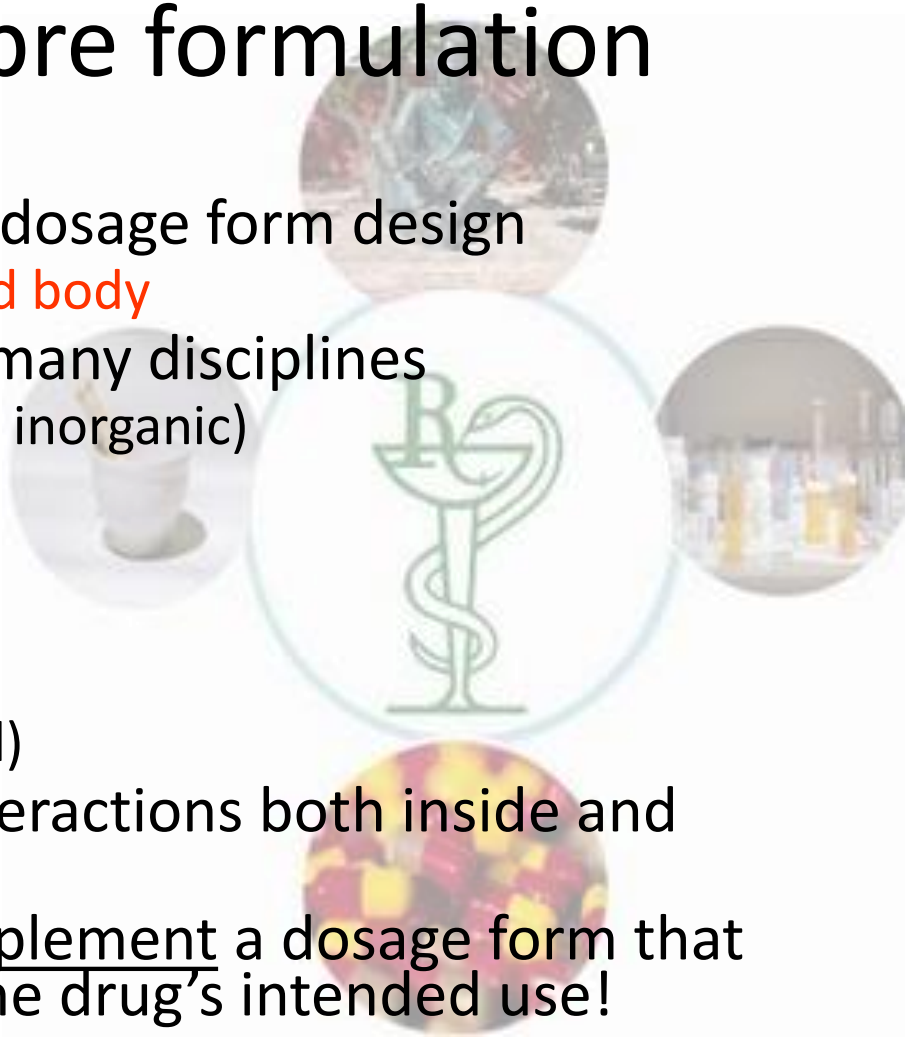
What is pharmaceutics? Formulation and pre formulation



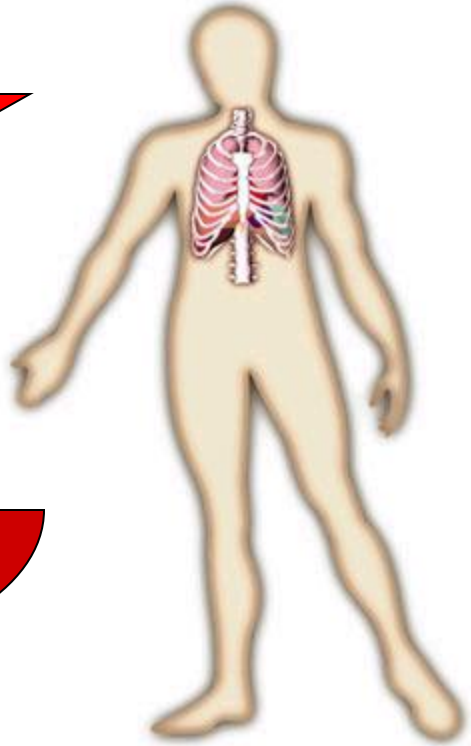
- The art and applied science of dosage form design
  - The interface between drug and body
- A broad field that draws from many disciplines
  - Physical chemistry (organic and inorganic)
  - Medicinal chemistry
  - Anatomy, physiology
  - Microbiology
  - Atomic physics
  - Engineering (chemical, material)
- Deals with many aspects of interactions both inside and outside the body
- It's not trivial to design and implement a dosage form that is both safe and effective for the drug's intended use!

Pharmaceutics is unique to pharmacy

- Physicians and other prescribers don't learn and apply physical pharmaceutical principles
- Chemists and engineers don't learn a whole lot of biology
- Anyone can read the latest review article of a disease state and play armchair prescriber, but it takes a pharmacist to know how to deliver a drug safely and effectively!

PHARMACODYNAMICS

Site/mechanism of action, potency, efficacy, etc.



PHARMACOKINETICS

absorption, distribution, metabolism, excretion

ADME

From drug substance to pharmaceutical preparation

- Active drug substance (active pharmaceutical ingredient - API)

- Excipients (inactive pharmaceutical ingredients)
  - Technological, biopharmaceutical and/or stability reasons
  - Diluents/fillers, binders, lubricants, desintegrants, coatings, preservants and stabilizers, colorants and flavourings
  - Should always be stated in SPC (important in the case of allergies)

Logistical considerations of dosage form design

- **Storage**
  - Rate of degradation (expiry)
    - Liquid/solid?
    - What conditions?
      - Temperature
      - Humidity
  - What container
    - How inert is it? What is the risk for contamination?
- **Compatibility**
  - Active vs. active vs. “inert” ingredients
  - Container (again)
- **Organoleptic considerations**
  - Physical appearance, taste, smell, size
  - “Pharmaceutical elegance”
- **Manufacturing**
  - For a powder, how well does it flow?

What you must know to design a dosage form

- **Physicochemical properties of the drug**
  - Reactivity, stability
  - Solubility, acid/base, solid state behaviour
- **Biopharmaceutical considerations**
  - What is the intended site of action?
    - Systemic? Topical?
  - Where/how well is the drug absorbed?
  - What is the intended onset of action?
    - Immediate-release, sustained-release, pulse releases

Some questions

- About the drug
  - Aqueous solubility, pKa, partition coefficient
  - Chemical stability in solution
- About the dosage form
  - Dissolution characteristics
  - Transdermal characteristics
  - Stability in storage
- About the biopharmaceutics
  - Extent of absorption
  - First-pass metabolism
  - Intended use: topical vs. systemic?

Types of dosage forms

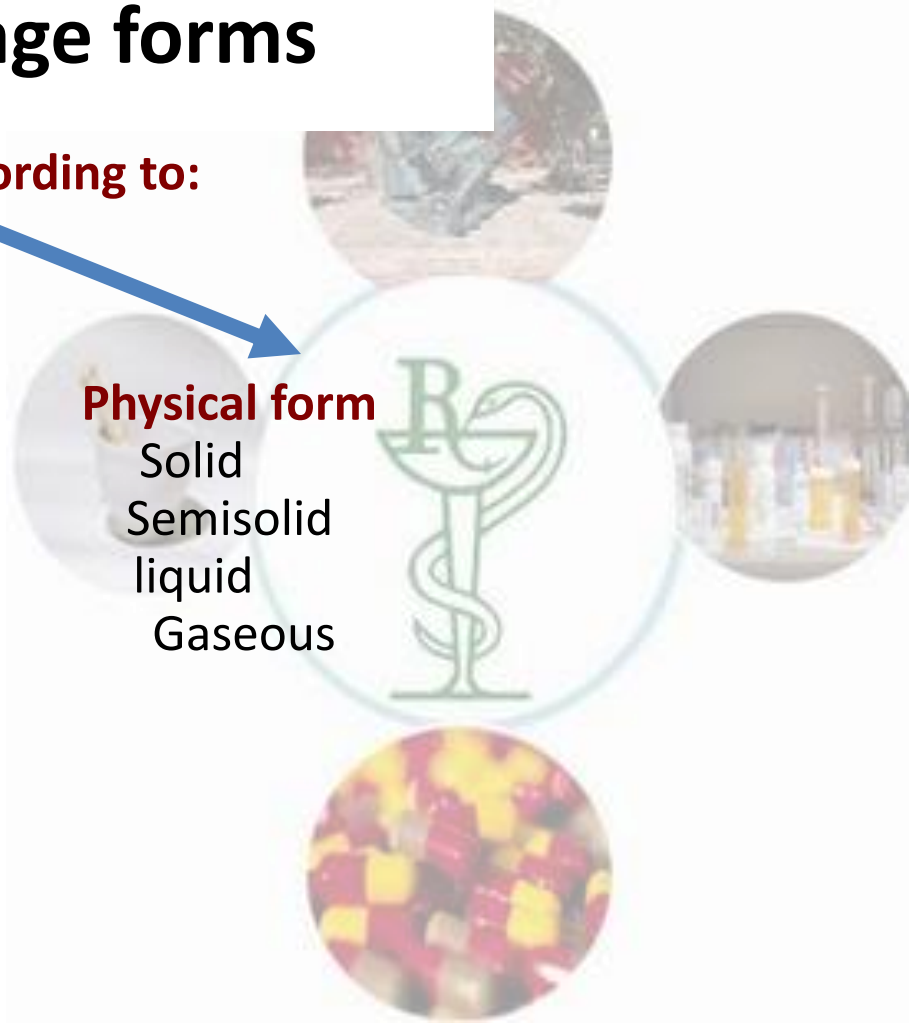
They are classified according to:

Route of administration

- Oral
- Topical
- Rectal
- Parenteral
- Vaginal
- Inhaled
- Ophthalmic
- Otic

Physical form

- Solid
- Semisolid
- liquid
- Gaseous

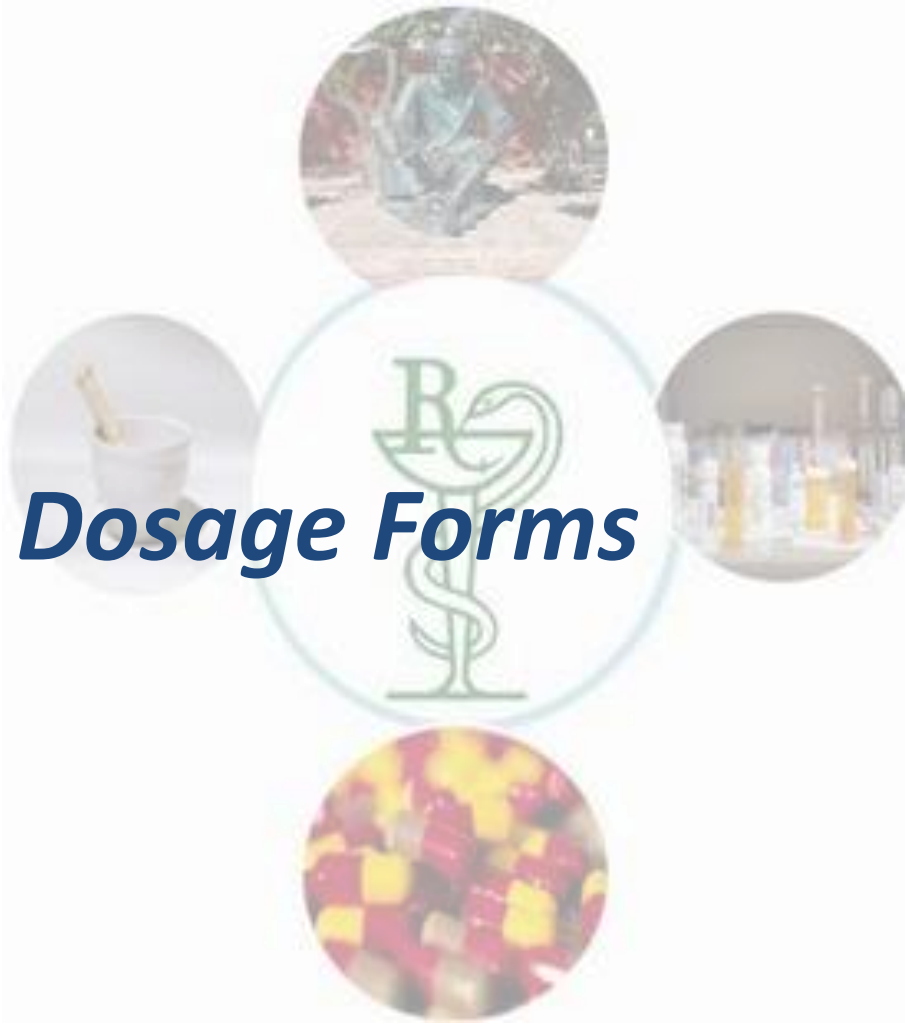


A list of dosage forms

- Solid dosage forms
  - Powders
  - Tablets
  - Capsules (hard, soft)
  - Suppositories*
  - Ointment, cream, gel, etc.*
  - Aerosol
  - Lozenge
  - Cigarette
- Liquid dosage forms
  - Solutions
  - Suspensions
  - (Gas)
- Light
  - UV
  - γ rays

- Many administration routes
  - Oral
  - Parenteral
    - IV, IM, SC, etc.
  - Ophthalmic, otic
  - Nasal
  - Rectal, vaginal, urethral
  - Buccal
  - Topical

1- The Need for Dosage Forms



1- The Need for Dosage Forms

1. To provide for the safe and convenient delivery of **accurate dosage**
2. For the protection of a drug substance from the destructive influence of atmospheric oxygen or moisture.

Examples: coated tablets, sealed ampules

3. For the protection of a drug substance from the destructive influence of gastric acid after oral administration.

Example: enteric coated tablets

4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle.

Example: suspension

5. To conceal the bitter taste, salty or odor of a drug substance.

Examples: Capsules, coated tablets, flavored syrups

1- The Need for Dosage Forms

6. To provide liquid dosage forms of substances soluble in desired vehicle.

Example: solution

7. To provide extended drug action through controlled release mechanisms

Examples: controlled release tablets, capsules, suspensions

8. To provide optional drug action from topical administration sites

Examples: ointments, creams, ophthalmic, ear and nasal preparations

9. To provide for insertion of a drug into one of the body's orifices

Examples: rectal and vaginal suppositories

10. To provide for the placement of drugs within body tissues.

11. To provide for the optimal drug action through inhalation therapy.

Examples: inhalants and inhalations

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

2. General Considerations in Dosage Form Design

Physiological factors

- Age
- Diurnal variation (fluctuations that occur during the day)
- Pregnancy
- Sex
- Menopause
- Body weight
- Time of administration
- Tolerance
- Temperature
- Physiological reserve

Factors Affecting Drug Presentation to the Body

- ❖ Route of drug entry into the body
- ❖ Physical form of the drug product
- ❖ Design and formulation of the product
- ❖ Method of manufacture of the product
- ❖ Physicochemical properties of the drug and excipients

❖Physicochemical properties of the drug product

❖Control and maintenance of location of drug at the absorption site

❖Control of the release rate of the drug from the drug product

2. General Considerations in Dosage Form Design

- neonates - birth up to one month;
- infants - one month up to 2 years of age;
- children - 2 years up to 12 years; and
- adolescents - 12 years up to 16 years.

Center for Drug Evaluation and Research (CDER) May 1996 FDA

2. General Considerations in Dosage Form Design

Design of Drug Products

- Effectiveness
- Safety
- Reliability
- Stability
  - Physical
  - Chemical
  - Microbiological

- Pharmaceutical elegance
  - Appearance
  - Organoleptic properties
- Convenience
  - Ease of use
  - Dosing frequency
  - Consumer acceptance

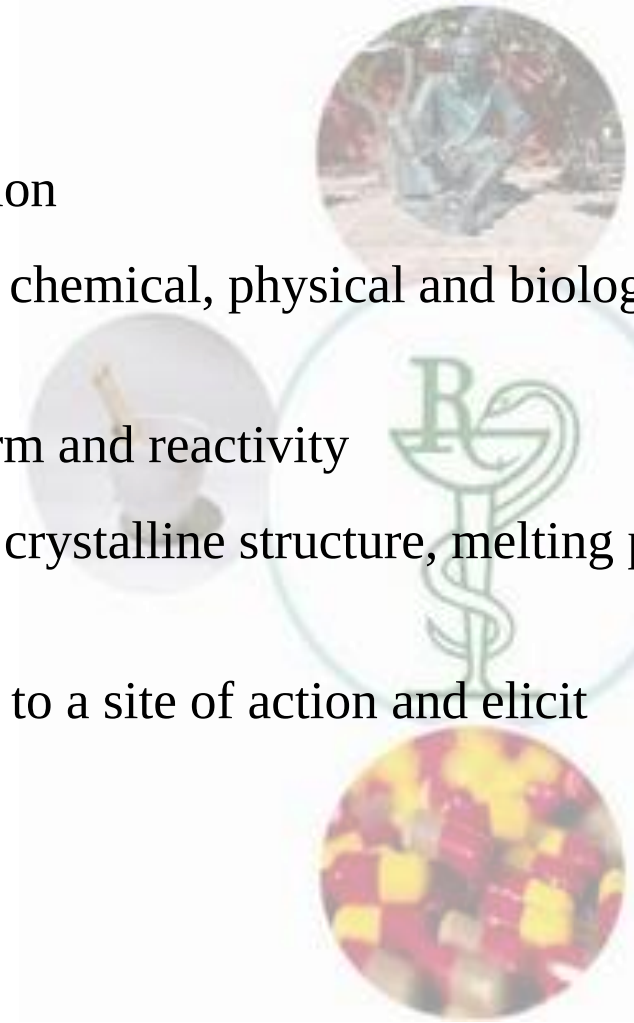
2. General Considerations in Dosage Form Design

2.1 Preformulation Studies

- Chemical characterization
- Physical characterization

2.2 Drug and Drug Product Stability

2.1. Preformulation Studies



1. Physical Description

- ***crystalline or amorphous*** constitution
- ***identification and evaluation*** of its chemical, physical and biologic properties
- ***Chemical properties*** - structure, form and reactivity
- **Physical properties** - particle size, crystalline structure, melting point and solubility
- **Biologic properties** - ability to get to a site of action and elicit biologic response
- ***Solids, liquids , gases***

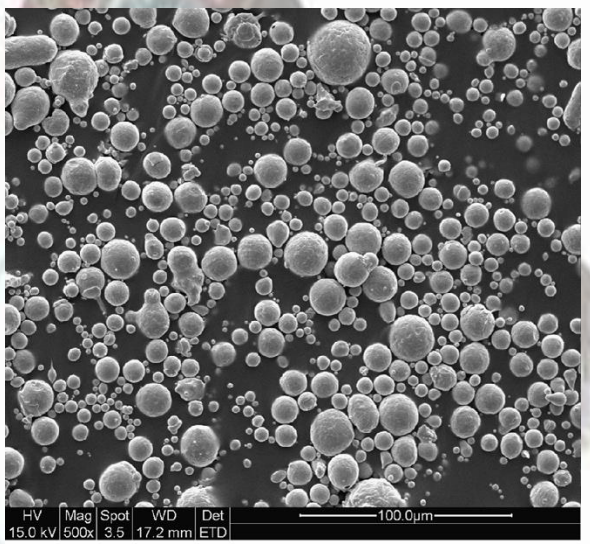
Amyl nitrite

Nitroglycerin

2.1. Preformulation Studies

2. Microscopic Examination

- Particle size
- Particle size range
- Crystal structure
- Particle shape



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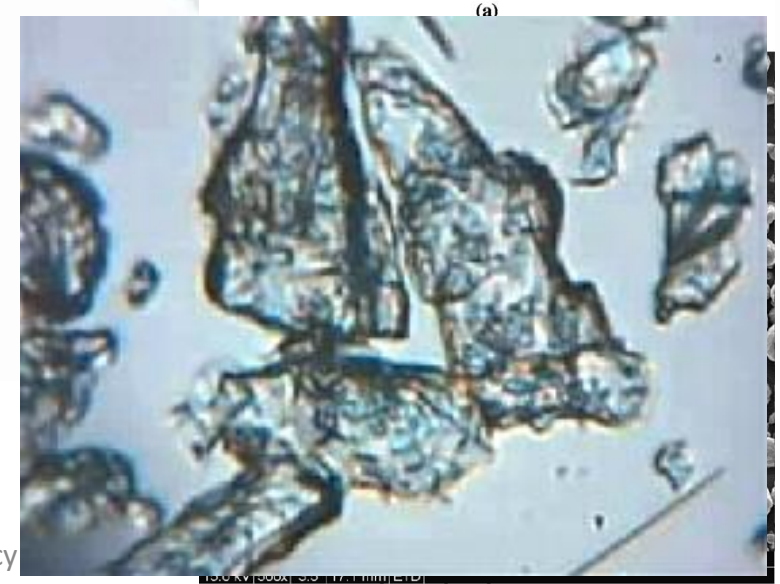

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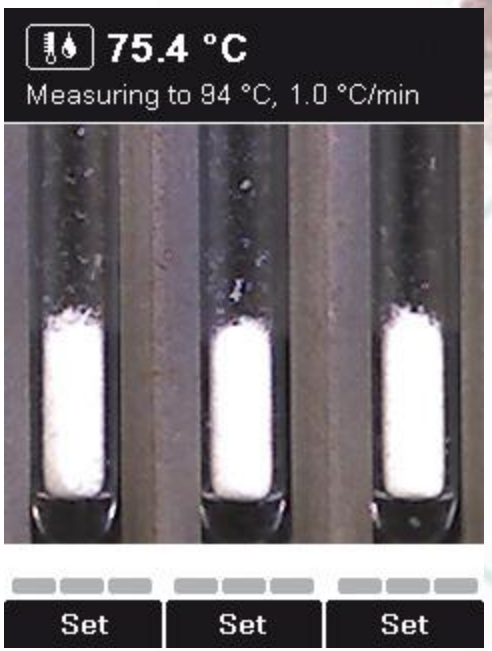
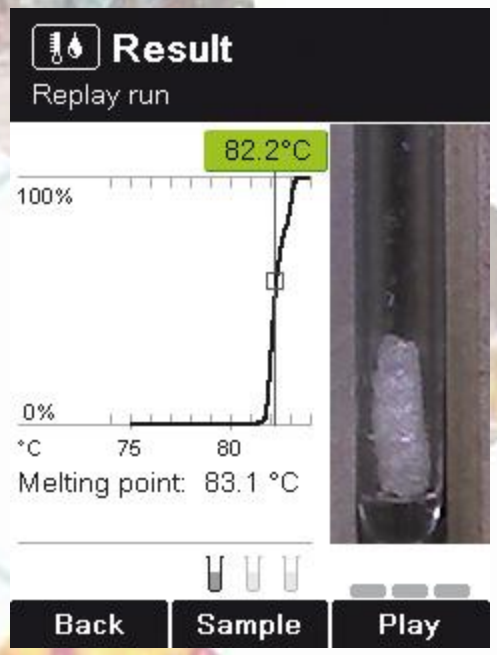
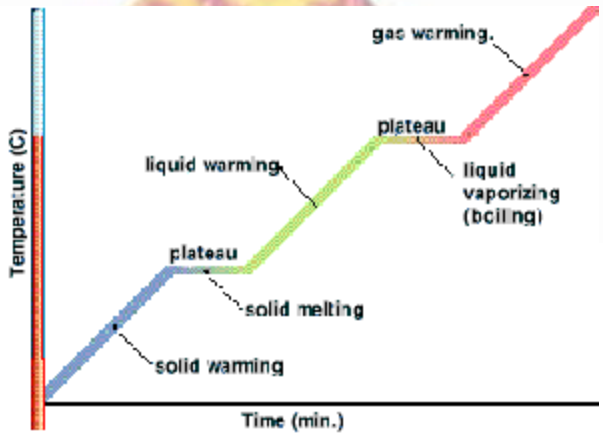
2.1. Preformulation Studies

3. Melting Point Depression



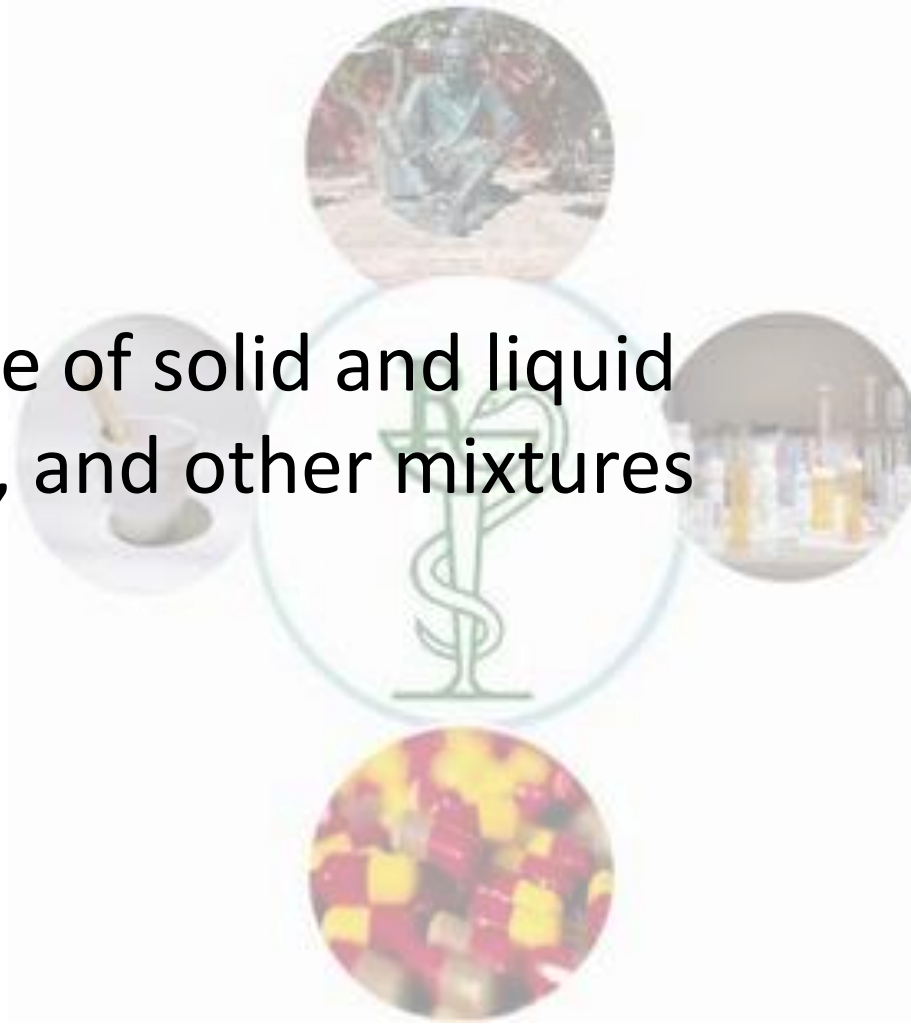


- ❖Purity determination
- ❖Identity



2.1. Preformulation Studies

4. The Phase Rule

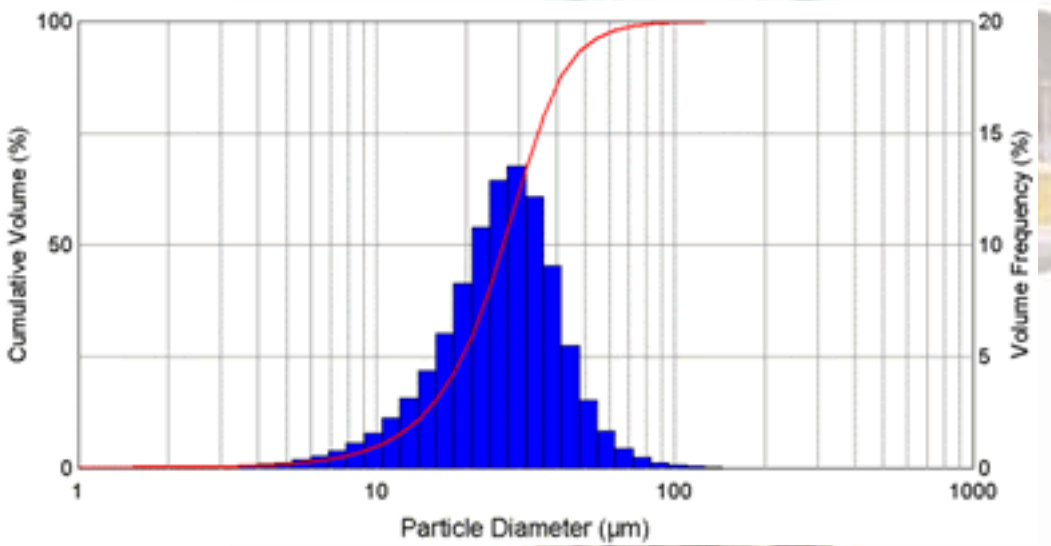


- Phase diagrams
- Visual picture of presence of solid and liquid phases in binary, ternary, and other mixtures

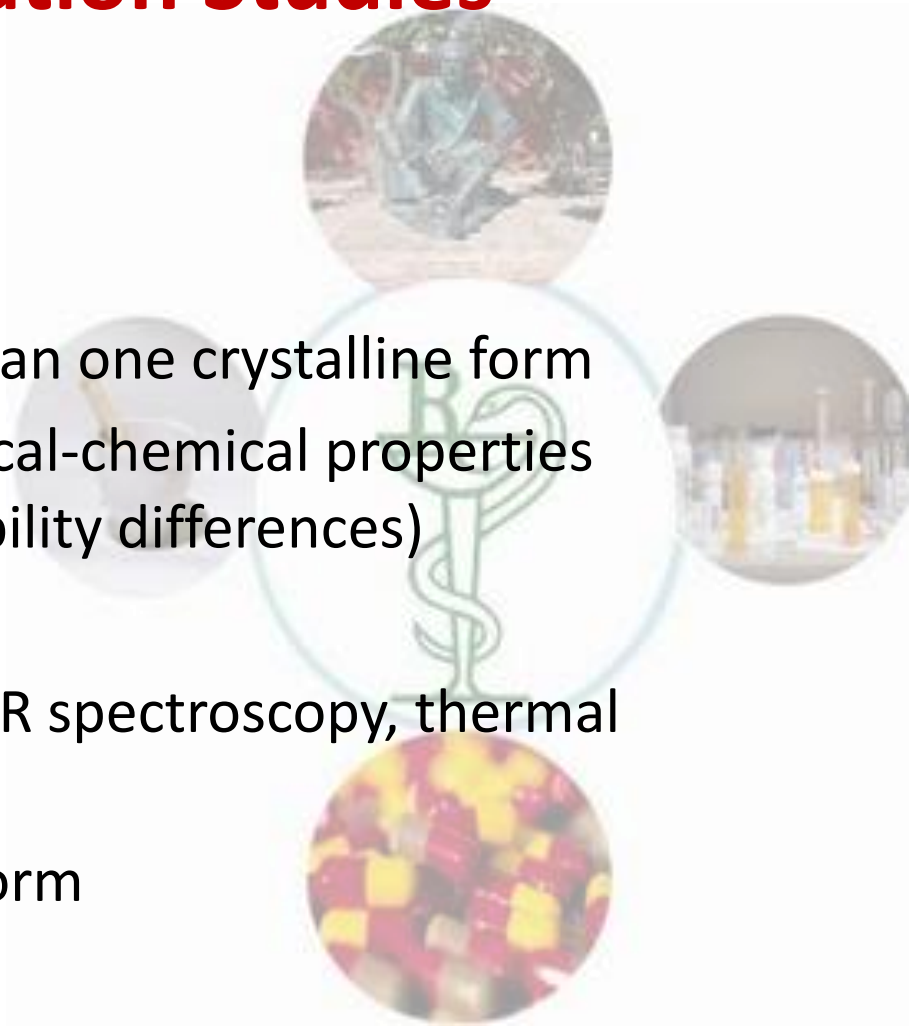
2.1. Preformulation Studies

5. Particle Size Particle Size Distribution

- Dissolution rate
- Bioavailability
- Content uniformity
- Taste
- Color
- Stability
- Flow characteristics
- Sedimentation rates



2.1. Preformulation Studies



6. Polymorphism

- substances can exist in more than one crystalline form
- Polymorphic forms – diff. physical-chemical properties (Melting point variation & Solubility differences)
- Evaluation of:

*crystal structure (microscopy, IR spectroscopy, thermal analysis, x-ray diffraction)

*polymorphism & *solvate form

2.1. Preformulation Studies

7. Solubility

- 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.**
- Chemical **modification of the drug** into salt or ester forms is frequently used to increase solubility

9. Solubility and Particle Size

10. Solubility and pH

2.1. Preformulation Studies

11. Dissolution

Dissolution is the process by which a solid solute enters a solution. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition.

Dissolution is dependent on many factors, both ***intrinsic and extrinsic***. The definition of intrinsic dissolution rate, IDR (**Intrinsic Dissolution Rate)** is the dissolution rate when extrinsic factors are held **constant** for a pure substance.

IDR is influenced by Intrinsic factors

- Crystal habit
- Crystallinity
- Polymorphism
- Pseudo-polymorphism
- Particle size and surface area

extrinsic factors

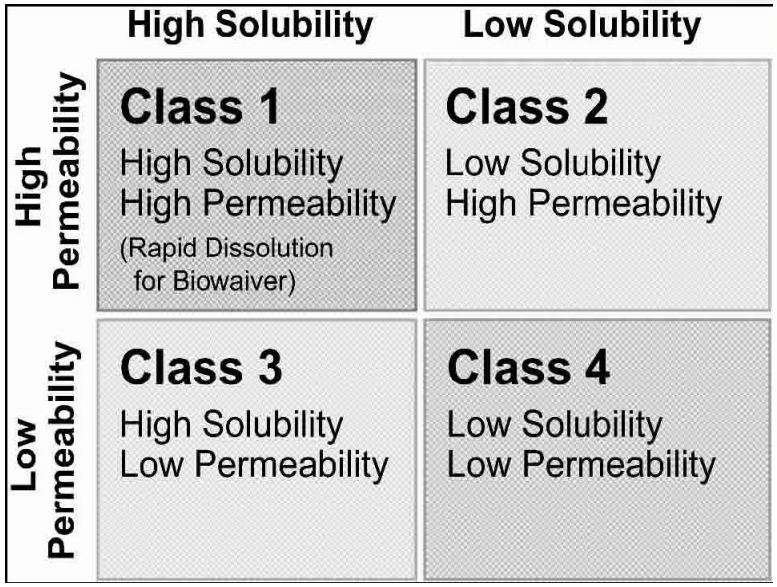
Agitation

- Surface area of tablet or sample
- Temperature
- pH
- Buffer strength
- Viscosity of the dissolution medium
- Ionic strength of the dissolution medium

2.1. Preformulation Studies

12. Dissolution

Solubility is based on the **highest dose strength** and is considered highly soluble if soluble in **250 mL** or less of aqueous media over the **pH range of 1.0-7.5**, otherwise considered to be poorly soluble.



2.1. Preformulation Studies

11. Dissolution

❖ **time for the drug to dissolve** in the fluids at the absorption site

⟹ rate-limiting step in absorption

❖ Dissolution rate of drugs - increased by

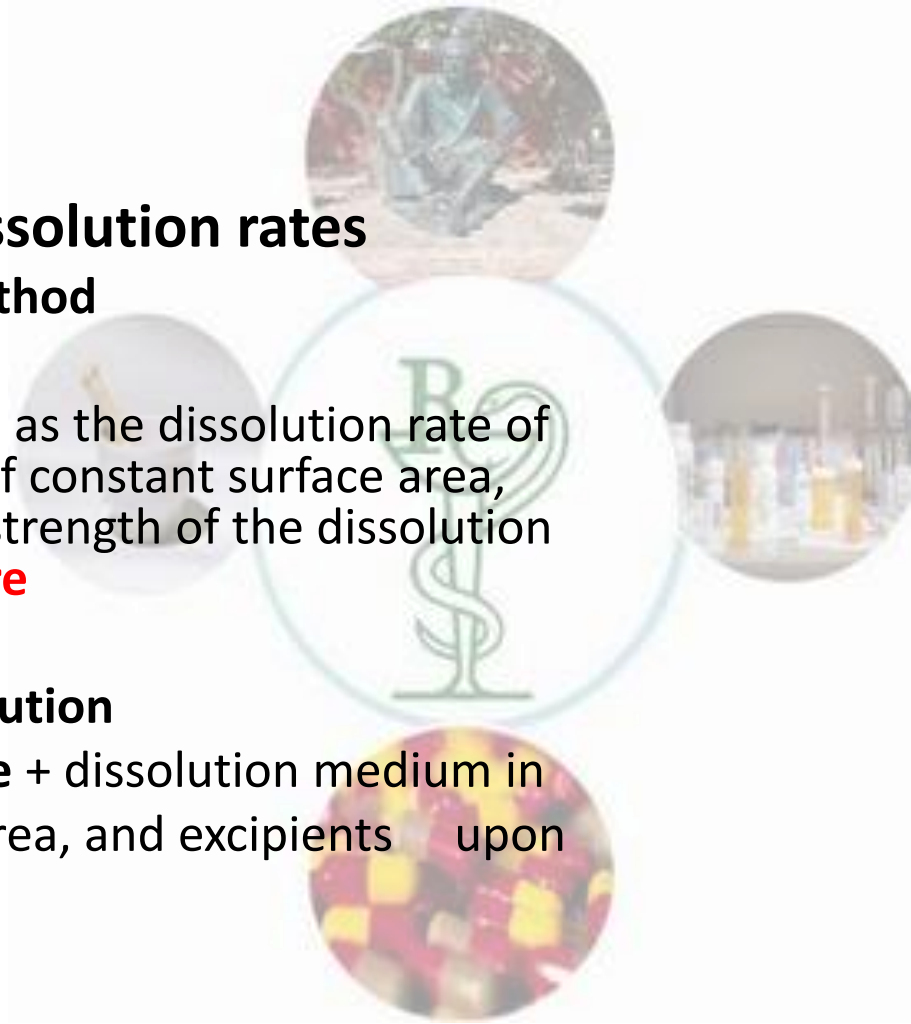
✓ ***decreasing the particle size.***

✓ ***increasing its solubility in diffusion layer***

✓ ***use a highly water soluble salt of the parent substance***.

2.1. Preformulation Studies

11. Dissolution



2 methods in determining dissolution rates

1.Constant surface method

- **intrinsic dissolution rate** of the agent
- The intrinsic dissolution rate is defined as the dissolution rate of pure substances under the condition of constant surface area, agitation-stirring speed, pH and ionic-strength of the dissolution medium. **mg dissolved/min/cm square**

2.**Particulate dissolution**

- **Weighted amount of powdered sample** + dissolution medium in
  - influence of particle size, surface area, and excipients upon the active agent

rotating disc method

2.1. Preformulation Studies

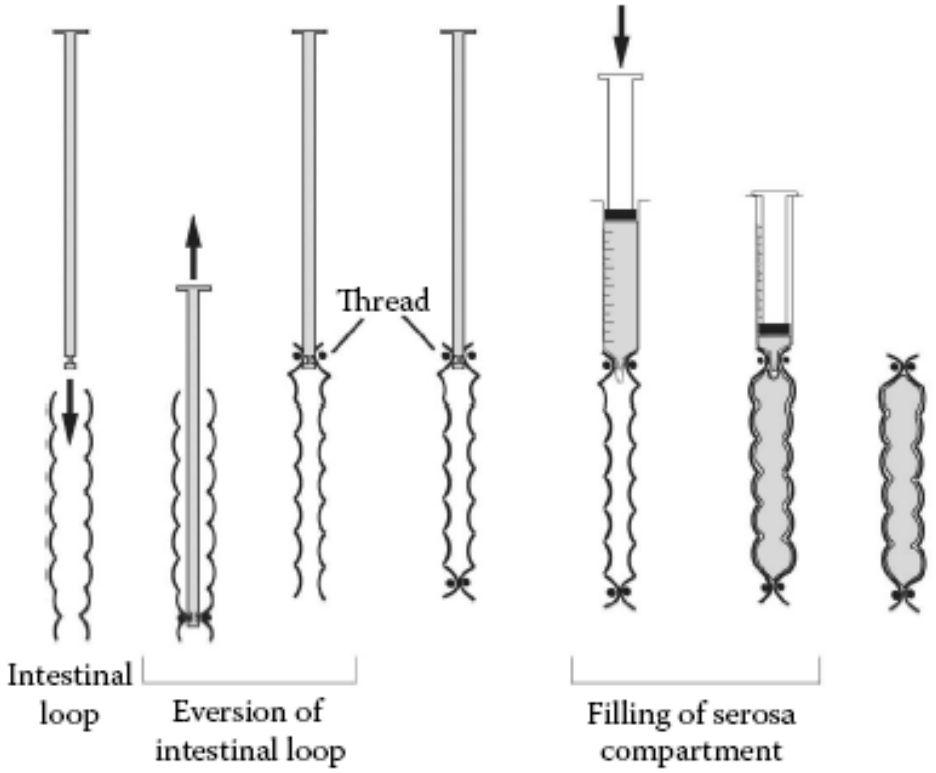
12. Membrane Permeability

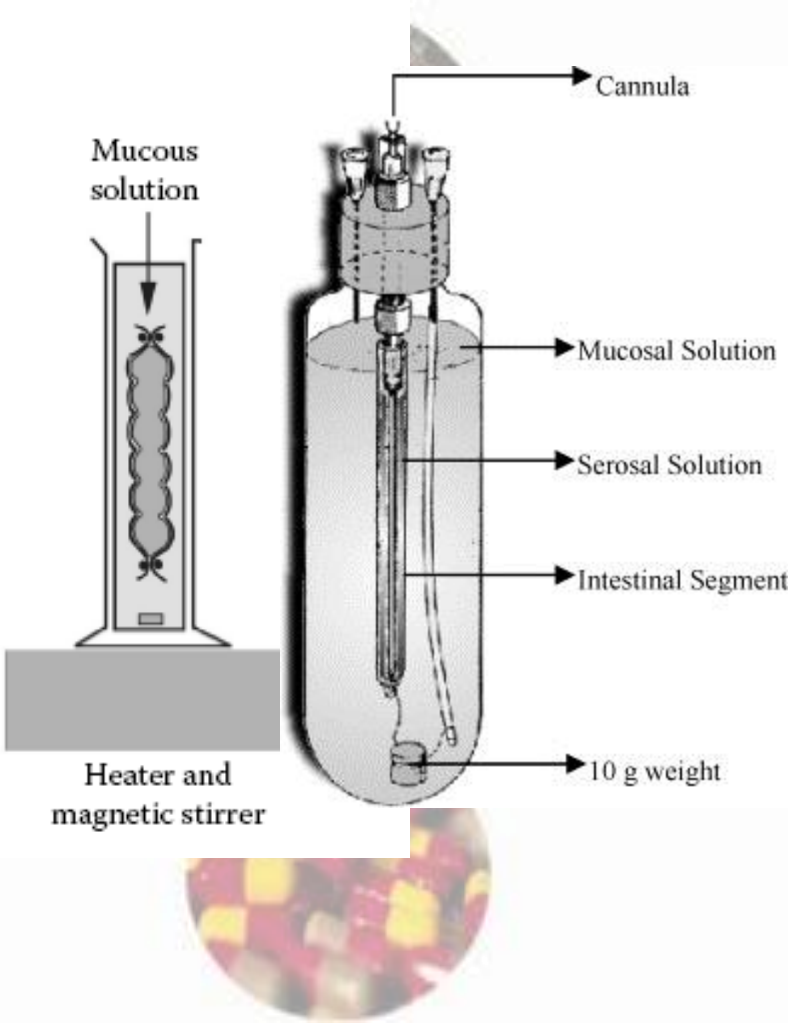
The drug molecule must first cross a biologic membrane. The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of **lipid-soluble substances by passive diffusion**, while **lipid insoluble substances** can diffuse across the barrier only with considerable difficulty

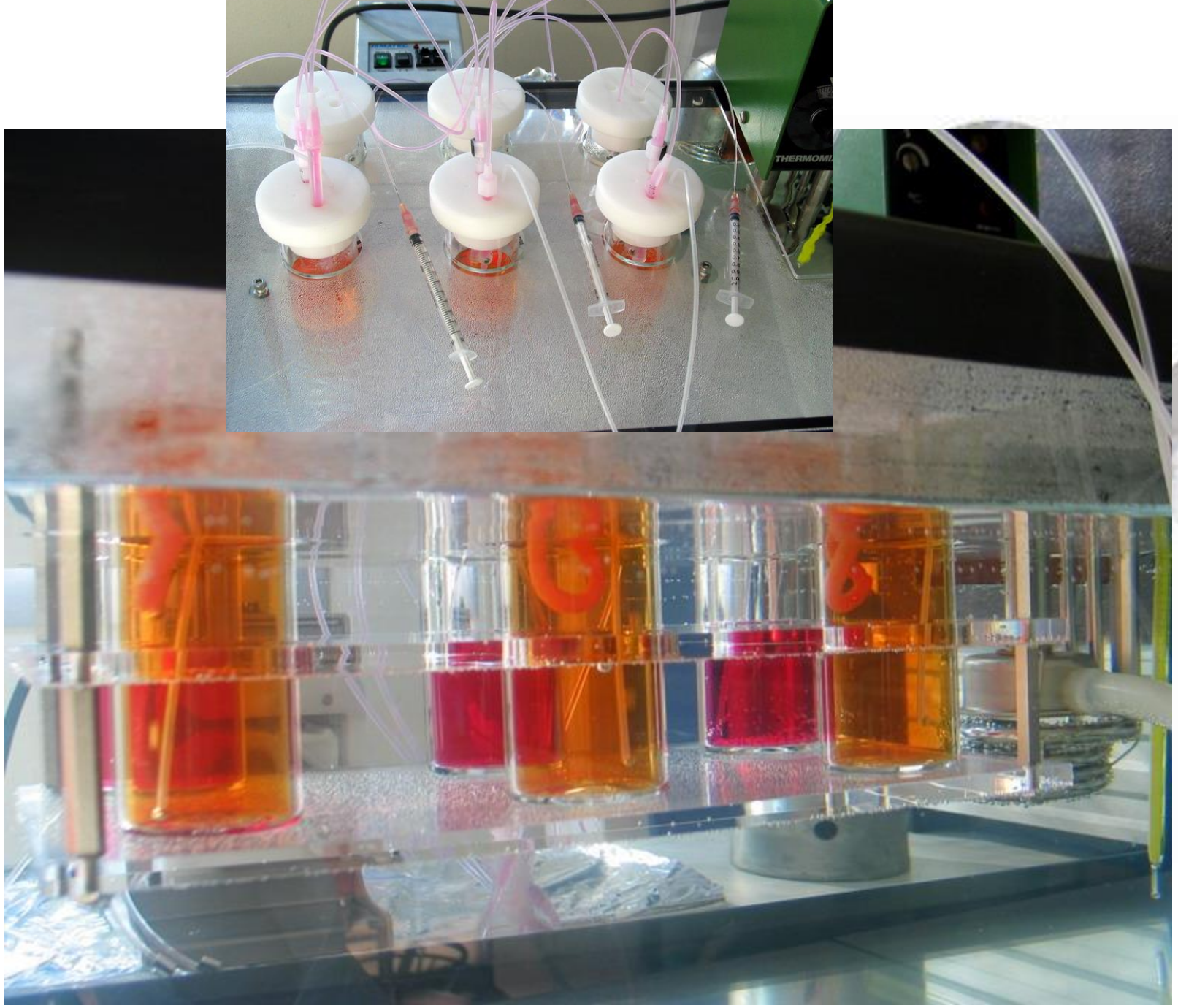
pKa, solubility, and dissolution rate data can provide an indication of absorption

Everted intestinal sac may be used to evaluate absorption characteristics of drug substances.

2.1. Preformulation Studies

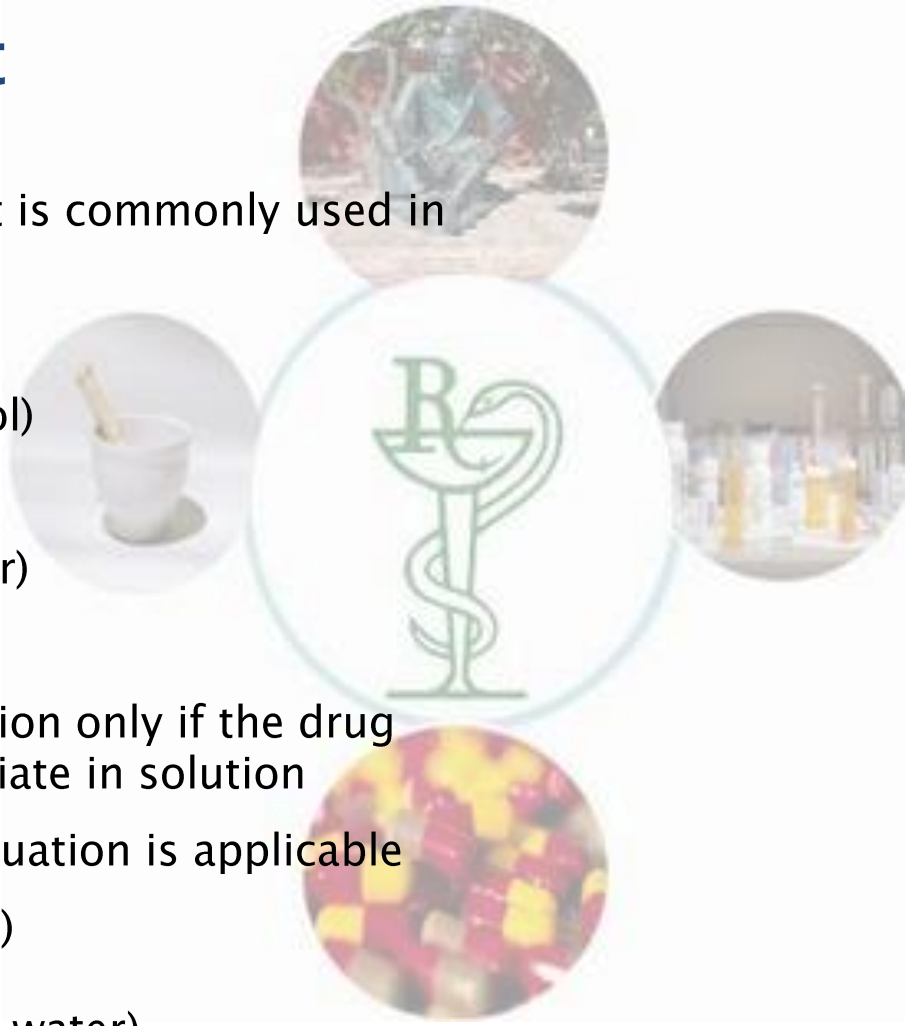






2.1. Preformulation Studies

13. Partition Coefficient



@ the octanol water partition coefficient is commonly used in formulation development

$$@ \quad P = \frac{\text{(conc. of drug in octanol)}}{\text{(conc. Of drug in water)}}$$

P depends on the drug concentration only if the drug molecules have tendency to associate in solution

@ in an ionizable drug, the following equation is applicable

$$P = \frac{\text{(conc. Of drug in octanol)}}{[1-\alpha\ ]\ \text{(conc. Of drug in water)}}$$

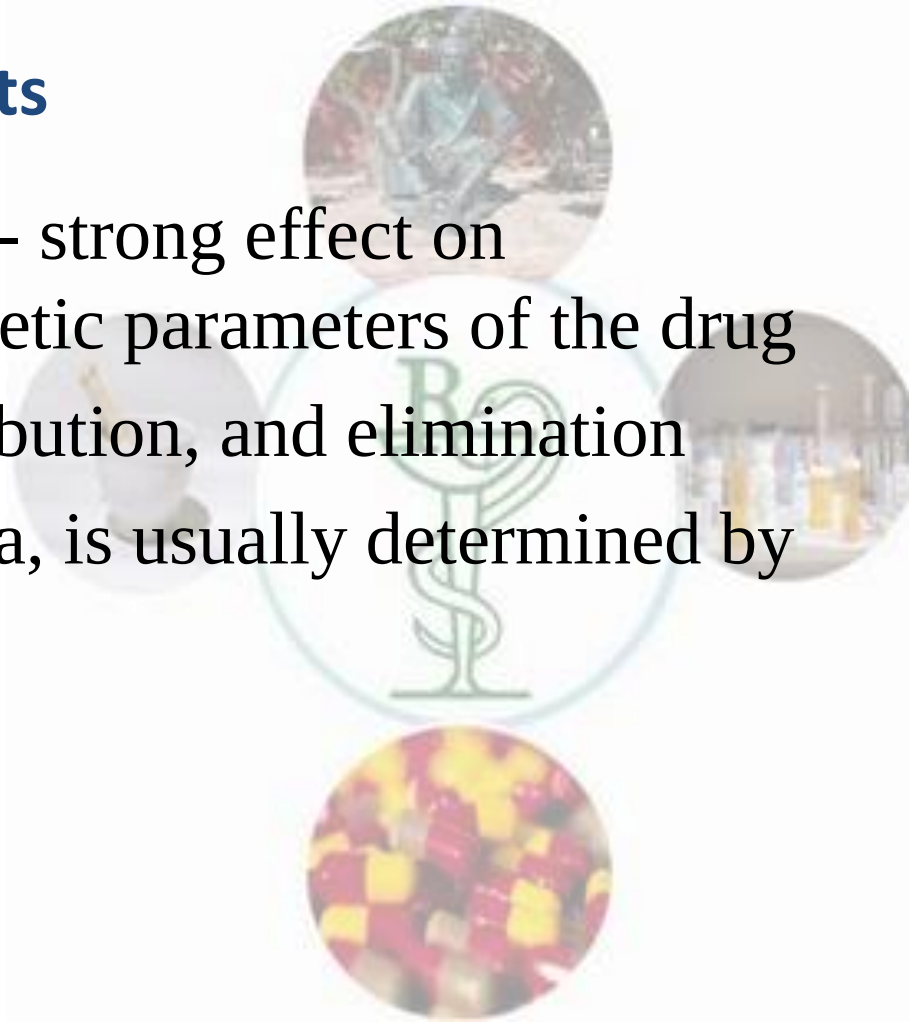
where α equals the degree of ionization

•

2.1. Preformulation Studies

14. pKa/Dissociation Constants

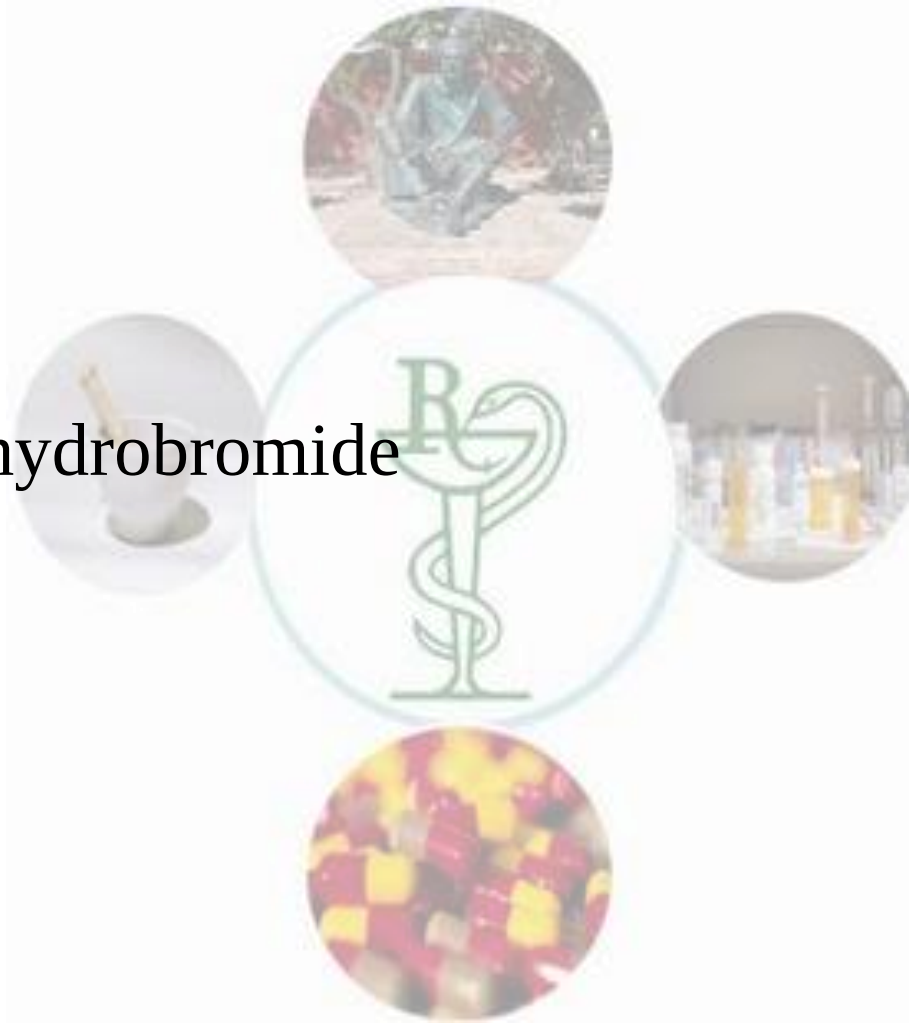
- extent of ionization of drug - strong effect on formulation & pharmacokinetic parameters of the drug
- Can affect absorption, distribution, and elimination
- dissociation constant, or pKa, is usually determined by **potentiometric titration.**



2.1. Preformulation Studies

15. Hydrates and Solveates

- Hydroscopic
- Deliquescent
- Efflorescent : scopolamine hydrobromide



2.1. Preformulation Studies

16. Organic Salt

2.2 Drug and Drug Product Stability

- Physical stability
- Chemical stability
- Shelf life of 2-3 years is generally desired

extent a product retains within specified limits and through its period of storage and use

Stability studies conducted in the preformulation phase:

Solid-state of the drug alone (active stability)

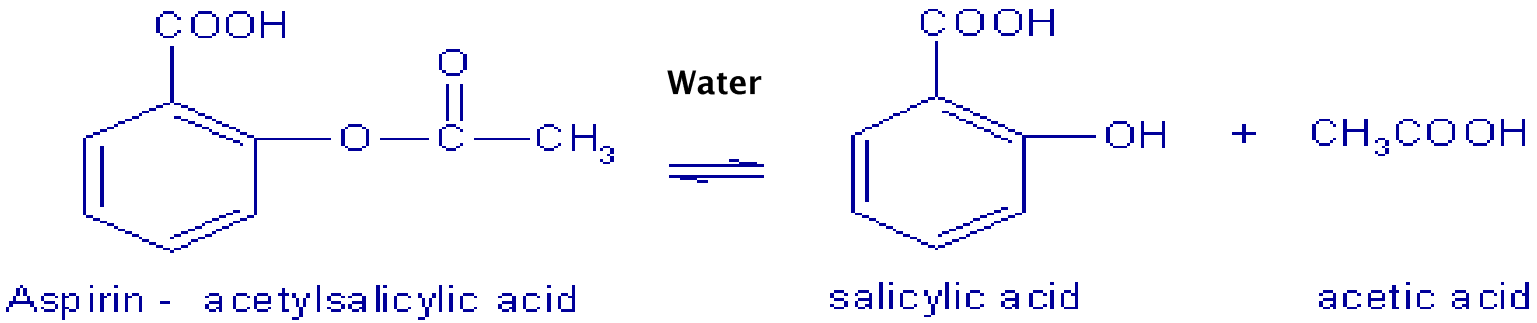
Solution phase (Accelerated)

with the expected excipients (incompatibility)

2.2 Drug and Drug Product Stability

Drug Stability: Mechanisms of Degradation

1-Hydrolysis (solvolysis process)
(drug) molecules interact with water molecule to yield breakdown product of different chemical constitution.



Great number of actives are esters or contain groups : amides, lactones, and lactams → hydrolysis

2.2 Drug and Drug Product Stability

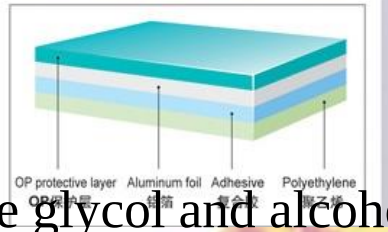
Some Functional Groups Subject to Hydrolysis

Drug type	Examples
Esters	Aspirin, alkaloids Dexmethasne sodium phosphate Nitroglycerin
Lactones	Pilocarpine Spironolactone
Amides	Chloramphenicol
Lactams	Penicillins Cephalosporins

2.2 Drug and Drug Product Stability

Drug Stability: Mechanisms of Degradation

So stabilize such preparation



1. Apply **waterproof** protective coating over the tablets
2. Enclose tablets in tightly close container

In case of liquid formulation

1. The use of anhydrous vegetable oils as vehicle
2. Substituting liquids such as glycerin, propylene glycol and alcohol for water

- **NOTE:** For certain **unstable antibiotic drugs,** when an aqueous preparation is desired the form for **reconstitution** is supplied then adding a specified volume of **purified water** just before dispensing.

2.2 Drug and Drug Product Stability

Drug Stability: Mechanisms of Degradation

2- OXIDATION

- loss of electrons from an atom or molecule;
- involves **free radicals (**molecules or atoms containing one or more unpaired electrons).
- destructive to: aldehydes, alcohols, phenols, sugars, alkaloids & unsaturated fats & oils

Oxidation occurs when the drug is:

1. **Generally** Not in the dry state
2. Maintained in the presence of oxygen and light
3. Incompatibilities with chemical agents in a formula

2.2 Drug and Drug Product Stability

Some Functional Groups Subject to Autoxidation

Functional group	Examples
Catechols	Catecholamines (dopamine)
Ethers	Diethylether
Thiols	Dimercaprol (BAL)
Thioethers	Chlorpromazine
Carboxylic acids	Fatty acids

2.2 Drug and Drug Product Stability

Remedied by the use of:

1. **Antioxidants** which act by providing electrons and easily available hydrogen atoms that acceptable more readily by the **free radicals**
2. In common practice, **vials and ampules** of easily oxidizable preparations for parenteral use are **packed in sealed container with inert gas nitrogen** replacing oxygen during process.
3. Protection from **light by using light resistant glass container**
4. **Storage in a cool place** for drugs affected by increase in temperature

2.2 Drug and Drug Product Stability

Drug Stability: Mechanisms of Degradation

3- Photolysis (Photo stability)

It means: decomposition by light

e.g. Sodium nitroprusside is administered by intravenous infusion for the management of acute hypertension.

If the solution is protected from light, it is stable for at **least 1 year**; if exposed to normal room light, it has a shelf life of only **4 hours.**

2.2 Drug and Drug Product Stability

Drug Stability: Mechanisms of Degradation

Relationship between wavelength and associated energy of various forms of light.

Type of radiation	Wavelength	Energy
U.V.	50 – 400	Kcal mol-1
Visible	400 – 750	287 – 72
I.r. (Infrared radiation)	750 – 10,000	36 - 1

2.2 Drug and Drug Product Stability

- **Photolysis is prevented by:**

1- suitable packing in amber colored bottles

2- packed in cardboard outers ????

3- aluminum foil over wraps

2.2 Drug and Drug Product Stability

Drug and Drug Product Stability: Kinetics and Shelf Life

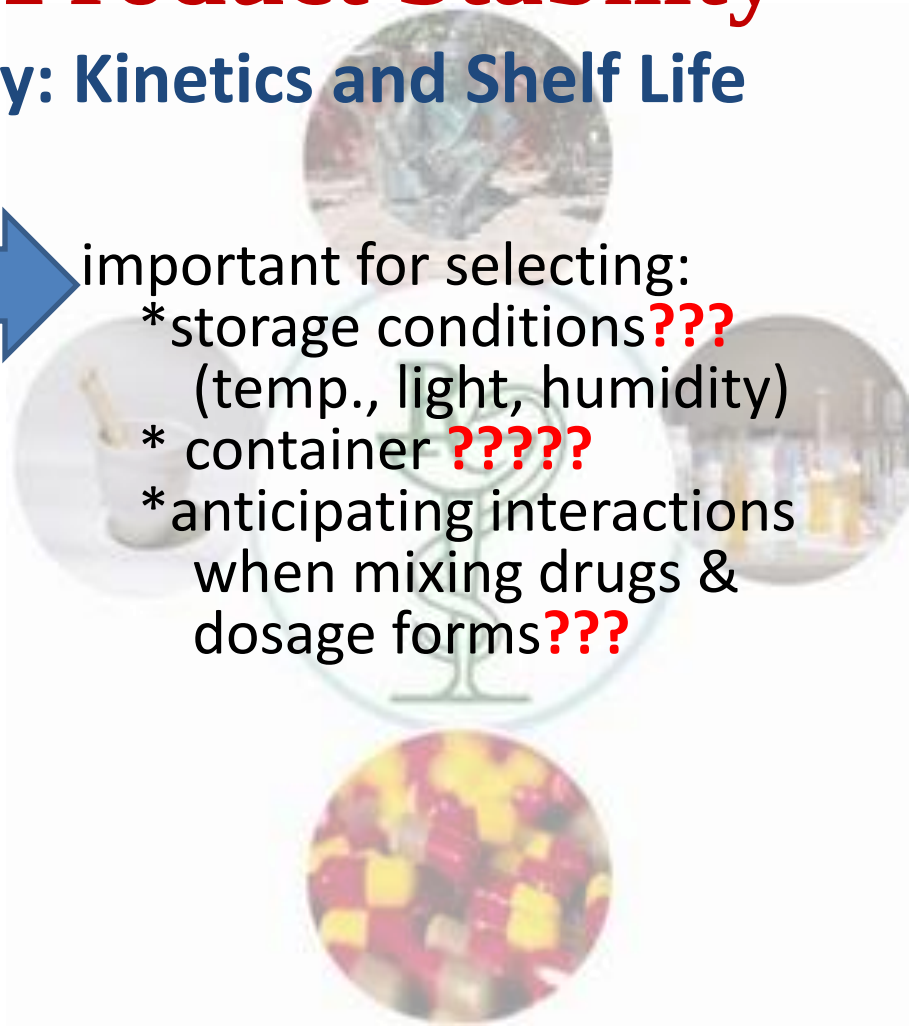
1. Chemical stability
2. Physical stability
3. Microbiological stability
4. Therapeutic stability
5. Toxicologic stability

important for selecting:

*storage conditions???
(temp., light, humidity)

* container ?????

*anticipating interactions when mixing drugs & dosage forms???



2.2 Drug and Drug Product Stability

Rate of reactions

❖ The reaction rate is description of the drug concentration with respect to time. Most commonly, **zero-order and first-order** reactions are encountered in pharmacy

❖If the loss of drug is independent of the concentration of the reactants and constant with respect to time (I.e 1 mg/mL/hour) the rate is **called zero order.**

❖ If the loss of drug is direct proportional to the concentration remaining with respect to time, it is called a **first-order reaction** and has the units of reciprocal time that is, time^{-1}.

2.2 Drug and Drug Product Stability

1) Definition of drug stability and drug kinetics

Stability Study

It is defined as the study of the extent to which the properties of a drug substance or drug product remain within specified limits at **certain conditions** . Properties may be physical, chemical, microbiological, toxicological or performance properties such as disintegration and dissolution**.**

Drug Kinetics : Change of drug concentration with respect to time

Accelerated Stability Testing

Studies designed to increase the rate of chemical or physical degradation by using exaggerated storage conditions

Expiration Date

The FDA defines an expiration date as "the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf life specifications if stored under defined conditions, and after which it **may** not be used."

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2.2 Drug and Drug Product Stability

Rate of reactions

Importance of studying kinetics

It determines:

- ✓ **Stability of drugs ($t_{1/2}$)**
- ✓ **Shelf life (($t_{0.9}$)**
- ✓ **Expiration date**

<u>Stability of drugs ($t_{1/2}$)</u>

The half life ($t_{1/2}$) is defined as the time necessary for a drug to decay **by** 50% (e.g., From 100% to 50%, 50% to 25%, 20% to10%)

<u>Shelf life ($t_{0.9}$)</u>

It is defined as the time necessary for the drug to decay **to** 90% of its original concentration.

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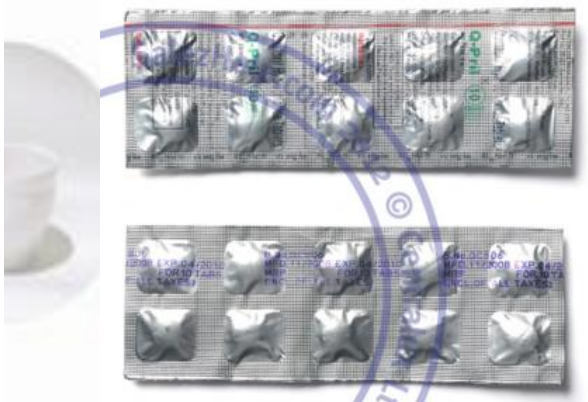
Enhancing Stability of Drug Products

1-Hyrdolysis

- Solid dosage form

water reduced or eliminated from the system.



- *liquid dosage form
  - **water replaced by glycerin, propylene glycol, oils……..**
  - **suspending them in nonaqueous vehicle**

Enhancing Stability of Drug Products

1-Hyrdolysis

- For unstable antibiotic drugs (aq. prepn desired)

  - supplied in dry form for reconstitution before dispensing

AUGMENTIN ORAL SUSPENSION (reconstituted suspension): store between 2-8°C in a refrigerator (but do not freeze). Under these conditions the shelf life is 7 days.

- For unstable preparations: storage under refrigeration
- pH – major determinant in stability

  - optimum stability: pH 5 & 6

  - buffering agents increases stability

Medical-grade refrigerators are manufactured using substantial, high quality materials and undergo thorough testing for their intended use. Stainless steel housings, synthetic gaskets, and efficient compressors enable a quick return to the programmed temperature after the refrigerators or freezers are opened.

Enhancing Stability of Drug Products

1-Oxidation

- prepared in dry state
- packaged in sealed containers with air replaced by inert gas (Nitrogen, carbon dioxide).
- add antioxidants

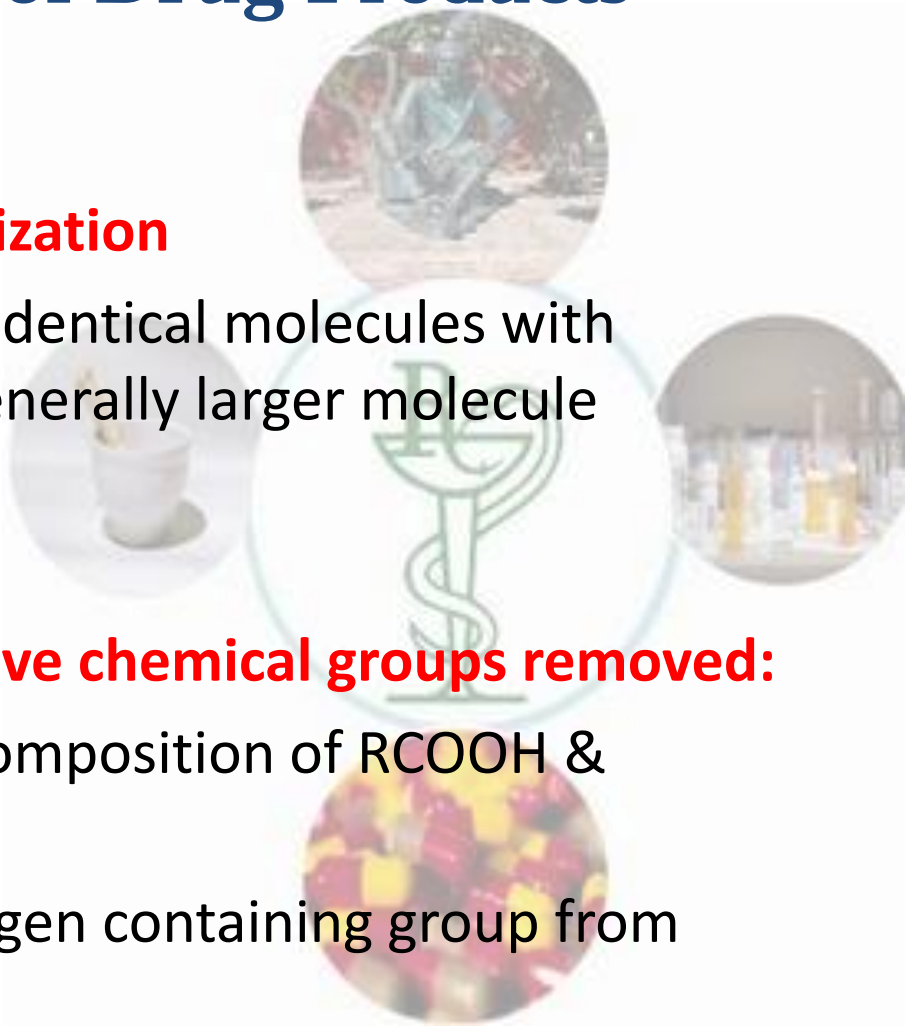
Antioxidants commonly used for	
Aqueous systems	**Oil systems**
Sodium sulfite hight pH Sodium bisulfte interm. pH Sodium metabisulfite low pH Sodium thiosulfate Ascorbic acid	Ascorbyl palmitate Butylaled hydroxy toluene Butylated hydroxy anisole Alpha-tocopherol

Enhancing Stability of Drug Products

2-Oxidation

- trace metals in drug, solvent, container or stopper
  - source of difficulty in preparing stable solution of oxidizable drugs
  - eliminated by:
    *purification of source of contaminant
    *complexing or binding metal by using specialized agents (chelating agents- Ca disodium edetate & EDTA)
- Light
  - catalyst to oxidation reactions
  - preparations packaged in light resistant or opaque containers

Enhancing Stability of Drug Products



3-Polymerization

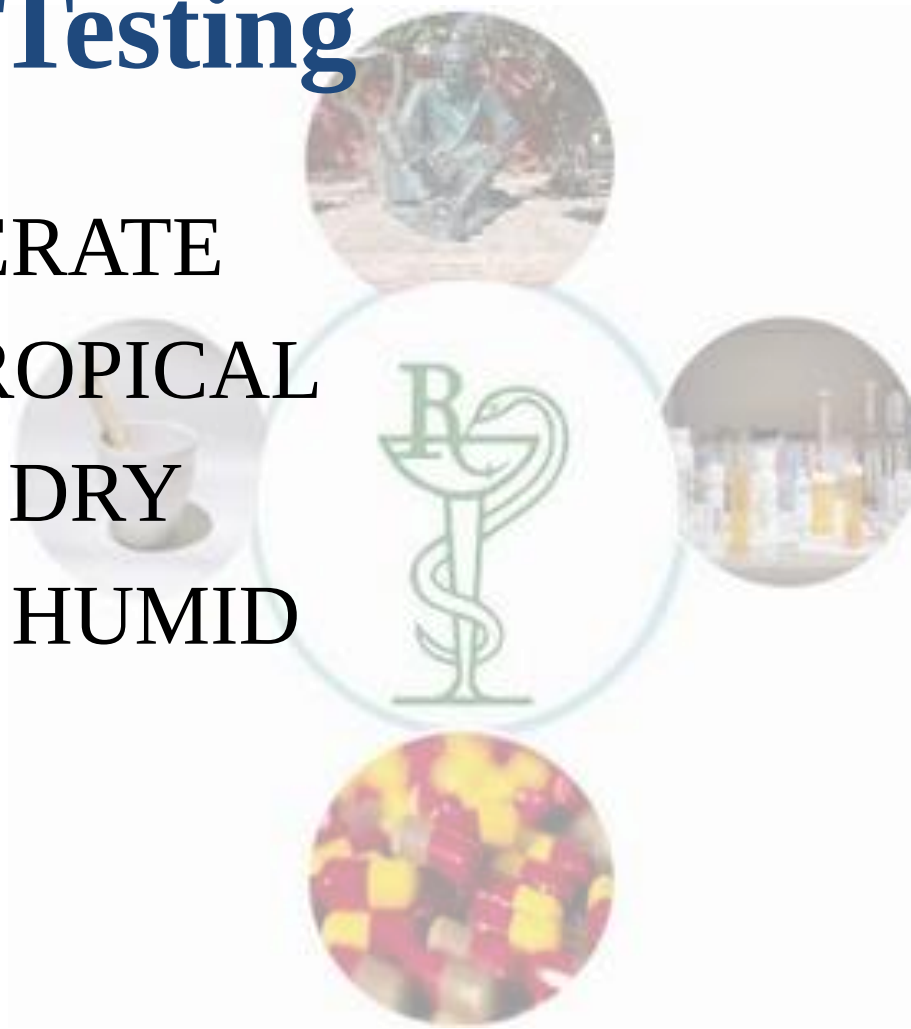
- reaction between two or more identical molecules with resultant formation of new & generally larger molecule (formaldhyde)

4-Process where one or more active chemical groups removed:

- Chemical decarboxylation (decomposition of RCOOH & release of CO2)
- Deamination (- removal of nitrogen containing group from organic amine (ex. Insulin))

Stability Testing

- ZONE I TEMPERATE
- ZONE II SUBTROPICAL
- ZONE III HOT & DRY
- ZONE IV HOT & HUMID



Study	Storage condition	Minimum time period covered by data at submission
Long-term[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as described in point 2.1.7
Intermediate[b]	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored (see Appendix 1). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH.

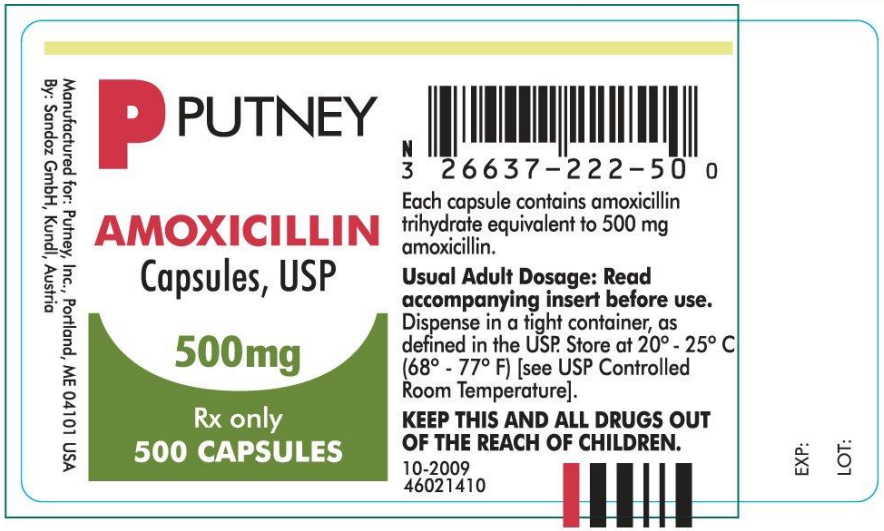
[b] If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months
Accelerated[a]	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

[a] Whether accelerated stability studies are performed at 25 ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe long-term condition can be an alternative to storage testing at 25 °C/60%RH or 30 °C/65%RH.

Responsibility of the Pharmacist

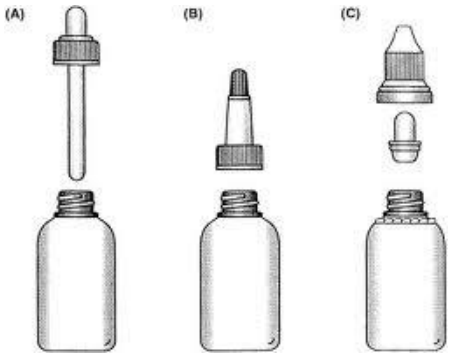
- Dispense oldest stock first and observe expiration dates.
- Store products under conditions stated in USP monographs and/or labeling.



- Observe products for evidence of instability.
- Properly treat/label products that are repackaged, diluted, or mixed with other products.

Responsibility of the Pharmacist

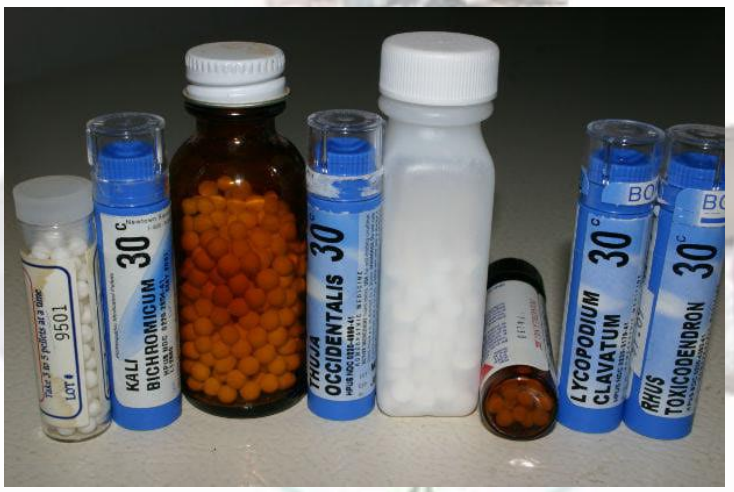
- Dispensing in proper container with proper closure



- Informing/educating patients concerning proper storage and use of products

PHARMACIST:

PHARMACIST:



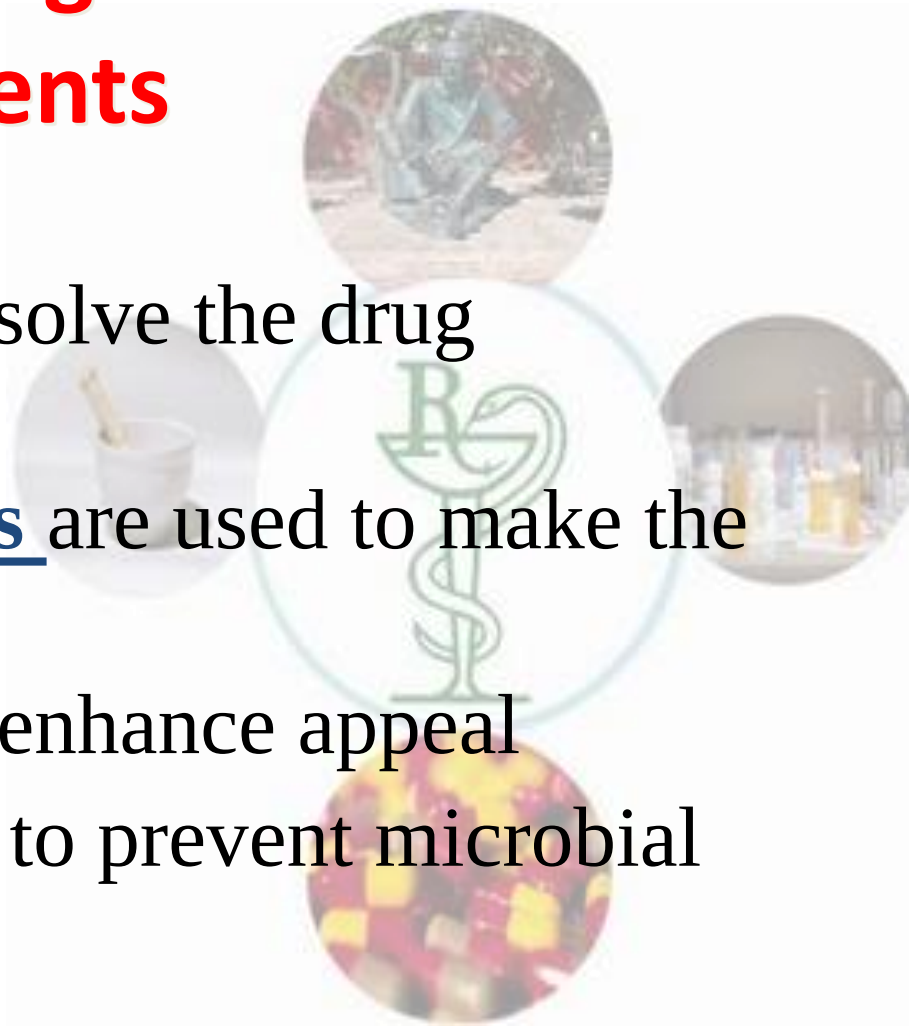
Pharmaceutical Ingredients and Excipients

Pharmaceutical ingredients added to prepare a dosage form

Pharmaceutical Ingredients and Excipients

Definition of terms

- **Solvents** are used to dissolve the drug substance.
- **Flavors and sweeteners** are used to make the product more palatable
- **Colorants** are added to enhance appeal
- **Preservatives** are used to prevent microbial growth



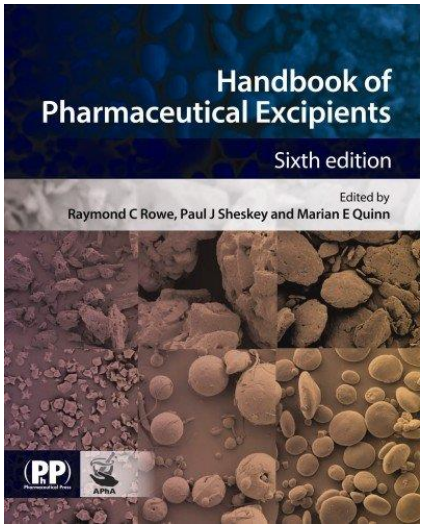
Pharmaceutical Ingredients and Excipients

- **Stabilizers (antioxidants and chelating)** - to prevent decomposition.
- **Diluents or fillers** - to increase the bulk of the formulation.
- **Binders** – to cause adhesion of the powdered drug and pharmaceutical substances.
- **Antiadherents or lubricants** to assist smooth tablet formation
- **Disintegrating agents** - promote tablet break up after administration
- **Glidants**: to increase flowability
- **Coatings** to improve stability, control disintegration or enhance appearance..

Pharmaceutical Ingredients and Excipients

- Coloring agents
- Sweetening agents
- Flavoring agents
- Surfactants
- Solubilizing agents
- Antioxidants
- Preservatives
- Thickening agents
- Suspending agents
- Binding agents
- Solvents
- Lubricants
- Perfumes
- Fats and oils

Pharmaceutical Ingredients and Excipients



Harmonization of Standards

- International harmonization of excipients
- Pharmaceutical industry is multinational
- Uniform standards needed ????

Inactive Ingredient Database -FDA

INACTIVE INGREDIENT	ROUTE;DOSAGE FORM	CAS NUMBER	UNII	MAXIMUM POTENCY
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, COATED			6.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL; TABLET, SUSTAINED ACTION, FILM COATED			54.00MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-21; TABLET			0.75MG
HYPROMELLOSE 2910 (15000 MPA.S)	ORAL-28; TABLET			0.75MG
HYPROMELLOSE 2910 (5 MPA.S)	ORAL; TABLET			2.02MG

Aspartame

7 Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets,[1,2] powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose.

Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.[3]

Aspartame

14 Safety

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetener and is generally regarded as a nontoxic material. However, the use of aspartame has been of some concern owing to the formation of the potentially toxic metabolites methanol, aspartic acid, and phenylalanine. Of these materials, only phenylalanine is produced in sufficient quantities, at normal aspartame intake levels, to cause concern. In the normal healthy individual any phenylalanine produced is harmless, however it is recommended that aspartame be avoided or its intake restricted by those persons with phenylketonuria.[11]

The WHO has set an acceptable daily intake for aspartame at up to 40 mg/kg body-weight.[12] Additionally, the acceptable daily intake of diketopiperazine (an impurity found in aspartame) has been set by the WHO at up to 7.5 mg/kg body-weight.[13]