pharmaceutics

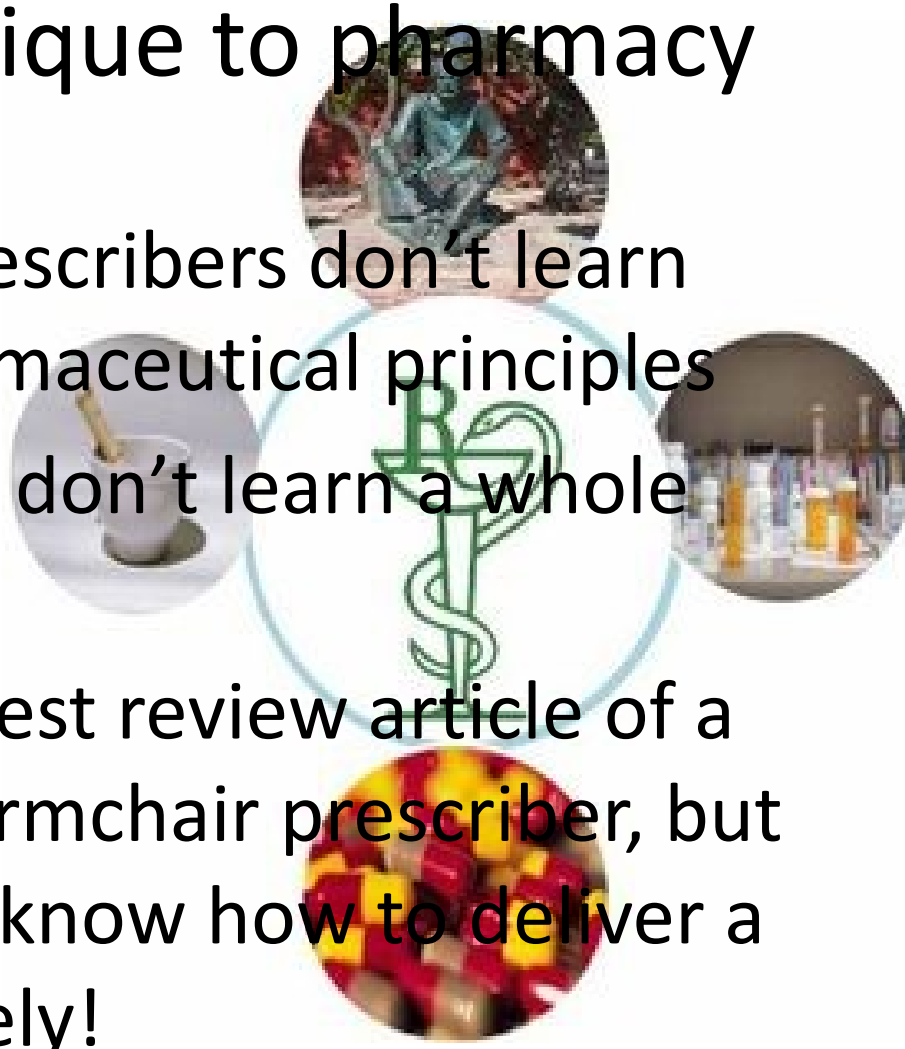
PHAR 331

Dr. Hani Shtaya

What is pharmaceutics?

- 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!

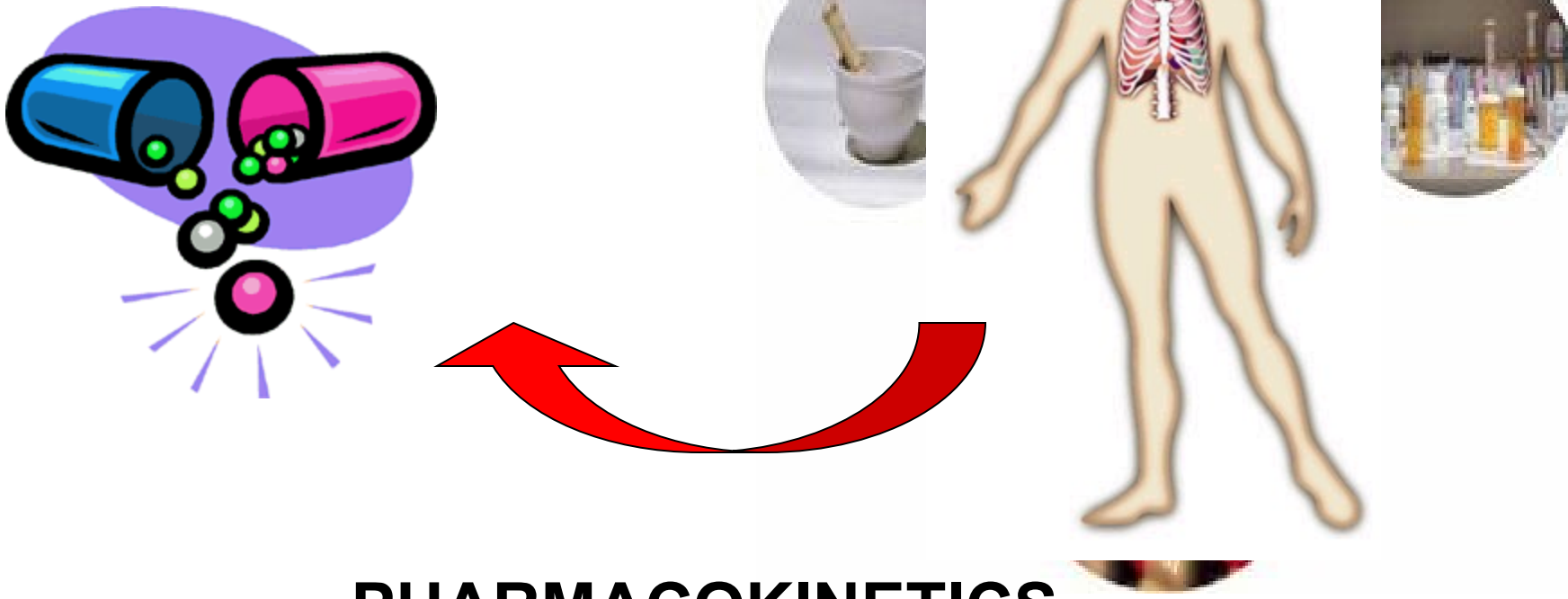
Pharmaceutics is unique to pharmacy



- 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)

From drug substance to pharmaceutical preparation

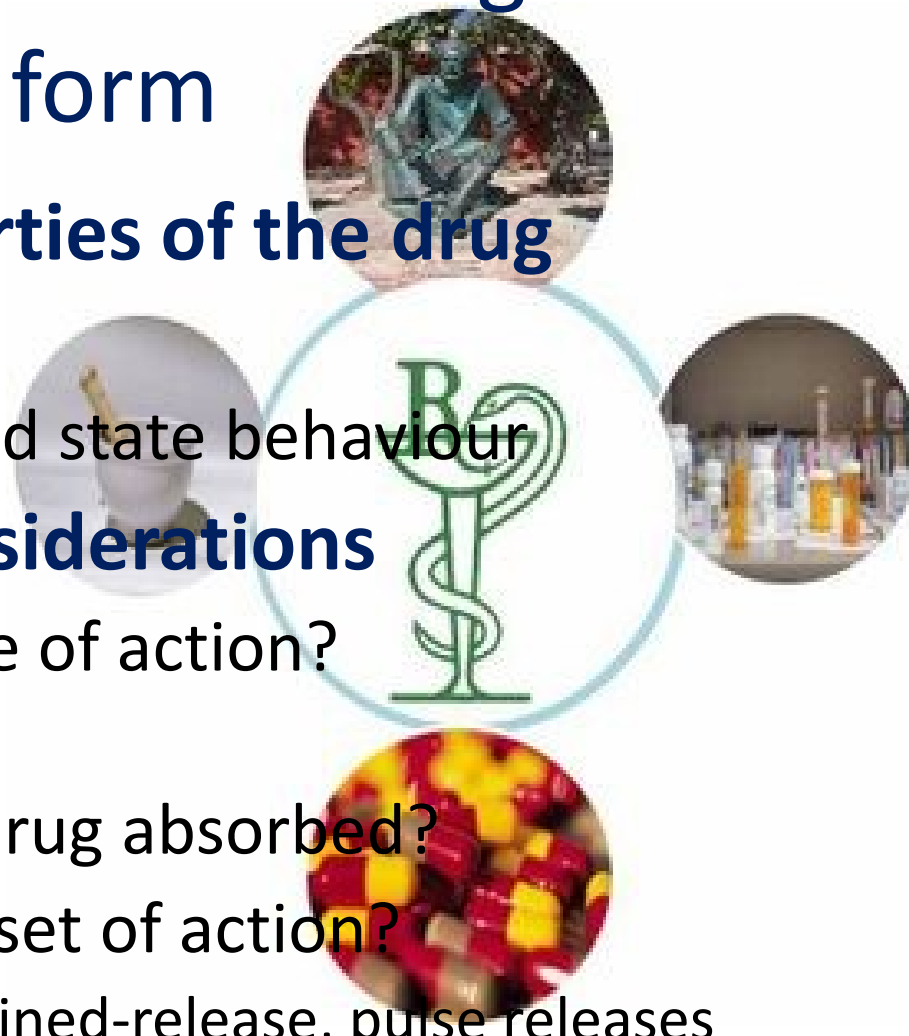
- Pharmaceutical dosage form
  - determines the physical form of the final pharmaceutical preparation
  - is a drug delivery system which is formed by technological processing (drug formulation)
  - must reflect therapeutic intentions, route of administrations, dosing etc.

- Pharmaceutical preparation (PP)
  - particular pharmaceutical product containing active and inactive pharmaceutical ingredients formulated into the particular dosage form.
  - Packed and labelled appropriately
  - Two major types of PP according the origin:
    - Manufactured in large scales by pharmaceutical industry (original and generic preparations)
    - Compounded individually in compounding pharmacies

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?

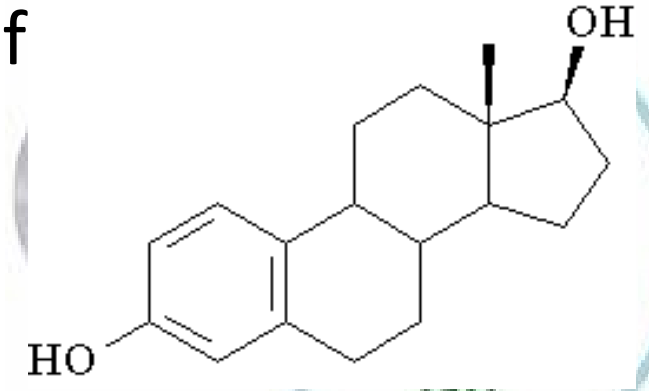
What you must know to design a dosage form



- **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

Example: estrogen

- Indication: hormone replacement therapy for treatment of symptoms of
- Molecule administered is
  - Conjugated estrogens
  - Estradiol
  - Estrone



- Dosage forms
  - Tablets (Estrace®)
  - Transdermal patch (Estraderm®, etc.)
  - Transdermal gel (EstroGel®)
  - Vaginal ring (Estring®)

Some questions

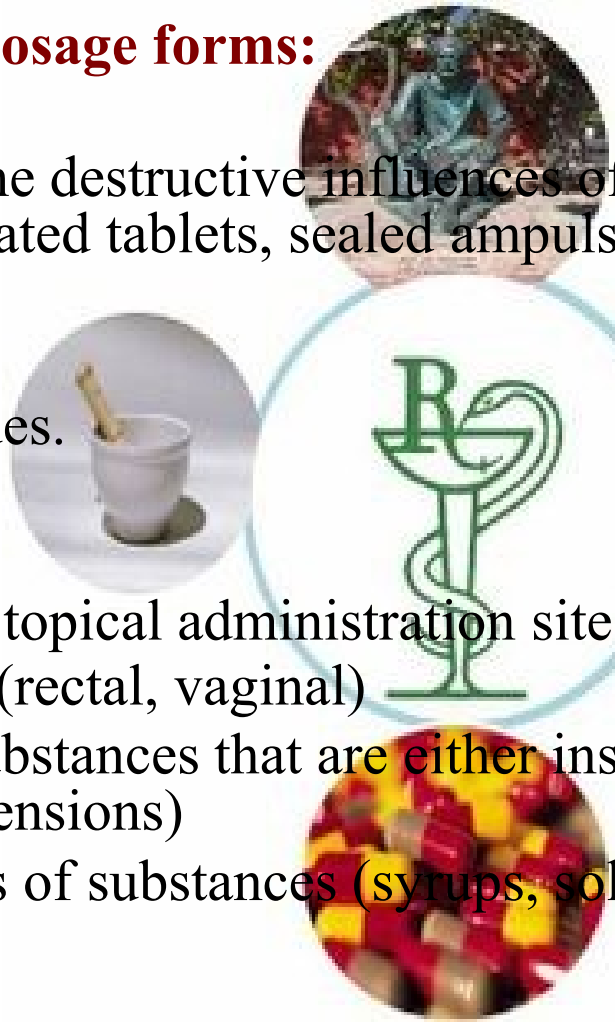
- About the drug
  - Aqueous solubility, pKa, partition coefficient
  - Chemical stability in solution
- About the dosage form
  - Dissolution characteristics
  - Transdermal characteristics
  - Stability in storage
- About the biopharmaceutics
  - Extent of absorption
  - First-pass metabolism
  - Intended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

Each dosage form caters to a different need

- Compressed tablet
  - Contains micronized estradiol
    - Micronization improves dissolution
  - 1 to 2 mg/day po
    - Estradiol is highly metabolized
- Transdermal
  - Bypasses first-pass metabolism
  - Patch: 0.05 to 0.1 mg/day, applied twice weekly
  - Gel: 0.75 mg/day
- Vaginal ring
  - Topical application of estradiol for local symptoms
  - Average 7.5 µg/day × 90 days

Why the drug should be converted into dosage forms ?

The need for dosage forms:



1- Accurate dose.

2- To protect the drug substance from the destructive influences of atmospheric oxygen or humidity (coated tablets, sealed ampuls).

3- Protection from gastric acid.

4- Masking taste and odour.

5- Placement of drugs within body tissues.

6- Sustained release medication.

7- Controlled release medication.

8- To provide optimal drug action from topical administration sites.

9- Insertion of drugs into body cavities (rectal, vaginal)

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

11-To provide clear liquid dosage forms of substances (syrups, solutions)

Types of dosage forms

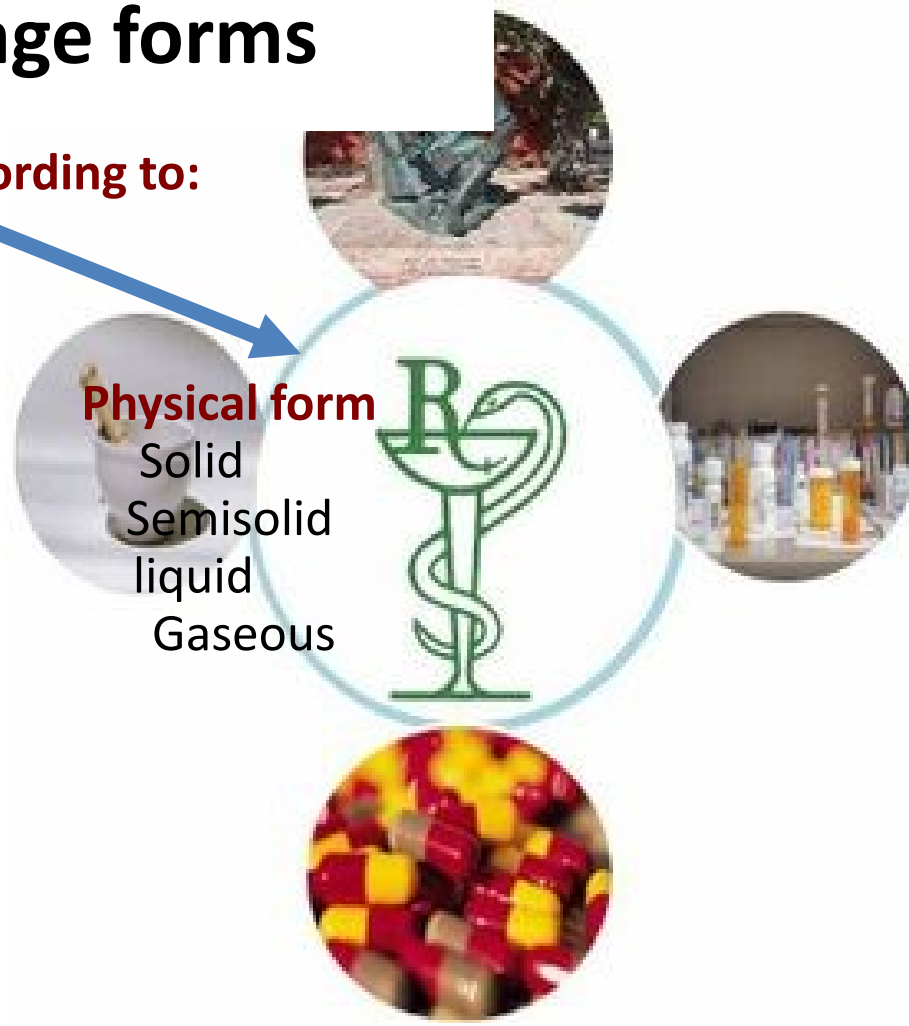
They are classified according to:

Route of administration

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

Physical form

- Solid
- Semisolid
- liquid
- Gaseous



Classification of pharmaceutical dosage forms according to its physical properties

- Dosage forms
  - Homogenous systems
  - Dispersion systems – one phase (dispersed phase) is distributed throughout another one (continuous phase, dispersion medium)
    - According to the size of dispersed particles (1 nm- 0,5 mm) a molecular, colloidal and coarse dispersions can be distinguished
    - May require shaking before administration

- According to the overall physical properties of dosage forms (both homogenous and dispersion systems) one can distinguish
  - Gaseous dosage forms(Aerosols, inhalation)
  - Liquid dosage forms(Ear drops, Elixirs, Syrup…..)
  - Semisolid dosage forms(Creams Jellies Ointments)
  - Solid dosage forms(Tablets ,Suppositories , Capsules ……)
  - Light dosage forms(UV, γ rays….)

Classification of pharmaceutical dosage forms according to the route of administration

- Oral (Powders, tablets, capsules, solutions, emulsions, syrups, elixirs, magmas, gels, cachets, pills.)
- Parenteral (Solutions, suspensions, emulsions.)
  - IV, IM, SC, etc.
- Ophthalmic, otic
- Nasal(Solutions, sprays, inhalations.)
- Rectal, vaginal, urethral (Suppositories, tablets, ointments, creams, douches, foams.)
- Buccal
- Topical
- Transdermal (Ointments, creams, powders, pastes, lotions, plaster)

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

Dosage Form Design: Pharmaceutical and Formulation Considerations
Chapter 4

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

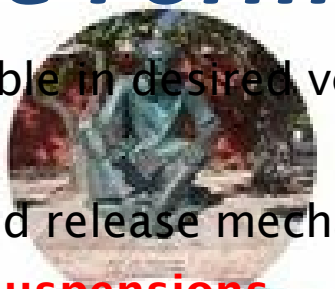
Examples: rectal and vaginal suppositories

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



1- The Need for Dosage Forms

- **Examples Of Drugs with Low Usual doses**

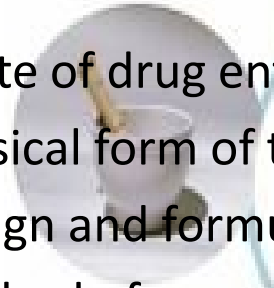
Phenobarbital	**30 mg**	**Sedative**
Diphenhydramine HCl	**25 mg**	**Antihistamine**
Morphine sulfate	**10 mg**	**Narcotic Analgesic**
Digoxin	**0.25 mg**	**Cardiotonic**
Clotrimazole	**10.00**	**Antifungal**
Chlorpheniramine maleate	**4.00**	**Antihistaminic**
Glyburide	**2.50**	**Antidiabetic**
Doxazosin Mesylate	**2.00**	**Antihypertensive**
Levorphanol tartrate	**2.00**	**Narcotic analgesic**

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

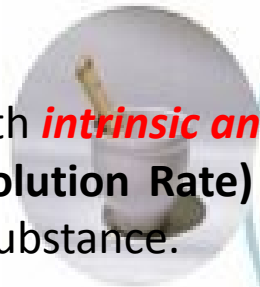
- Effectiveness
- Safety
- Reliability
- Stability
  - Physical
  - Chemical
  - Microbiological

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

2.1. 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

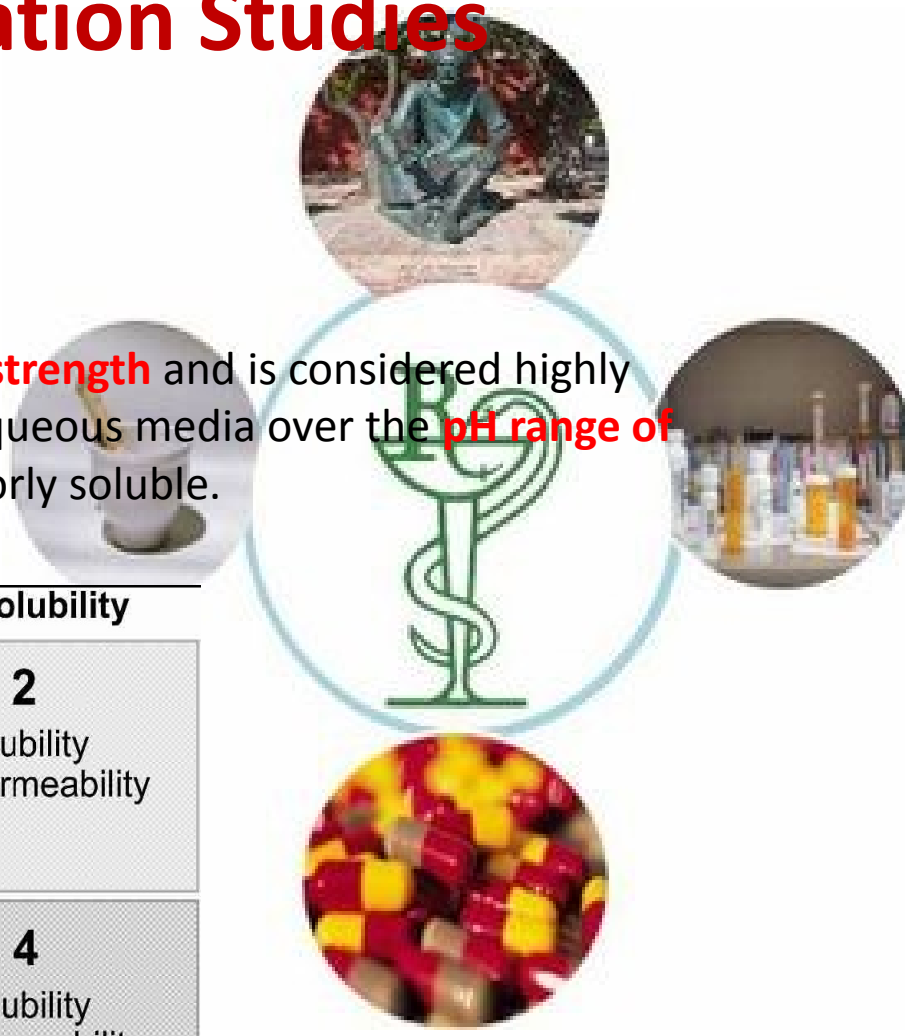
Agitation

- 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

11. Dissolution

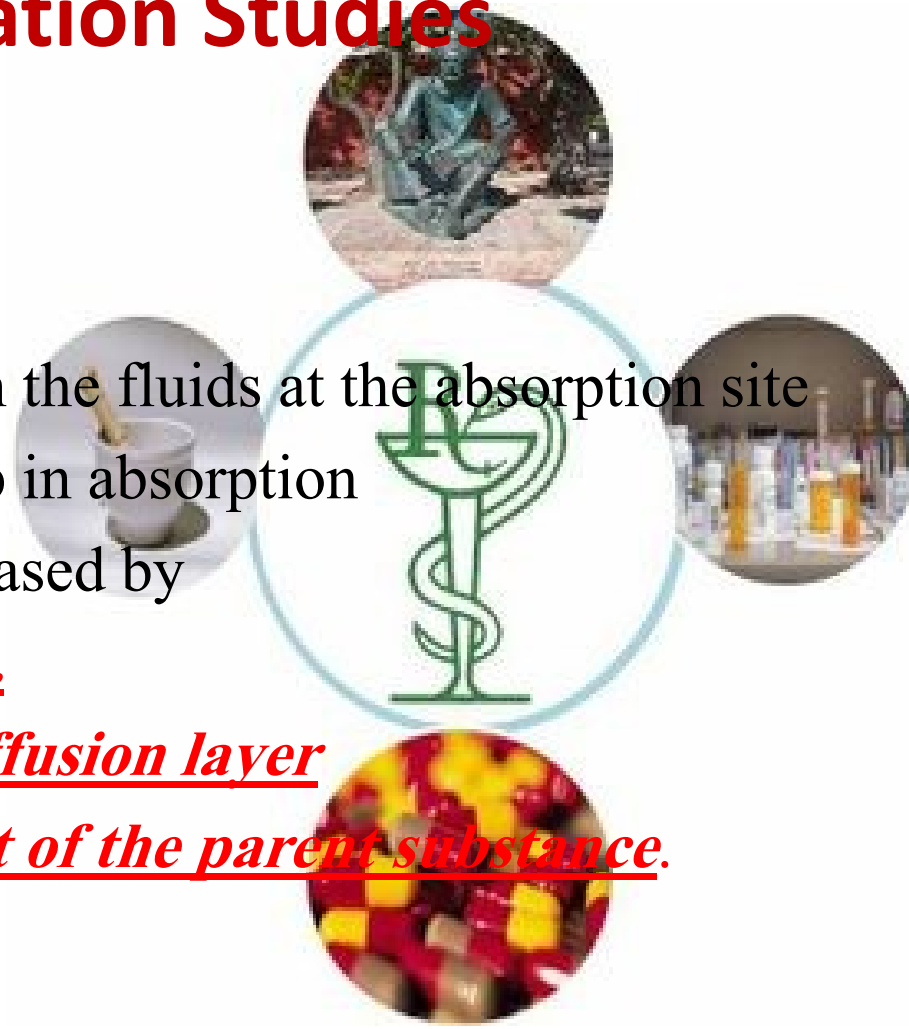
Solubility is based on the **highest dose strength** and is considered highly soluble if soluble in **250 mL** or less of aqueous media over the **pH range of 1.0-7.5**, otherwise considered to be poorly soluble.



	High Solubility	Low Solubility
High Permeability	**Class 1** High Solubility High Permeability (Rapid Dissolution for Biowaiver)	**Class 2** Low Solubility High Permeability
Low Permeability	**Class 3** High Solubility Low Permeability	**Class 4** Low Solubility Low Permeability

2.1. Preformulation Studies

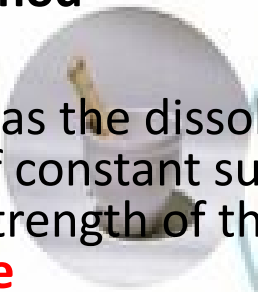
11. Dissolution



- **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

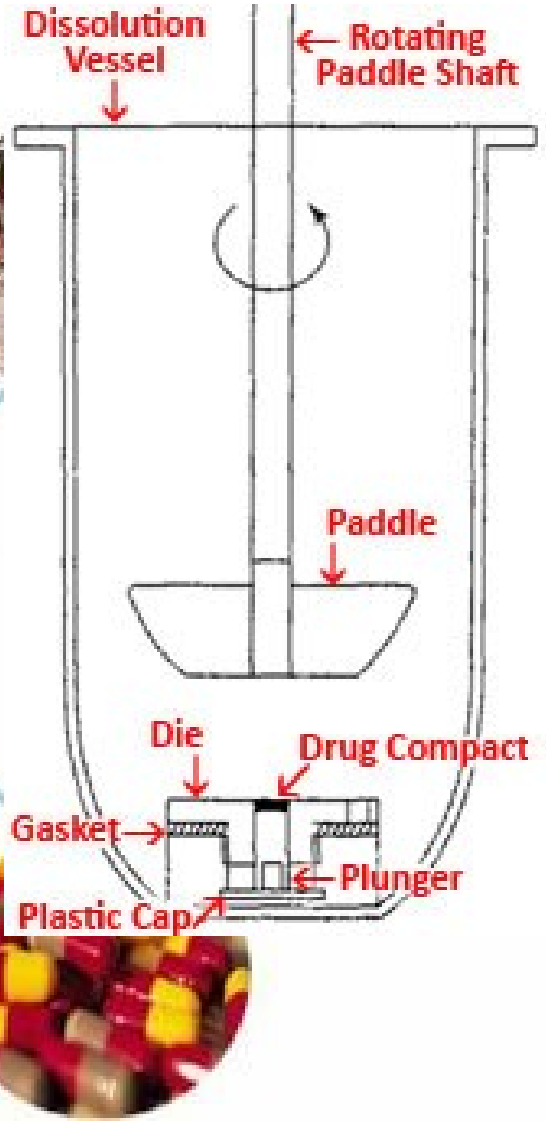
1.Constant surface method

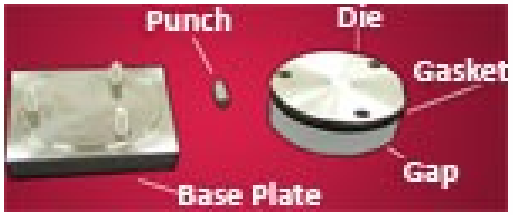
- **intrinsic dissolution rate** of the agent
- The intrinsic dissolution rate is defined as the dissolution rate of pure substances under the condition of constant surface area, agitation-stirring speed, pH and ionic-strength of the dissolution medium. **mg dissolved/min/cm square**

2.**Particulate dissolution**

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

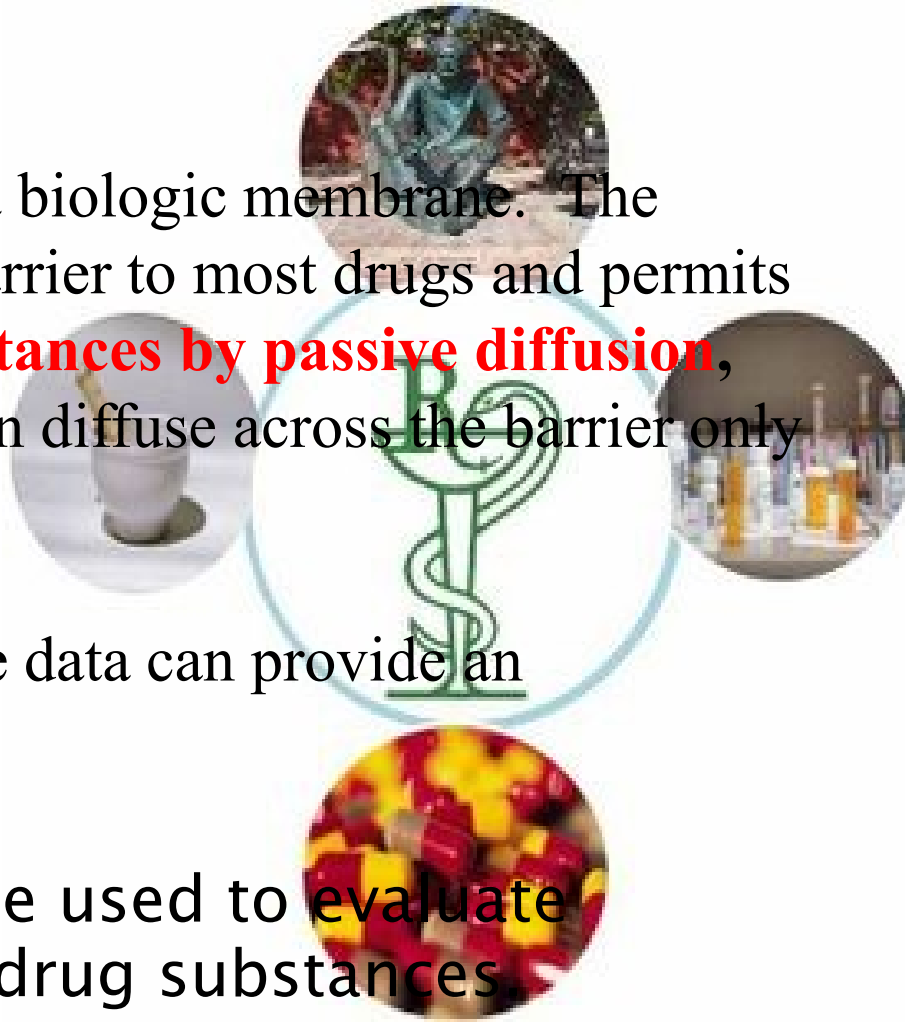
rotating disc method





2.1. Preformulation Studies

12. Membrane Permeability

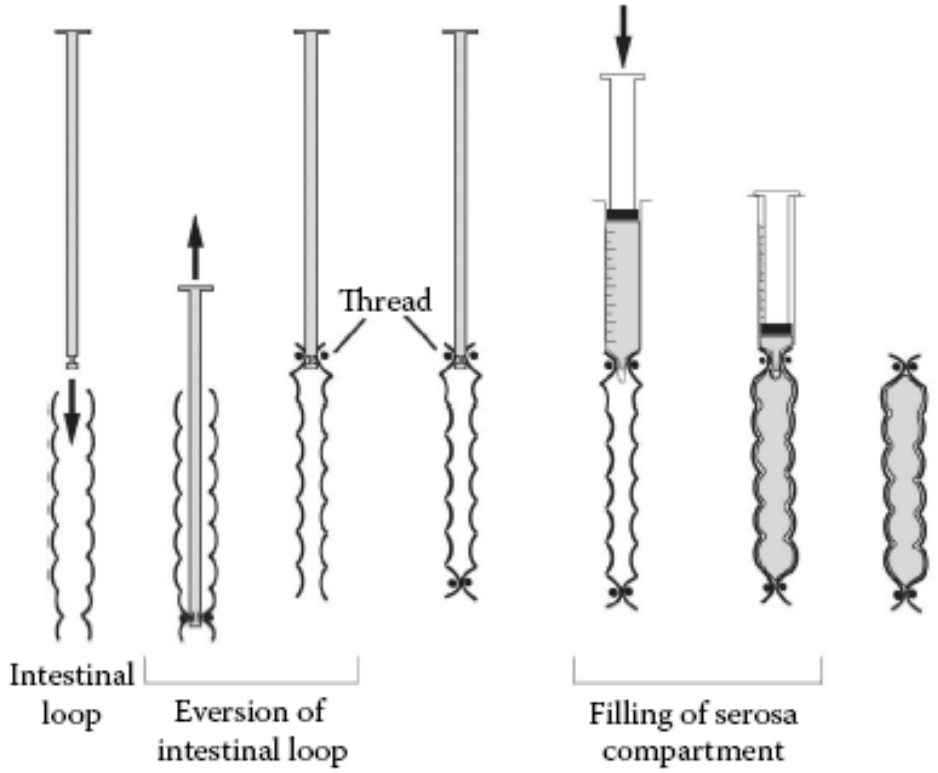


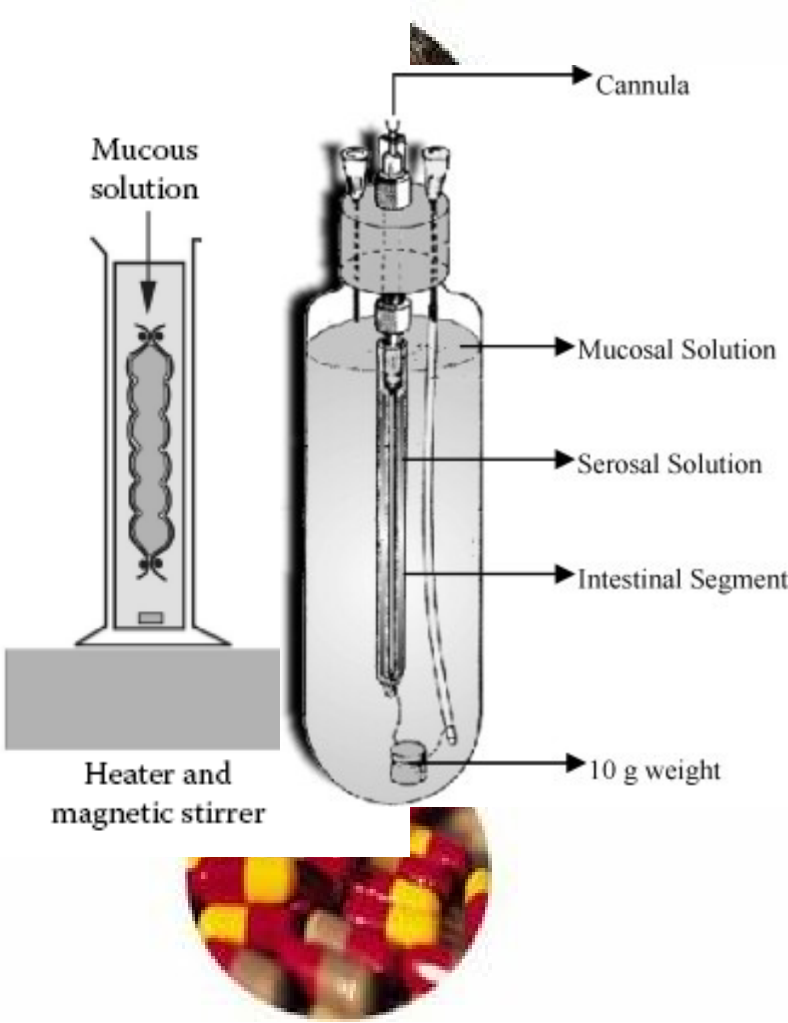
The drug molecule must first cross a biologic membrane. The biologic membrane acts as a lipid barrier to most drugs and permits the absorption of **lipid-soluble substances by passive diffusion**, while **lipid insoluble substances** can diffuse across the barrier only with considerable difficulty

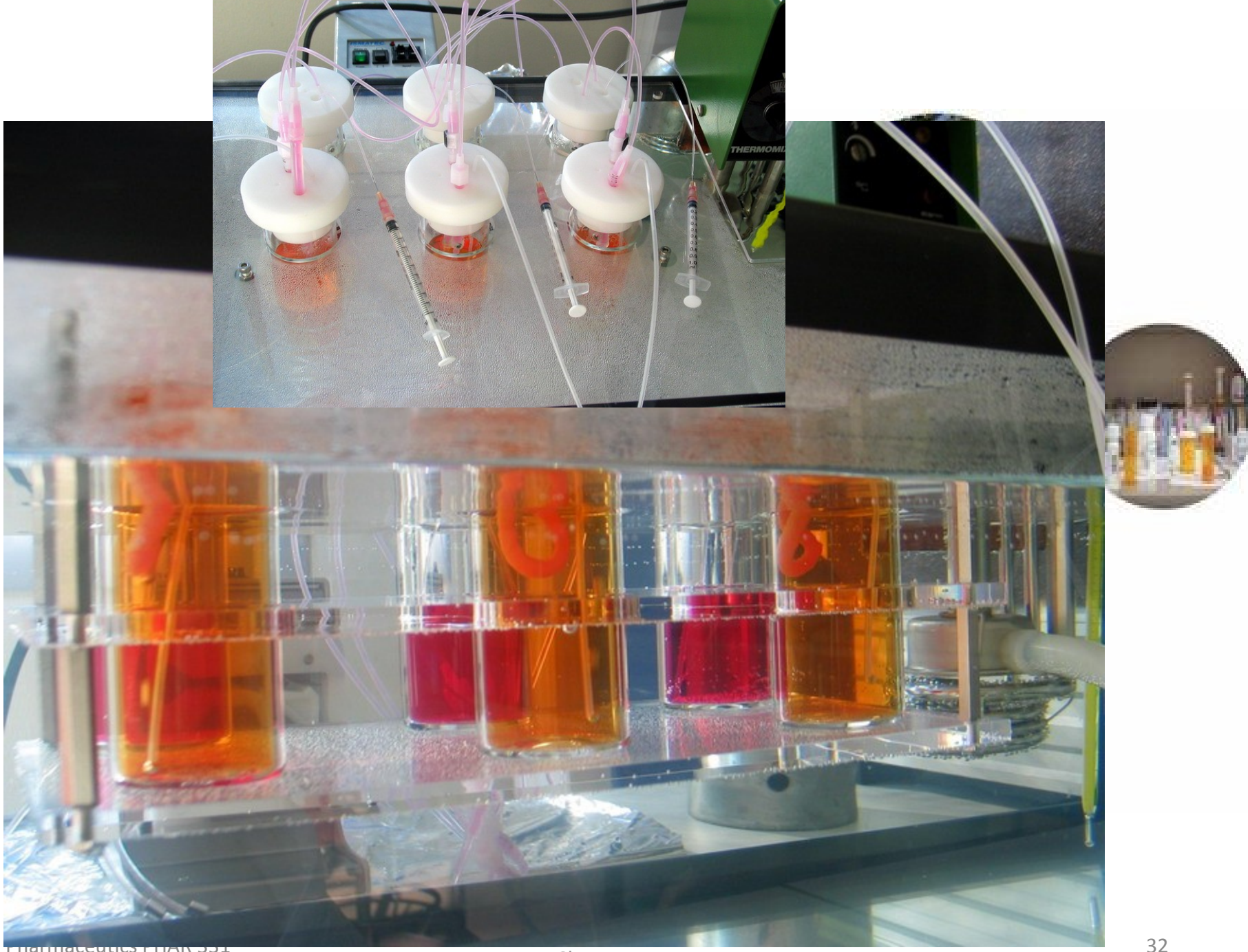
pKa, solubility, and dissolution rate data can provide an indication of absorption

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

2.2 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

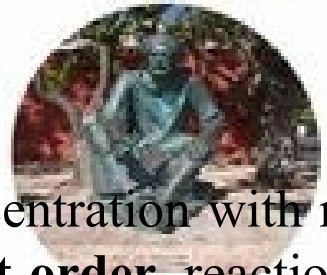
- **Photolysis is prevented by:**

1- suitable packing in amber colored bottles

2- packed in cardboard outers ????

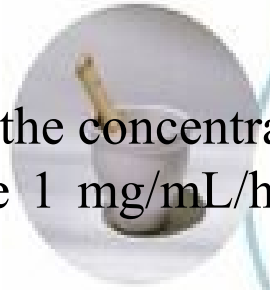
3- aluminum foil over wraps

2.2 Drug and Drug Product Stability



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



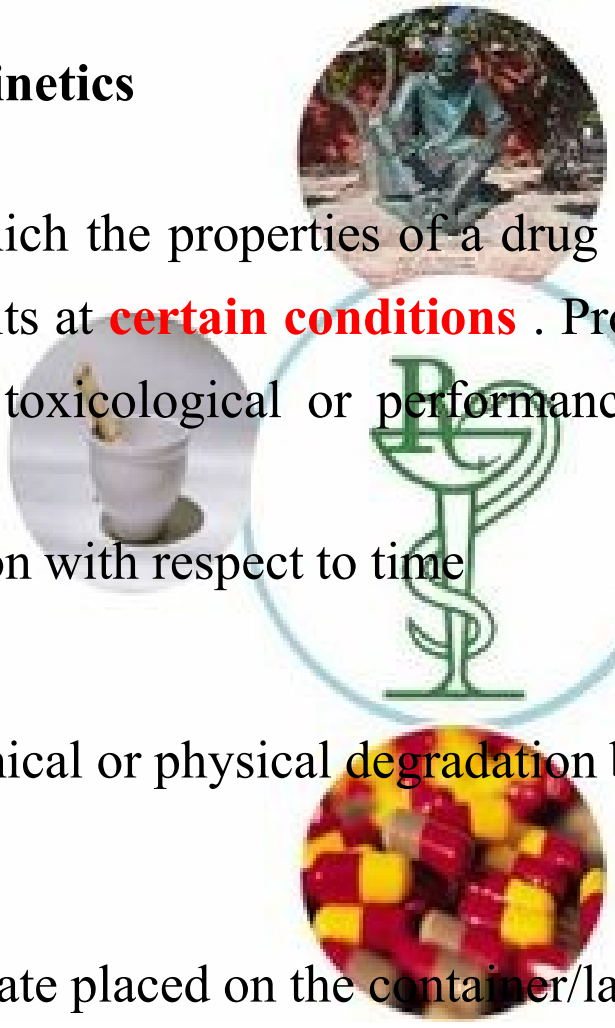
❖If the loss of drug is independent of the concentration of the reactants and constant with respect to time (I.e 1 mg/mL/hour) the rate is **called zero order.**

❖ 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}.

Q_{10} Method of Shelf Life Estimation

Estimate shelf life for a product that has been stored or is going to be stored under a different set of conditions.

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**

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

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%)

Shelf life ($t_{0.9}$)

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

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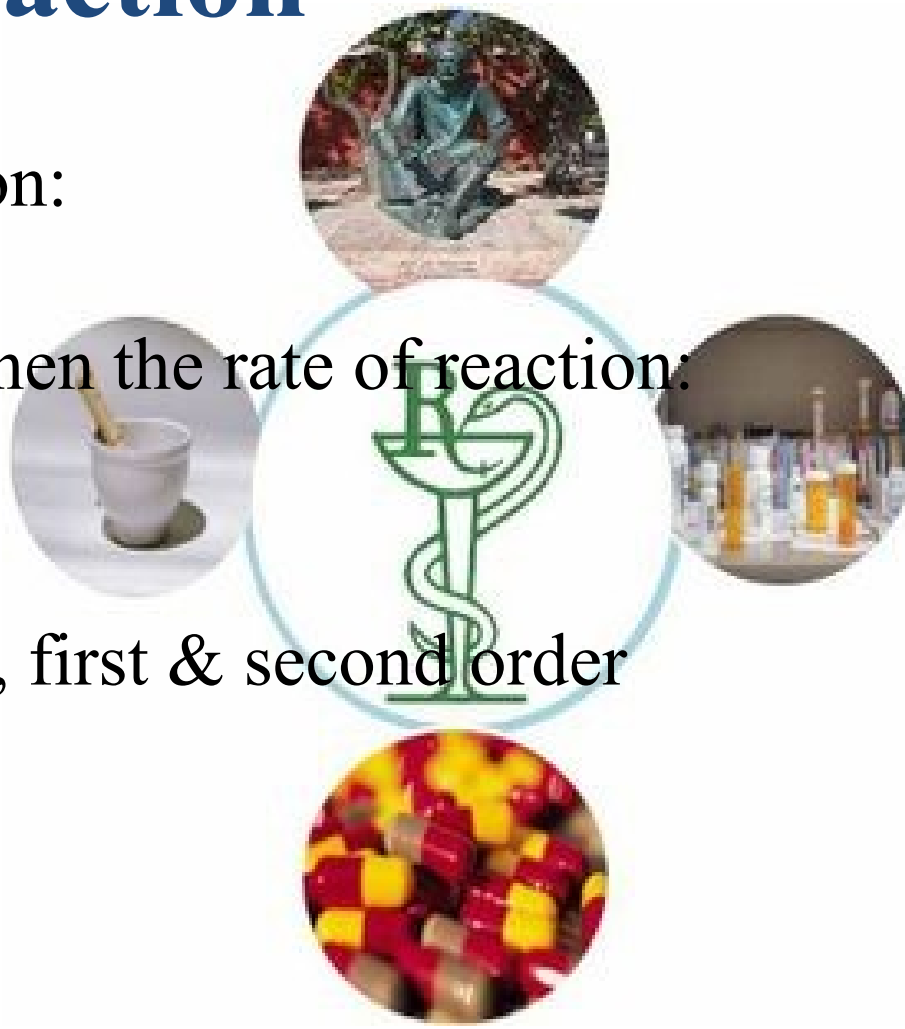
Rate of Reaction

Expressing speed of a reaction:

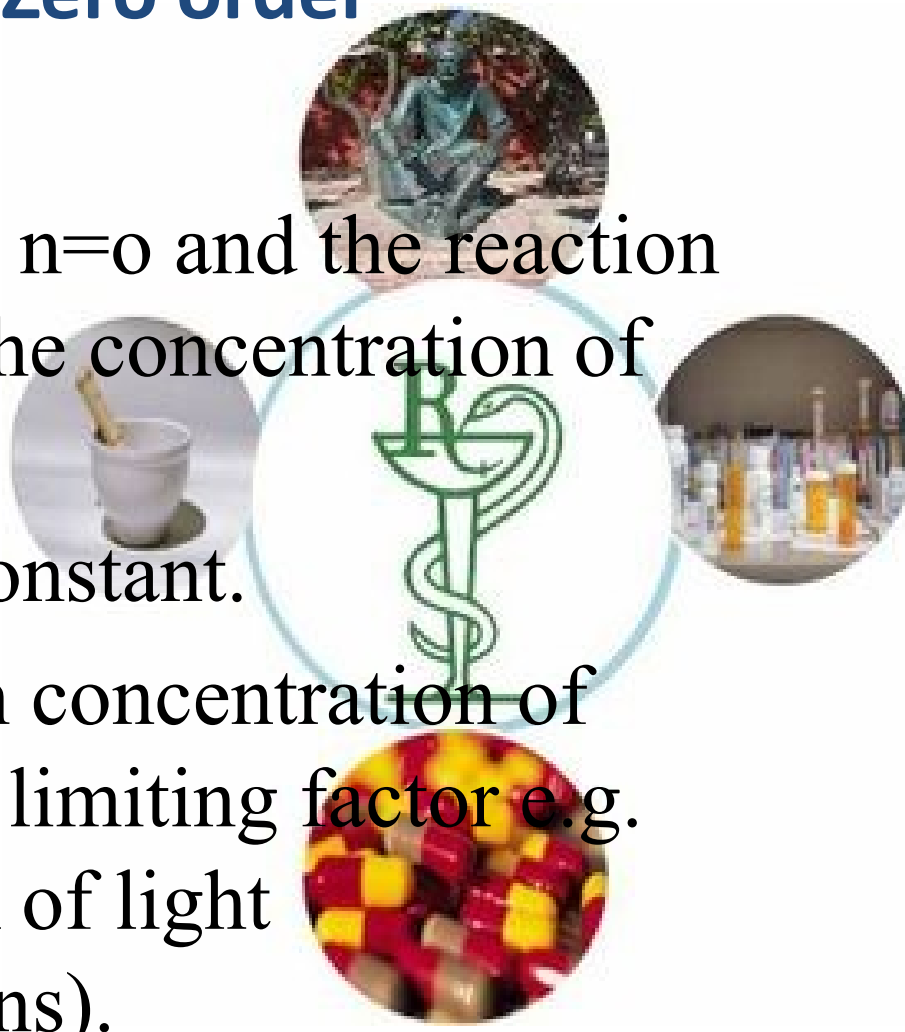
- If C is the concentration, then the rate of reaction:

$$\frac{dC}{dt} \alpha C^n$$

- where n=0,1 or 2 for zero, first & second order reactions respectively



Rate of Reaction-Zero order



- In this type of reaction, n=o and the reaction rate is independent of the concentration of the reacting substance.
- The rate of change is constant.
- Here, factors other than concentration of reactants constitute the limiting factor e.g. solubility or absorption of light (photochemical reactions).

Rate of Reaction-Zero order

- Zero order Equation:

$$\frac{dC}{dt} \propto C^n \xrightarrow{n=0} \frac{-dC}{dt} = k$$

$$C_t = C_o - kt$$

C_t= drug conc. at time t,

C_o= drug conc. at time o

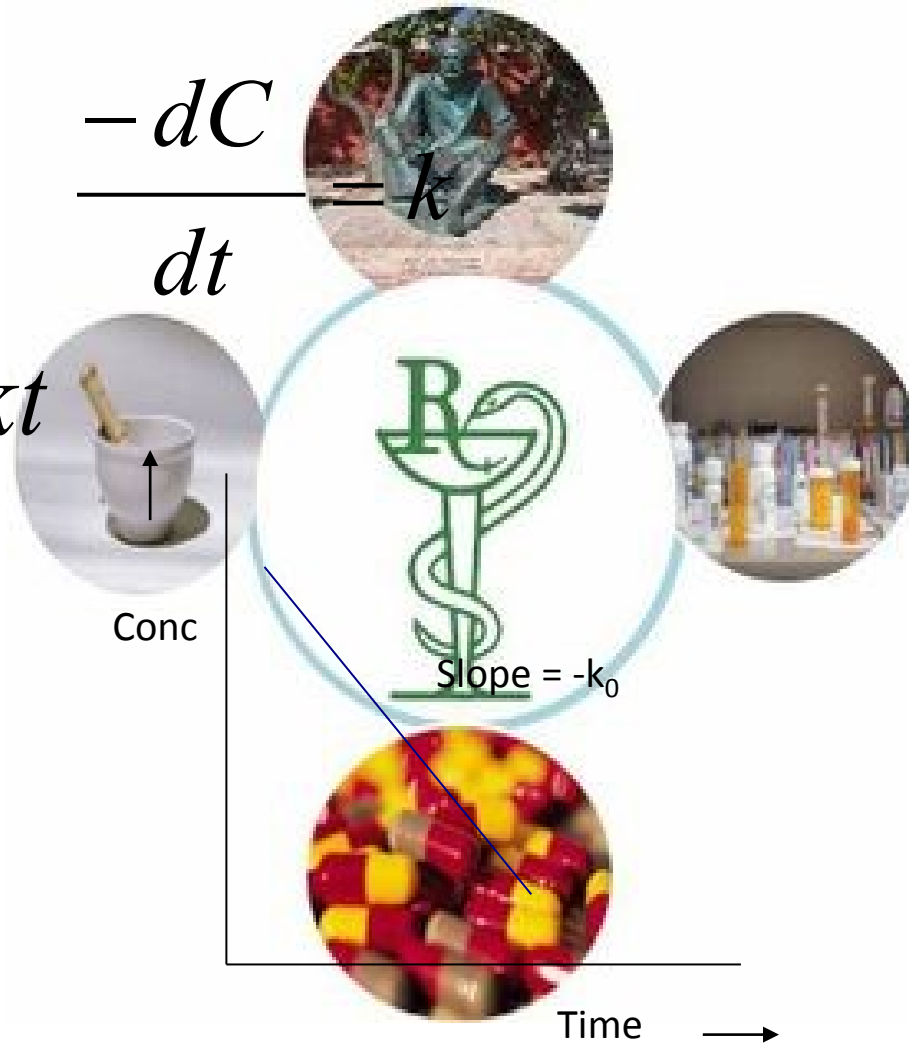
dt= change in time.

k=zero order rate constant

K = Concentration / time

mole / liter . second

= mg/ml sec



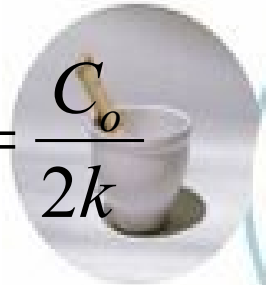
Rate of Reaction-Zero order

half-life

$$C_t = C_o - kt$$

For a zero order reaction, the time for 50% reaction, $t_{½}$, is given as:

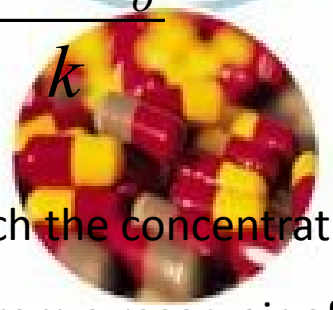
$$t_{1/2} = \frac{½ C_o}{k} = \frac{C_o}{2k}$$



Determination of $t_{0.9}$

Let c = 0.9 co and t= $t_{0.9}$

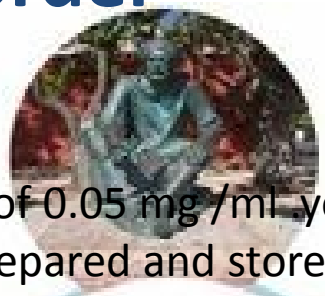
$$t_{90\%} = t_{90\%} = \frac{0.1C_o}{k}$$



❖Suspensions are a special case of zero order kinetics, in which the concentration of drug in solution depends on its solubility.
❖As the drug in solution decomposes, more of it is released from a reservoir of suspended particles thereby making the concentration in solution constant

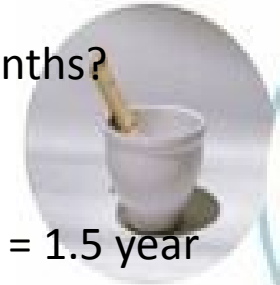
Rate of Reaction-Zero order

half-life



Drug X degrades by a zero-order process with a rate constant of 0.05 mg /ml .year at room temperature. If a 1% weight/volume (w/v) solution is prepared and stored at room temperature:

1. What concentration will remain after 18 months?
2. What is the half-life of the drug?



1- C_0 = 1% w/v = 10 mg/ml; t =18 months = 1.5 year

$$C_t = C_o - kt \quad \Rightarrow C_t = 10 - (0.05x1.5) = 9.91 mg/ml$$

2-

$$t_{1/2} = \frac{\frac{1}{2}C_o}{k} = (0.5x10)/0.05 = 100 years$$

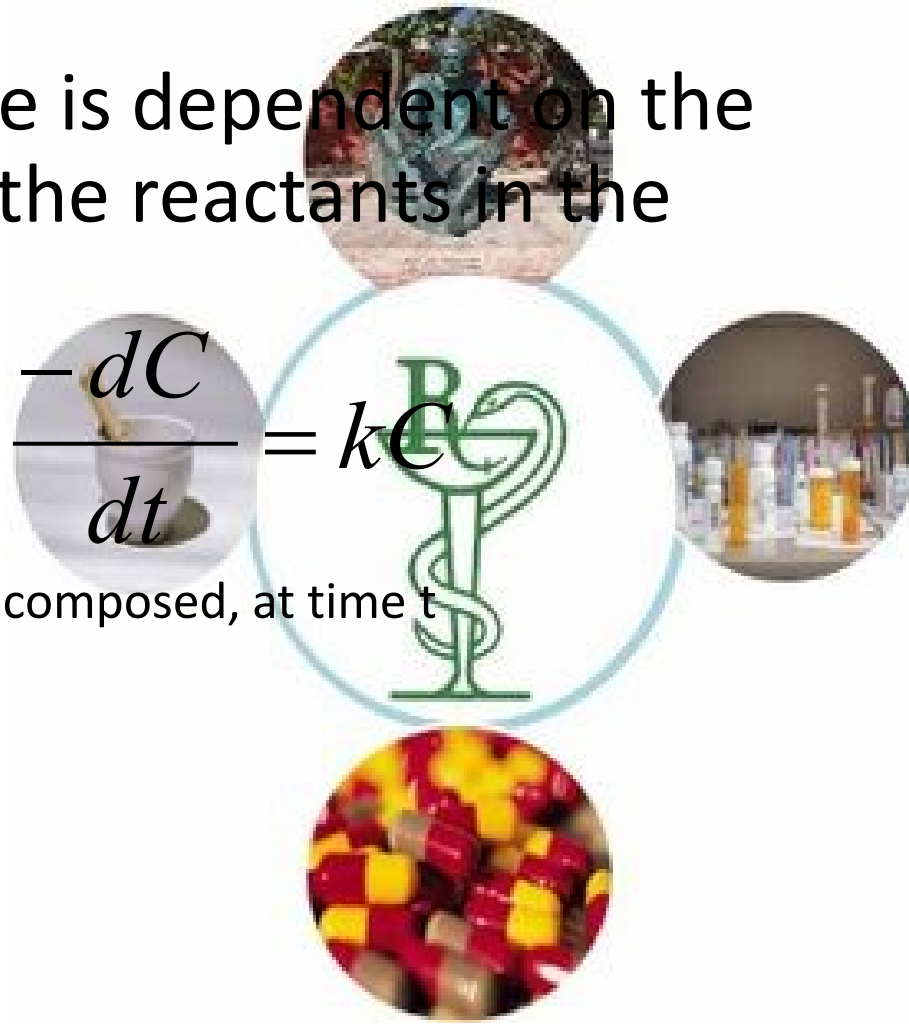
$$t_{90\%} = \frac{0.1C_o}{k} = \frac{0.1x10}{0.05} = 20 year$$

Rate of Reaction-First order

- n=1 and the reaction rate is dependent on the concentration of one of the reactants in the formulation.

$$\frac{dC}{dt} \propto C^n \quad \xrightarrow{n=1} \quad \frac{-dC}{dt} = kC$$

- C is the concentration remaining un-decomposed, at time t
- k is the first order rate constant.



Rate of Reaction-First order

$$\frac{-dC}{dt} = kC$$

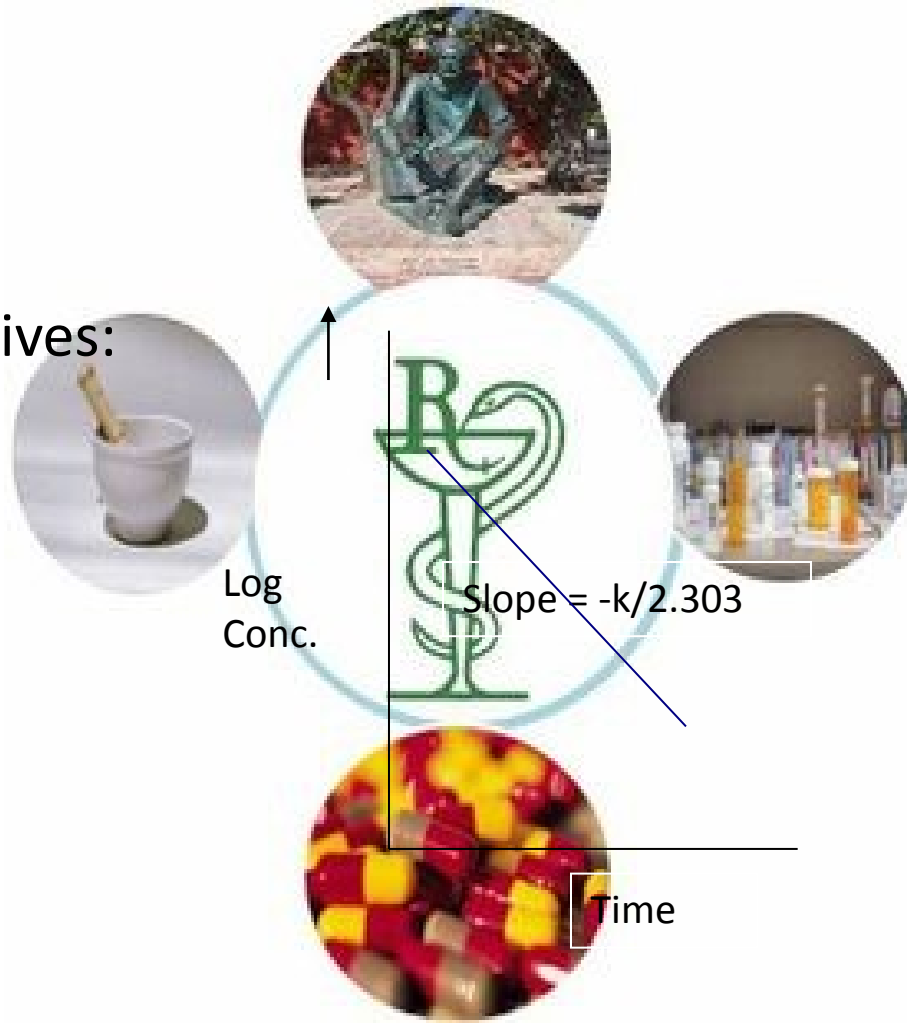
integration, the equation above gives:

$$\ln C_t = \ln C_o - kt$$

rearrangement and conversion

to log in base 10:

$$\log C_t = \log C_o - \frac{kt}{2.303}$$



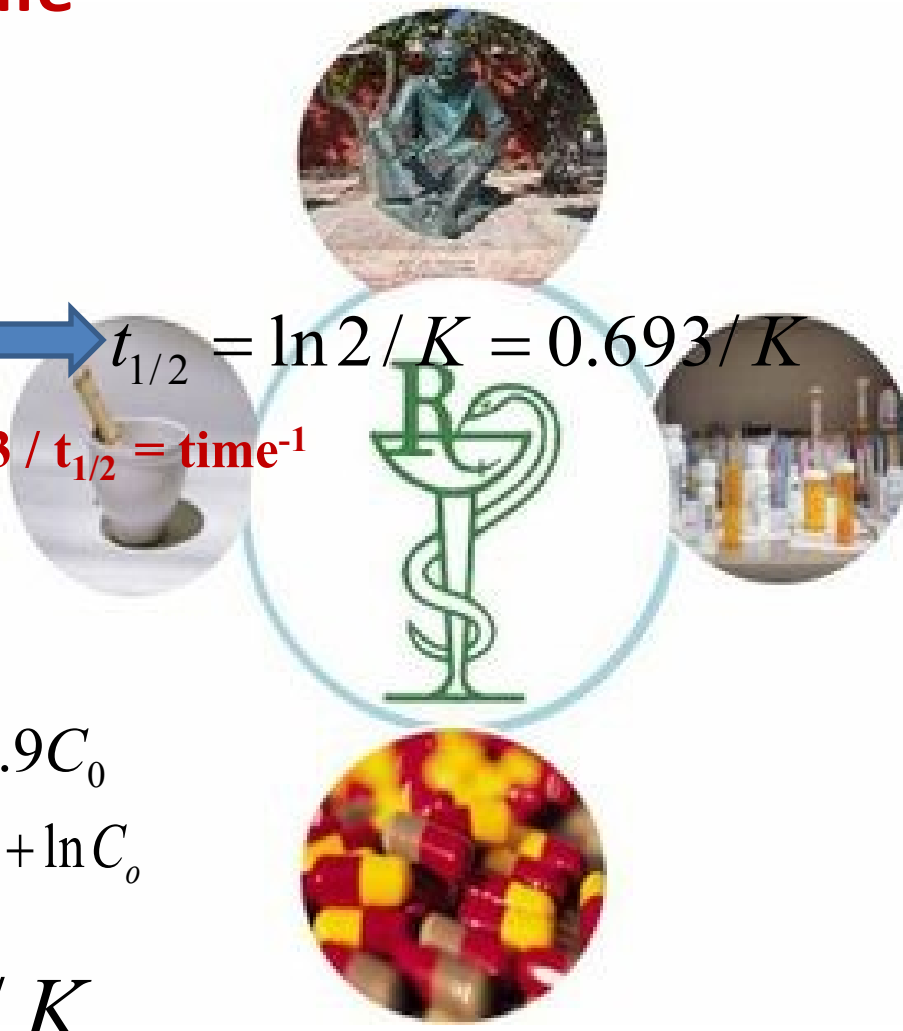
Rate of Reaction-First order
half-life

Determination of $t_{1/2}$

Let $t = t_{1/2}$ and $C = C_0 / 2$

substitute in $\ln C = -kt + \ln C_o$ $\Rightarrow$ $t_{1/2} = \ln 2 / K = 0.693 / K$

K units = 0.693 / $t_{1/2}$ = time^{-1}



Determination of $t_{0.9}$

Let $t = t_{0.9}$ and $C = 0.9C_0$

substitute in $\ln C = -kt + \ln C_o$

$$t_{0.9} = 0.105 / K$$

Rate of Reaction-First order

A 5 gm/100 ml solution of drug X is stored in a closed test tube at 25°C. If the rate of degradation of the drug is 0.05 day−1, calculate the time required for the initial concentration to drop to (a) 50% (half-life) and (b) 90% (shelf-life) of its initial value.

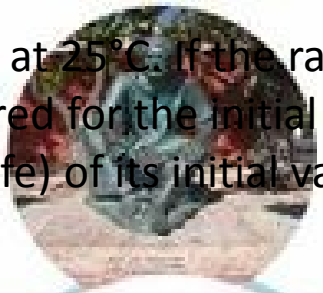
$$\ln C = \ln C_o - kt$$

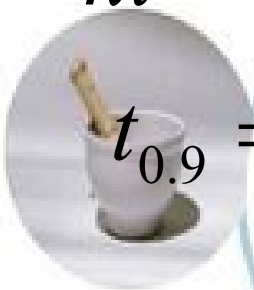
$$t_{1/2} = \ln 2 / K = 0.693 / K$$

$$t_{0.9} = 0.105 / K$$

$$t_{1/2} = 0.693 / 0.5 = 13.9 days$$

$$t_{0.9} = 0.105 / 0.5 = 2.1 days$$



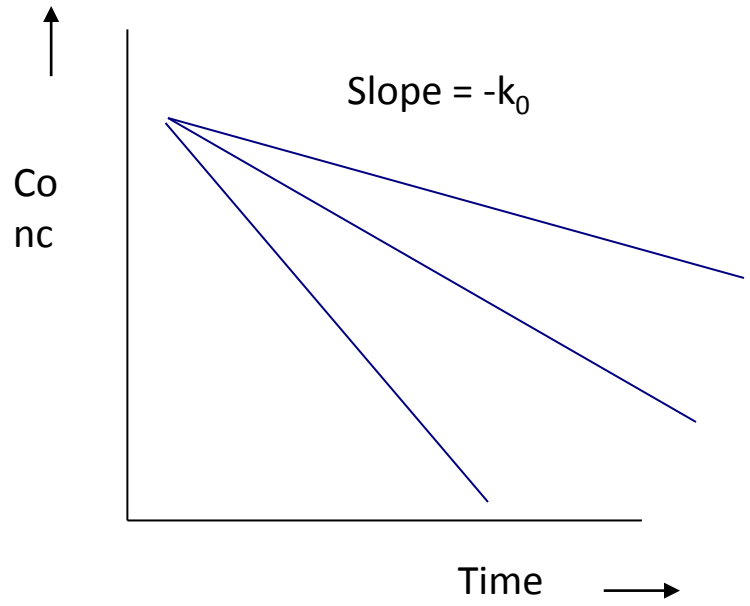


Zero order

$$C_t = C_o - kt$$

$$t_{1/2} = \frac{\frac{1}{2}C_o}{k} = \frac{C_o}{2k}$$

$$t_{90\%} = t_{90\%} = \frac{0.1C_o}{k}$$

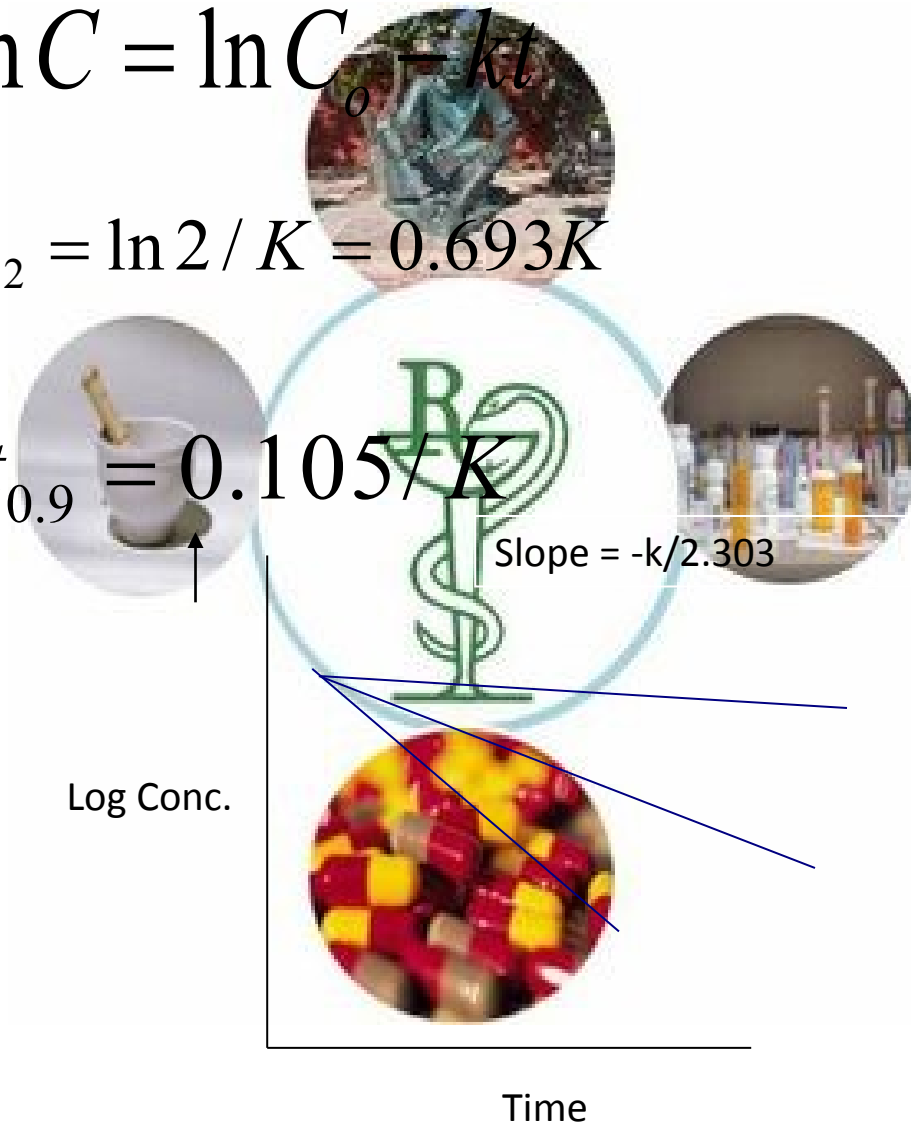


First order

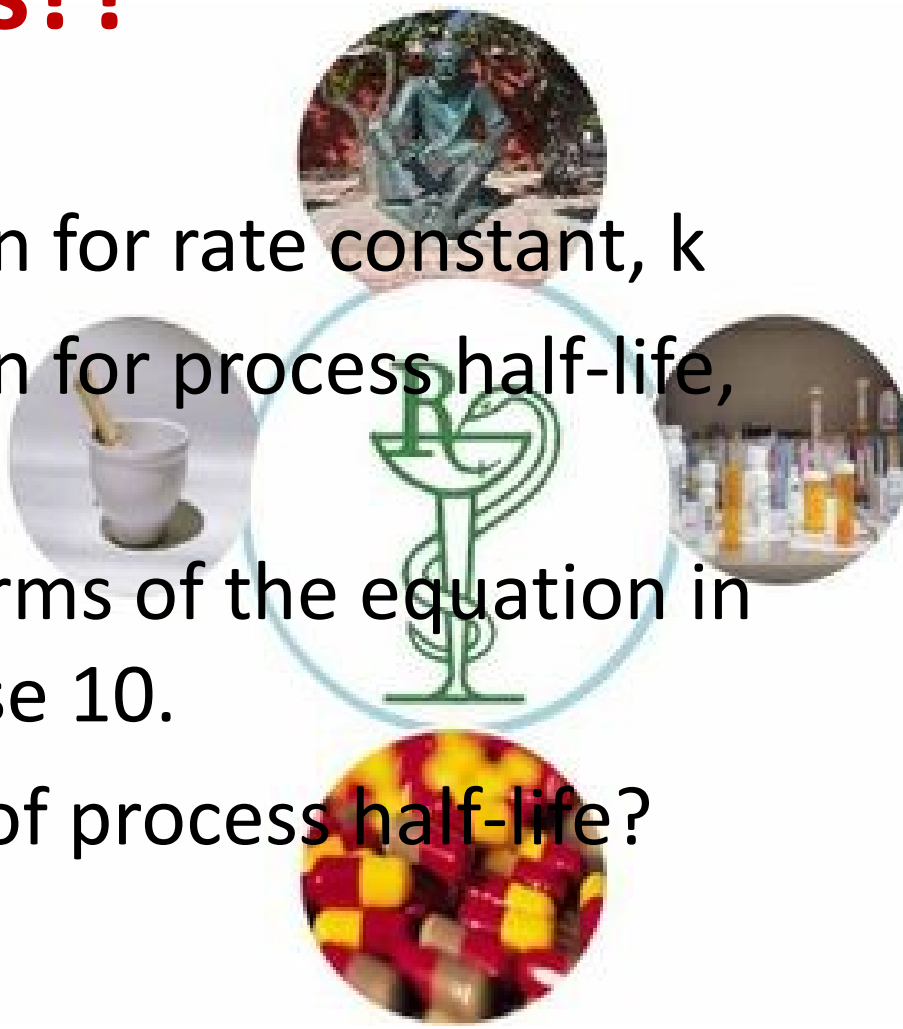
$$\ln C = \ln C_o - kt$$

$$t_{1/2} = \ln 2 / K = 0.693K$$

$$t_{0.9} = 0.105/K$$



Exercises??



- Determine the expression for rate constant, k
- Determine the expression for process half-life, $t_{1/2}$, $t_{0.9}$
- Write the exponential forms of the equation in natural log and log in base 10.
- What is the significance of process half-life?

Determination of Order of Reaction..

- Half life method
  - For a zero order reaction, t ½ is proportional to initial concentration of reactant (Co),
  - t½ for a first order reaction is independent of Co, .

$$t_{1/2} = \frac{\frac{1}{2}C_o}{k} = \frac{C_o}{2k}$$

$$t_{1/2} = \ln 2 / K = 0.693K$$

- Graphical method – For a zero order, plot of **C vs. t** is linear; for first order reaction, plot of **log (Co-Ct) vs. t** is linear.

$$C_t = C_o - kt$$

$$\ln C = \ln C_o - kt$$

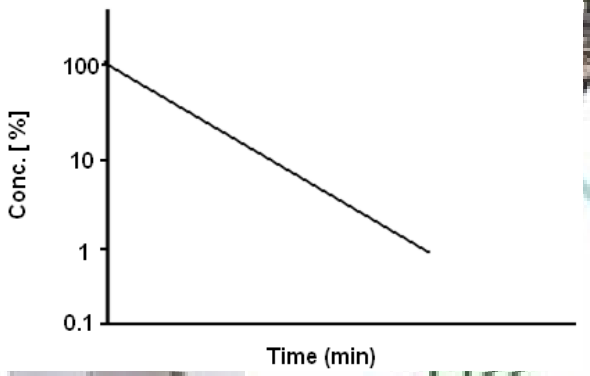
$$\log C = \log C_o - \frac{kt}{2.303}$$

$$t_{1/2} = \ln 2 / K = 0.693K$$

Example: A drug degrades according to the following:

Time (min.)	Conc.	Log C
0	100	2
1	65.6	1.82
2	43.0	1.63
3	28.19	1.45
4	18.49	1.27
10	1.50	0.176

Plot c against t on semi log paper and determine slope, K and t1/2



Solution:

log 28.195 = 1.45 and log 1.5 = 0.176

slope = 1.45 – 0.176 / 3 – 10 = 1.27 / -7 = - 0.181

Equation; log c = log co – Kt / 2.303

slope = -K/ 2.303

- 0.181 = - K / 2.303

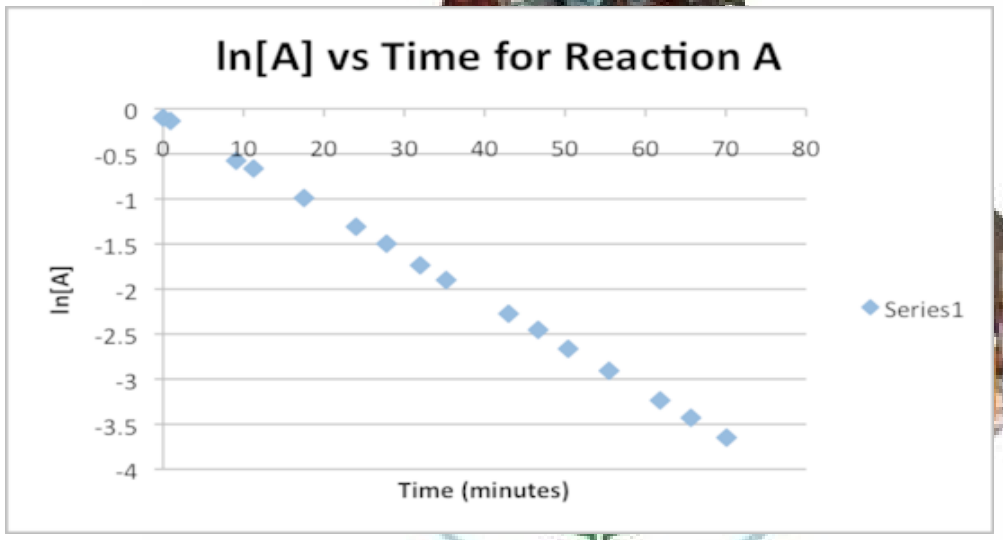
K = 0.417 min^{-1}

$t_{1/2}$ = 0.693 / K

t1/2 = 0.693 / 0.417 = 1.66 minute

In the laboratory, one may collect a sample of data consisting of measured concentrations of Drug A at different times. This sample data may look like the following :

Time (min	C (M)	Ln C
0	0.906	-0.098715973
0.9	0.8739	-0.134789326
9	0.5622	-0.575897621
11.2	0.5156	-0.662424008
17.5	0.3718	-0.989399204
23	0.2702	-1.308592853
27.7	0.2238	-1.497002483
32	0.1761	-1.736703263
35	0.1495	-1.900458886
43	0.1029	-2.273997636
47	0.086	-2.453407983
50	0.0697	-2.663554961
55	0.0546	-2.907721396
61	0.0393	-3.23653076
65	0.0324	-3.429596856
70	0.026	-3.649658741



We can see clearly that the graph of ln[C] vs time is a straight line. Therefore the reaction associated with the given data is a first order reaction.

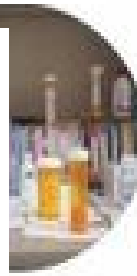
Stability of Valsartan under stress conditions

Table No 5. Data for forced degradation Study on Valsartan

Drug Name	Stress behaviour	Time(hrs)	Rt(min)	% Degradation	% of Active drug present after degradation
Valsartan	Control	12	7.041	---	---
	Acid hydrolysis	12	7.007	0.50789	99.49214
	Alkaline hydrolysis	12	6.775	3.735128	96.26487
	Thermal stress	12	6.3387	9.999983	90.00002
	Oxidative stress	12	6.5267	7.328535	92.67147

Table 9. Effect of some pharmaceutical excipients on the reaction rate of CEF-3H_2O sunlight, UV light, and thermal decomposition

Excipient name	Concentration %w/w	pH	Reaction rate (k)- min^{-1}		
			Sun	UV	At 70 °C
NaC- Dibasic	0.05%	6.95	0.0025	0.0013	0.0005
Monobasic Na-ph	0.05%	6.95	0.0015	0.0009	0.0010
EDTA	0.05%	7.02	0.0016	0.0021	0.0007
Mg-Stearate	0.01%	7.29	0.0014	0.0025	0.0001
Talc	0.01%	7.29	0.0042	0.0039	0.0011
Na C -Tribasic	0.05%	7.32	0.0025	0.0013	0.0018
Dibasic Na-ph	0.05%	7.65	0.0023	0.0014	0.0020
Control (CEF-3H_2O without excipients)	-	6.85	0.0034	0.0012	0.0014



The concentration of drug X in aqueous solution drops by 10% per month when stored at room temperature. What concentation will remain if a 5 mg/ml solution of the drug is stored under the same condetions after 3 months???

1- If the degradation occurs by zero order?

$$C_t = C_o - kt$$

$$0.9C_0 = C_o - k$$

$$k = 0.1C_0 \xrightarrow{for\ 5mg/ml} k = 0.5$$

$$C_{3m} = 5 - 0.5x3 = 3.5mg/ml$$

5-[(5X0.1) X3]=3.5 mg/ml

2- If the degradation occurs by first order?

$$\ln C = \ln C_o - kt$$

$$\ln 0.9C_0 = \ln C_o - k$$

$$k = \ln \frac{C_0}{0.9C_0} = 0.105$$

$$\ln C_{3m} = \ln 5 - 0.105x3$$

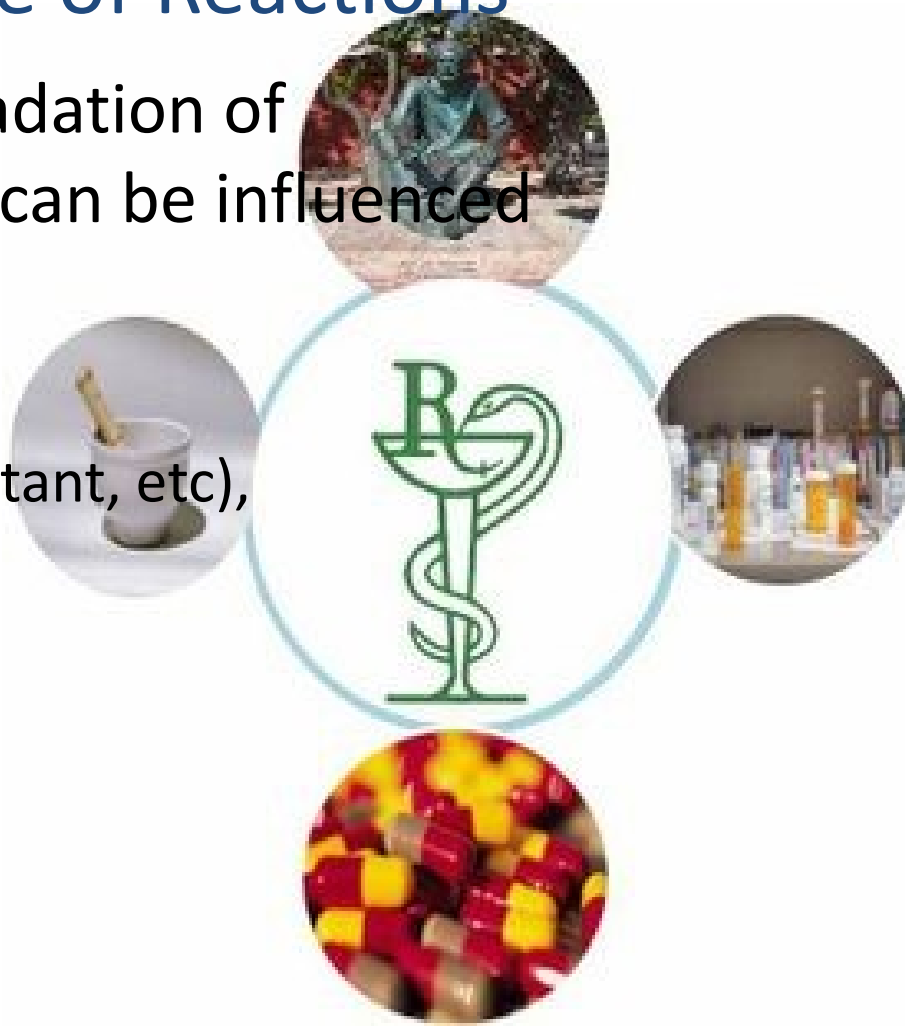
$$\ln C_{3m} = 1.6094 - 0.315 = 1.2944$$

$$C_{3m} = 3.65mg/ml$$

2- 5X0.9X0.9X0.9=3.65 mg/ml

Factors Affecting Rate of Reactions

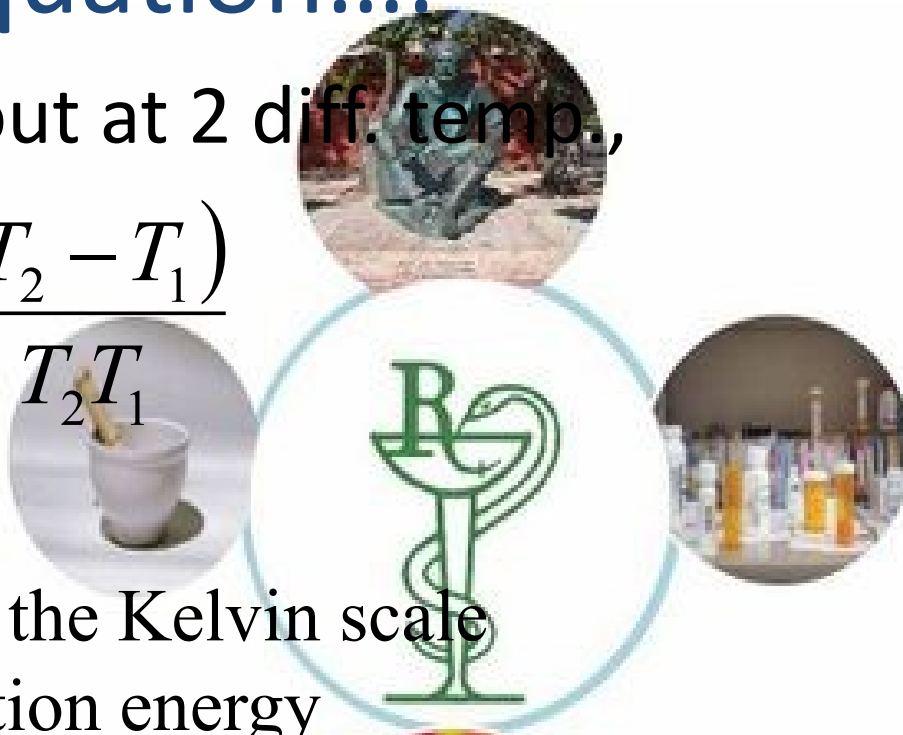
- The rate of reaction (degradation of pharmaceutical products) can be influenced
  - temperature,
  - moisture,
  - solvent (pH, dielectric constant, etc),
  - light (radiation),
  - catalysts,
  - oxygen and
  - concentration of DRUG (s).



Arrhenius equation….

- For a reaction carried out at 2 diff. temp.,

$$\log\frac{k_2}{k_1} = \frac{E_a}{2.303R}\frac{(T_2 - T_1)}{T_2 T_1}$$



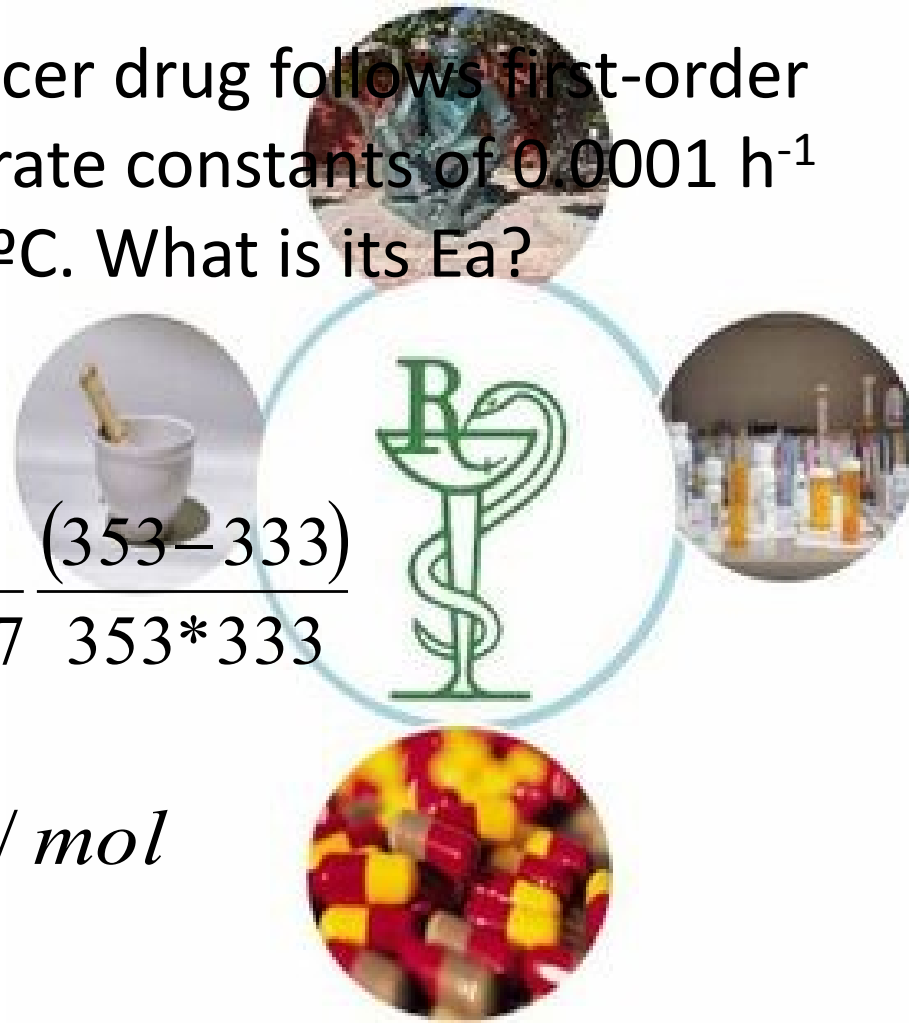
k = reaction rate,

T = is absolute temperature in the Kelvin scale

R = gas constant, Ea = activation energy

If the activation energy at one temperature are known, one can easily determine the rate constant at any other temperature. This is important in the determination of expiration date of a new pharmaceutical product

The degradation of a new cancer drug follows first-order kinetics and has degradation rate constants of 0.0001 h^{-1} at 60 ºC and 0.0009 h^{-1} at 80 ºC. What is its Ea?



$$\log\frac{0.0009}{0.0001} = \frac{E_a}{2.303*1.987}\frac{(353-333)}{353*333}$$

$$E_a = 25.651 cal/mol$$

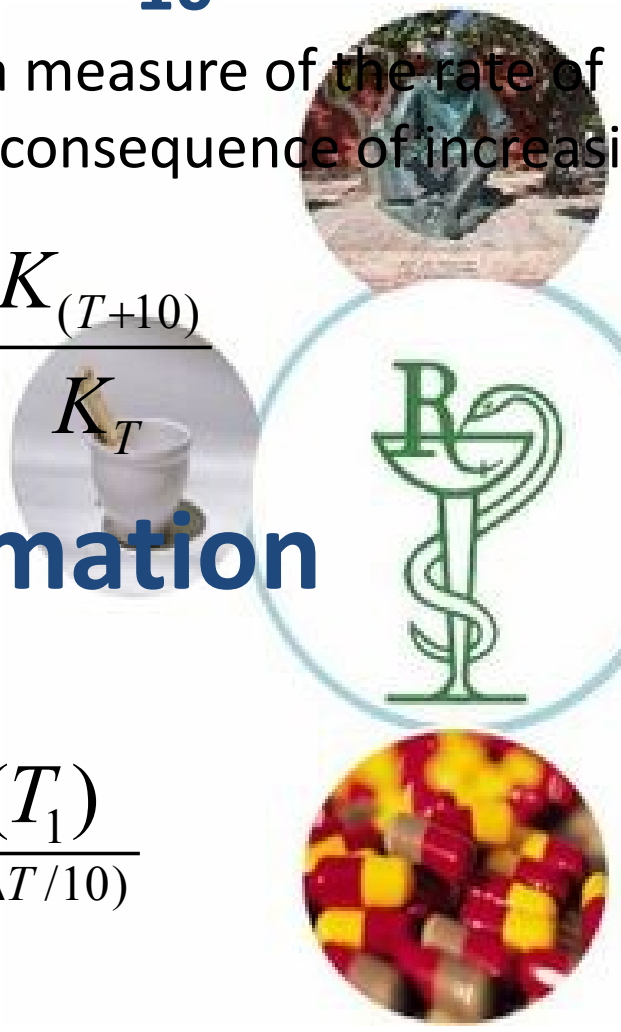
Example: The rate constant for first-order degradation of a drug (activation energy is 20.0 Kcal/mol) in a solution (5.0 mg/ml) at 70°C is 1.50×10^{-3} h^{-1}.

1. Calculate the amount remaining after storage for one week at room temperature (25°C).
2. Calculate the amount remaining after one week if the drug is kept at 70°C.
3. Calculate the shelf life of the drug at room temperature.
4. Calculate the half-life of the drug at room temperature.
5. Calculate shelf- life of the drug at 70°C.
6. Calculate the half-life of the drug at 70°C.
7. Discuss what you learned from this exercise.

Concept of Q_{10}

The ***Q_{10}* temperature coefficient** is a measure of the rate of change of a biological or chemical system as a consequence of increasing the **temperature** by 10 °C

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$



Q_{10} shelf life estimation

$$t_{0.9}(T_2) = \frac{t_{0.9}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

Example: The shelf life of a liquid drug is 21 days at 5°C. Approximately how long will the drug be stable at 37°C?

$$\text{Life at } 37^\circ\text{C} = 21 \text{ days} / 5^{[(37-5)/10]} = 21/5^{3.2} = 21/172.47$$

$$= 0.12 \text{ day or } 2.92 \text{ h}$$

$$t_{0.9}(T_2) = \frac{t_{0.9}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

Alternatively, using Q_{10} values as 2, 3 or 4

$$\text{Life at } 37^\circ\text{C} = 21 \times 2^{-3.2} = 2.28 \text{ days } (Q = 2, \text{ possible})$$

$$= 21 \times 3^{-3.2} = 0.62 \text{ days } (Q = 3, \text{ likely})$$

$$= 21 \times 4^{-3.2} = 0.25 \text{ days } (Q = 4, \text{ conservative})$$

Example: A drug in solution is stable for 2 years at room temperature (25°C). How long may the drug be theoretically stable at refrigerator temperature (5°C)?

Using the table value, life at 5°C = 2 years/$2^{[(5-25)/10]}$ = $2/2^{-2}$ = 8 years

Alternatively, using Q_{10} values of 2, 3, or 4

$$\text{Life at } 5^\circ\text{C} = 21 \times 2^2 = 8 \text{ years } (Q = 2, \text{ conservative})$$

$$= 21 \times 3^2 = 18 \text{ years } (Q = 3, \text{ likely})$$

$$= 21 \times 4^2 = 32 \text{ years } (Q = 4, \text{ possible})$$

$$t_{0.9}(T_2) = \frac{t_{0.9}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

TABLE 8.4
Simplified Q_{10} Values

When Chemical Life Is	Use Q_{10} of
Known at a cooler temperature and to be estimated at a warmer temperature	$Q \Uparrow$
Known at a warmer temperature and to be estimated at a cooler temperature	$Q \Downarrow$

Example: The ampicillin monograph states that the reconstituted suspension is stable for 14 days in a refrigerator. If the product is left at room temperature for 6 h, what is the reduction in the expiration period?

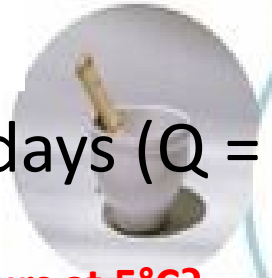
$$t_{0.9}(T_2) = \frac{t_{0.9}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

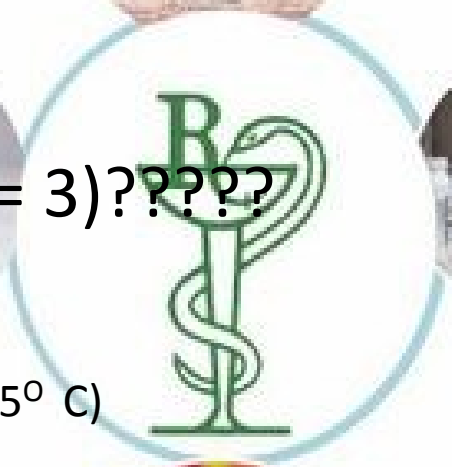
Shelf life= 14 / 3^2 = 1.56 days (Q = 3)????

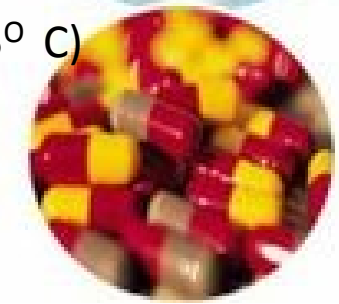
The question to be addressed here is:
Life at 25°C for 6 h (0.25 days) = how many hours at 5°C?

1.56 day(T=25^O C) ⟷ 14 day(T=5^O C)

0.25 day(T=25^O C) ??? day(T=5^O C)





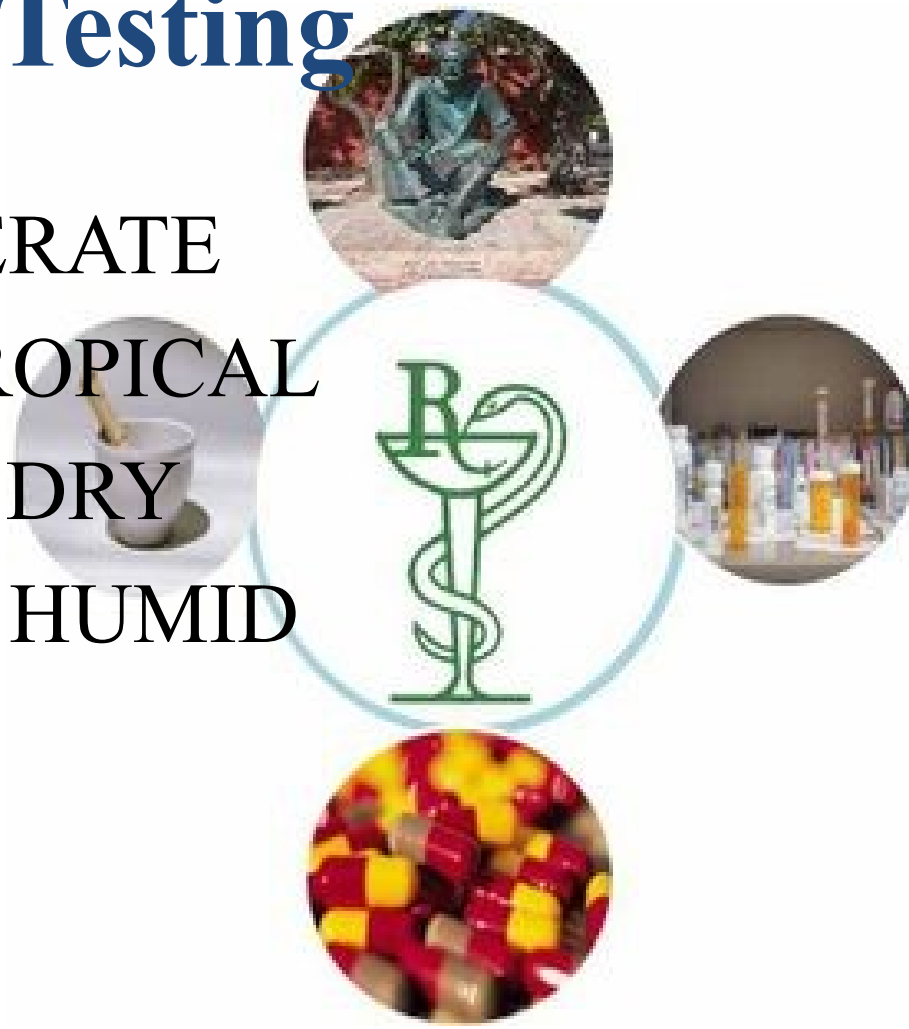


0.25 × 14/1.56 = 2.243 days

$$t_{reduction}(T_2 = 5^O C) = \frac{0.25}{3^{(5-25/10)}} = 0.25 \times 3^2 = 2.25 \text{ days}$$

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.

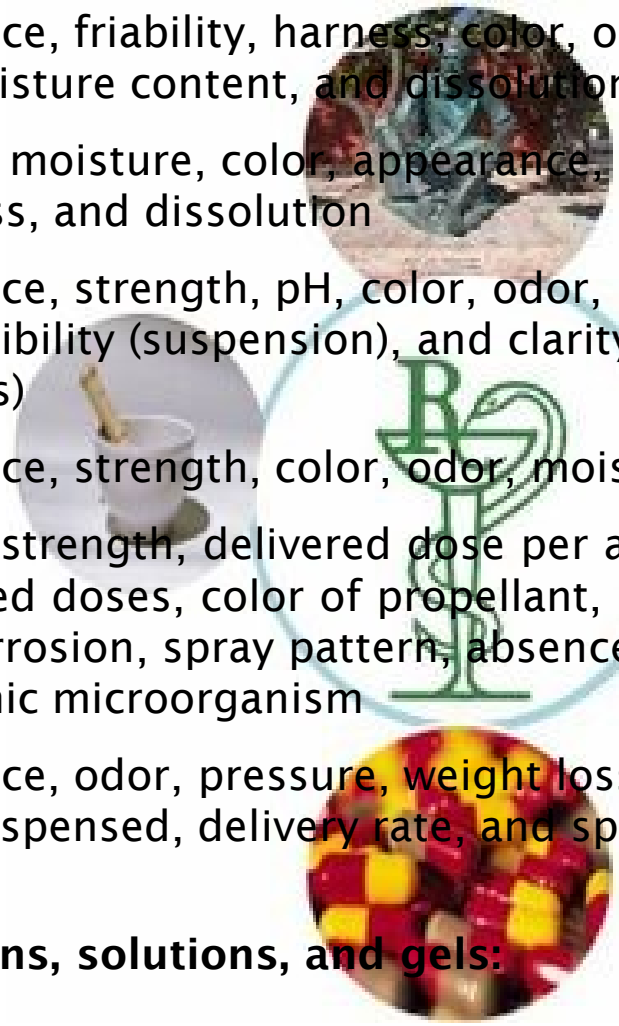
[b] If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

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.

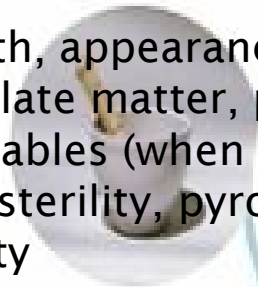
Signs Of degradation Of Specific Dosage Forms

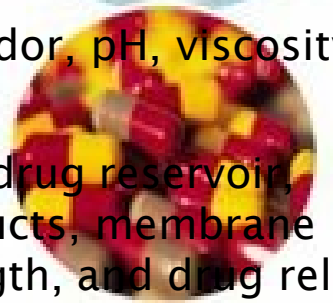
1. Tablets	appearance, friability, harness, color, odor, odor, moisture content, and dissolution
2. Capsules	strength, moisture, color, appearance, shape, brittleness, and dissolution
3. Oral solutions suspensions	appearance, strength, pH, color, odor, redispersibility (suspension), and clarity (solutions)
4. Oral Powders	appearance, strength, color, odor, moisture
5. Metered-dose number inhalation aerosols	strength, delivered dose per actuation, of metered doses, color of propellant, pressure, valve, corrosion, spray pattern, absence of pathogenic microorganism
6. Topical non metered aerosols	appearance, odor, pressure, weight loss, net weight dispensed, delivery rate, and spray pattern
7. Topical Creams ointments, lotions, solutions, and gels:	appearance, color, homogeneity, odor, pH, resuspendibility (lotions), consistency, particle size, distribution, strength, weight loss



Signs Of Degradation Of Specific Dosage Forms

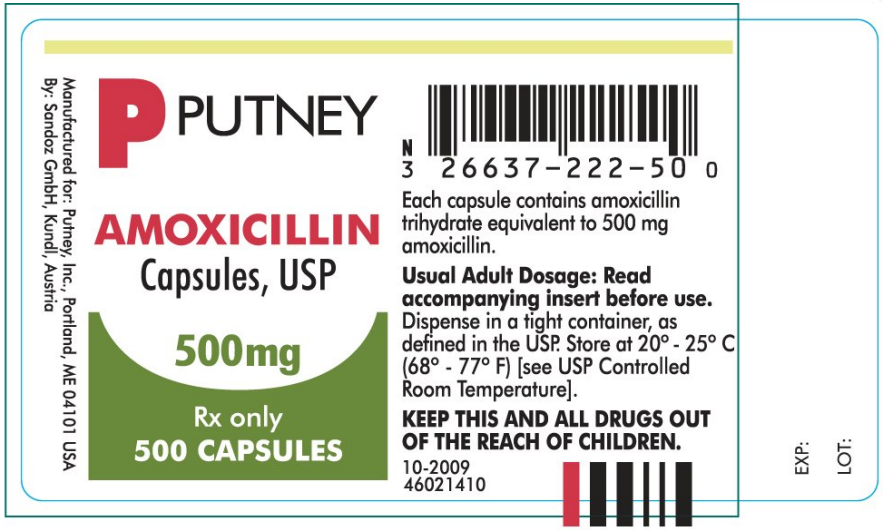
8. Ophthalmic Preparations	appearance, color, consistency, pH, clarity (solutions), particle size, resuspendibility (suspensions, creams, ointments), strength, and sterility
9. Parenterals	strength, appearance, color, clarity, particulate matter, pH, volume and extractables (when plastic containers are used), sterility, pyrogenicity, and closure integrity
10. Suppositories	strength, softening range, appearance, and dissolution
11. Emulsion	appearance, color, odor, pH, viscosity, and strength
12. Transdermal	seal strength of the drug reservoir, decomposition products, membrane integrity, drug strength, and drug release rate

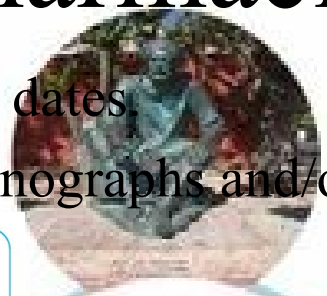





Responsibility of the Pharmacist

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

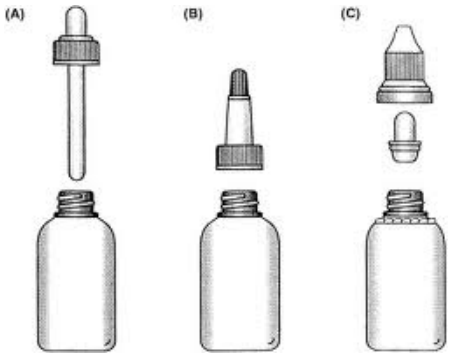




- Observe products for evidence of instability.
- Properly treat/label products that are repackaged, diluted, or mixed with other products.

Responsibility of the Pharmacist

- Dispensing in proper container with proper closure



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

PHARMACIST:

PHARMACIST:


PHARMACY
Rx
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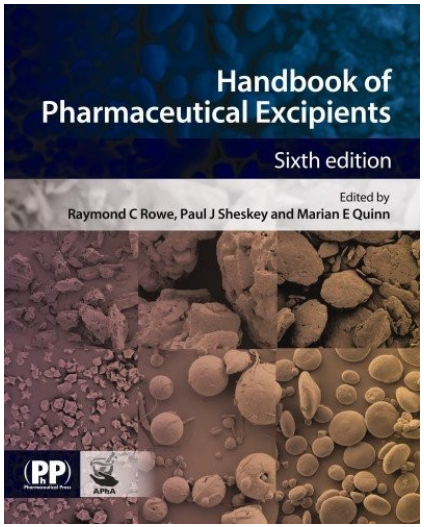
KALI BICHROMICUM 30c
THUJA OCCIDENTALIS 30c
LYCOPODIUM CLAVATUM 30c
RHUS TOXICODENDRON 30c

Pharmaceutical Ingredients and Excipients

Pharmaceutical ingredients added to prepare a dosage form

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]