INDUSTRIAL PHARMACY

↳ The pharmacy which used in industries (company) etc..

- It is the branch of pharmacy in which we study about the manufacturing, development, marketing and distribution of drug products including quality assurance of these activities.

UNIT-1ST

PRE-FORMULATION STUDIES

- Syllabus :-
  - Introduction to preformulation studies
  - Physico-chemical properties (physical + chemical)
  - BCS
  - Stability of Dosage form.

PRE-FORMULATION

Pre → Before

formulation → to make

- The study of physical and chemical properties of drug substance before formulation. — development of new medicines

- Objective →
  - To determine the physicochemical (physical + chemical) properties of the new drugs.
  - To determine its kinetic (movement of drug in body) and stability of drugs.
  - To establish compatibility (no interaction) with common excipients.

- Goal → To develop stable, safe and effective dosage form. max. bioavailability + therapeutic response

• Physicochemical characteristics of drug substance

- for development of new medicine, it is much more important to know about its ~~phys~~ properties.

eg.

API → Identification test → Paracetamol

Compound identify ← properties

- Same for excipient.
- then study about their properties
- Also check their therapeutic response, bioavailability, Adverse effect
- then analyze everything (find out issue)
- then start development of drugs.

Physicochemical
- Physical properties
- Chemical properties.

• Physical properties

— Organoleptic properties →

Organs → leptic → lower sensory organs

Those properties which can we find out through our sensory organs.

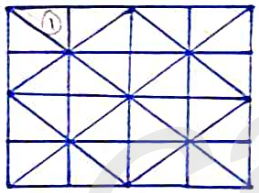
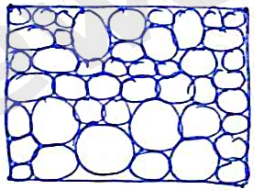
eg. Colour (हरा, पीला, सफेद), Odour (odourless, pungent), Taste (Acidic, Sweet, bitter), Texture (चिकना, खुरदरा, फिसलन, etc.)

— Physical form →

Drug can be
- Solid
- liquid
- Gases

• Mostly used Solid
- easy to formulate
- stable
- easily store & transport.

- On the basis of their internal structure it can be i) Crystal ii) Amorphous.

(i) Crystalline form	(ii) Amorphous form
• In Crystalline solid, atoms and molecules are arranged in definite lattice form.	• In Amorphous solid, atoms and molecules are not arranged in definite lattice pattern.
	
• fixed internal structure	• do not have fixed internal structure
• Sharp M.P & B.P	• M.P & B.P are in wide range
– More Stable ↑.	– less Stable ↑.
– less solubility & dissolution rate.	– More solubility & dissolution rate

- Also the degree of crystallinity of a drug substance has marked effect on its hardness, density, transparency and diffusion.
- On storage, Amorphous solids reverts to its more stable form.

eg. The crystalline form of penicillin G potassium is more stable and more therapeutic response than amorphous form.

penicillin G → used to treat bacterial infections / sepsis, diphtheria, meningitis, gonorrhea.

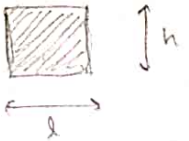
— Particle size, shape and Surface Area

These properties also affects the biopharmaceutical behaviours of drugs.

biopharma – drugs effect on body.

- Particle size → A term which is used to measure (find out) the dimension of particles.

Solid Liquid Gases



• Particle size affects solubility, dissolution, bioavailability.

eg. particle size ↓ → solubility ↑
- easy to mix
- affects flow properties.

- Small particle size (fine powder) is also susceptible to attack by heat, atmosphere, light or humidity which further cause stability issues. (may be harmed)

- In bulk form (at constant volume) particle size also affects surface area

particle size ↓ = surface area ↑

• Particle size can be determined by → microscopy, sieving method, light scattering method etc. etc.

• Particle shape → overall shape of particle
- texture of a particle.
- overall dimension of particle.

eg. ○ → circle shape (sphere)
□ → Square shape

- it affects the flow properties.
- determine using microscope

• Surface area →
surface area
- area of a surface
circumference of a particle.
- determined by BET equation
theory of adsorption.

flow Properties

- An ability of a particles to flow.
- depends upon particles size, shape and density, hygroscopicity (absorbed moisture).
- affects formulation and efficacy

- flow properties ↑ ⇒ Production↑, mixing↑ (flow Rate)
- flow rate ↓ ⇒ Uniformity ↓
- flow properties determined by Angle of Repose, Carr's index, Hausner ratio etc..
- Hygroscopicity → Ability of a particles to absorb moisture

- Density → Bulk density
  - Density of powder (solid)
- It affects the flowability of powders.

$$\text{density} = \frac{\text{mass}}{\text{volume}}$$

- Bulk density (poured density)
- True density (Tapped density)
- mass of powder divided by the bulk volume

$$B.D = \frac{\text{Mass}}{\text{bulk volume}}$$

- True density (absolute density)
  - mass of powder divided by a volume of the powder excludes pores / voids.

$$T.D = \frac{\text{mass}}{\text{True Volume}}$$

- **Angle of Repose →**

The internal angle b/w the surface of the pile and the horizontal surface is know as the angle of repose.

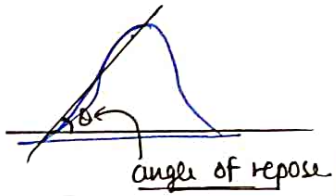
$$\tan \theta = \frac{h}{r}$$

where,
h = height of pile.
r = Radius of pile.
θ = Angle of repose

Angle of Repose ↓ = flow property ↑

→ flow properties — Angle of Repose

Excellent	25-30
Good	31 – 35
fair (aid not needed)	36 - 40
Passable - may hang up	41 - 45
Poor - must agitati, vibrati	46 - 55
Very poor	56 - 65
Very, very poor	>66



- **Carr's Index →**

$$= \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

- **Hausner Ratio →**

$$= \frac{\text{Tapped density}}{\text{Bulk density}}$$

flow property	Carr's Index	Hausner's Ratio
Excellent	≤10	1.00 – 1.11
Good	≤11-15	1.12 – 1.18
fair	16-20	1.19 - 1.25
Passable	21-25	1.26 - 1.34
Poor	26 - 31	1.35 - 1.45
Very poor	32 - 37	1.46 - 1.59
Very Very Poor	>38	>1.60

- **Solubility Profile**

Solubility → It is defined as the max. amount of solute particles that can be dissolved in a given solvent at constant temperature

- It is an important parameter to know before formulation.

Solubility ↑ — Absorption ↑

a) Ionization Constant (pka) → The conversion of ionized form to unionized is known as ionization.

Eg. $CH_3COOH \rightleftharpoons CH_3COO^- + H^+$

Unionized — Ionized form

50% — 50%

- Unionized form → Lipid solubility → Lipophilic Absorption ↑
- Ionized form → Water soluble → Hydrophilic ↳ Absorption ↓
- pka can be calculated using the Henderson-Hasselbalch equations.

— for acidic drugs :-

$$pH = pka + \log \frac{Ionised}{Unionised}$$

— for Basic drugs :-

$$pH = pka + \log \frac{Unionised}{Ionised}$$

- Different analytical techniques
  - Spectrophotometric determination, potentiometric titration, etc.

Eg.	Ionization	pKa
Very weak acid	Unionized at all pH	>8.
Moderately weak acid	Unionized at gastric pH 1.2	2.5-7.3
Strong acid	Ionized at all pH	<2.5
Very weak base	Unionized at all pH	>5
Moderately weak base	Unionize at intestinal pH	5-11
Strong base	Ionize at all pH	>11

$HCl \rightarrow -8$

$H_2O \rightarrow 14$

b) pH ⇒ Power of Hydrogen.

OR

Potential of Hydrogen.

- Used to check that particles are acidic / basic.
- It can also affects the solubility of particles.

— By changing the pH, the solubility of the acidic or basic drug can be changed.

— Solubility may be improved with the addition of an acidic or basic excipient.

Eg. Solubility of aspirin can be enhanced by addition of alkaline buffer.

- Dissolution → It is a process by which a solid substance enters the solvent phase to make solution.

Solubility ↑ = (Solution ↑) = Absorption ↑

- Common Ion effects →

↓ Decrease solubility of particles (drug).

eg. When in the solution of acetic acid, Sodium acetate is added. It suppress the dissociation of acetic acid.

$CH_3COOH \rightleftharpoons CH_3COO^- + H^+$

$CH_3COONa \rightleftharpoons CH_3COO^- + Na^+$

Common ion

c) Partition Coefficient →

It is the ratio of unionized drug in oil phase to water phase

$$K_{o/w} = \frac{X_o}{X_w}$$

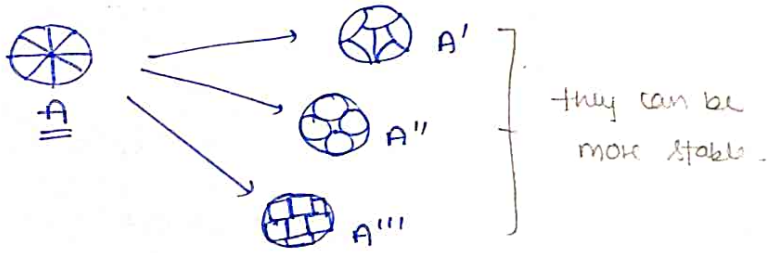
where, X_o = conc. of drug in organic (oily) phase

X_w = conc of drug in aqueous phase

- Drug molecules having higher $K_{o/w}$ will cross the lipid cell membrane

- Polymorphism → Poly — many, morph — form.

- An ability of a drug substance to exist in more than one crystalline phases called polymorphs and this phenomena is known as polymorphism.



— they have different arrangements and may be different melting point, pattern, solubilities, stability & therapeutic activity.

- Compounds which show polymorphism →

Chloramphenicol, indomethacin, sulphonamide,

barbiturates show different polymorphic forms in their solubilities, stability and also their pharmacological activities.

- two types —

i) Enantiotropic → polymorph can be reversibly changed.

ii) Monotropic → irreversible.

- **Chemical Properties**

i) Hydrolysis
ii) Oxidation
iii) Reduction
iv) Racemization
v) Polymerization

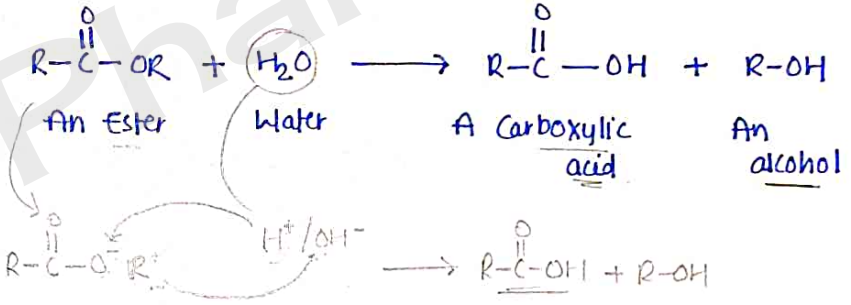
In this, we studied about degradation of drug substance (instability).

i) Hydrolysis → (most common)

When drug substance comes under moisture/water then it react with water and get hydrolysed (breakdown of drug substances). (degradation)

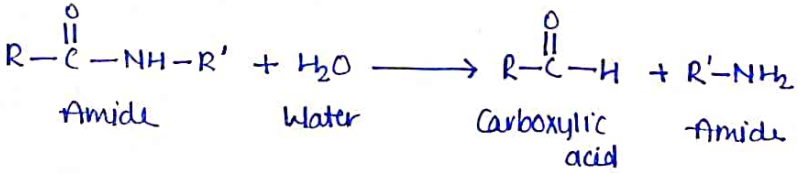
- Mostly drugs with function group ester, amide and lactams (cyclic amides) undergoes hydrolysis.

- Hydrolysis of Ester



(eg) drugs which undergoes hydrolysis — Atropin, procaine, Aspirin etc..

- Hydrolysis of Amide



(eg) Barbiturates, Dibucaine etc—

— prevention →

- Make distance from moisture - use moisture resistance pack for drug substance.
- By use of buffers.
- hydrolysis of procain, benzocain can be prevented by addition of caffeine.
- By modification in chemical structures. etc.

ii) Oxidation — most common

iii) Reduction

- Generally pharmaceutical dosage form (drug substance) oxidized in the presence of atmospheric oxygen.

Oxidation → Addition of Oxygen
Removal of Hydrogen.
Loss of electron.

Reduction → Addition of Hydrogen
Removal of Oxygen
Gain of electron.

- Oxidation occurs due to Oxygen, Heavy metal ions, Light.

— Aldehydes, alcohols, phenols, alkaloids and fats and oil are more susceptible to oxidation.

eg ① Rancidity of oil.

② R—OH $\xrightarrow{O_2}$ R—COOH
alcohol carboxylic acid

③ Hydrogenation of oil (Reduction rxn).

—prevent →

- use of antioxidants such as BHA (Butylated hydroxyl anisole) and BHT (Butylated hydroxyl toluene) etc.
- use of reducing agent to prevent oxidation. (sodium metabisulfite).
- pharmaceutical containers
  | Replaced Oxygen with nitrogen

iv) Racemization →

It is the process in which one enantiomer of a compound is convert into another.

- which can alter pharmacokinetic, pharmacological and taxological properties.
- It depends on temperature, solvent, catalyst and presence or absence of Light.

eg

① L-Epinephrine is 15-20 time more active than D-epinephrine.

② Methadone → one isomer → opioid agonist
→ one isomer → NMDA antagonist

Optically active compound → optically inactive (racemic)

v) Polymerization →

In which two or more identical molecules joined to form large complex or Polymers.

- Chemical degradation.

eg. Degradation of aldehydes.

formaldehyde soln when stand in cold may cause formation of white deposit.

- **BCS** - Biopharmaceutical Classification System

  BCS is a system, which is used to differentiate the drugs on the basis of their Solubility and permeability.

- This classification system based upon USP - United states pharmacopoeia

- Acc. to BCS, drug substances are classified into four classes upon their solubility and permeability.

	Solubility	Permeability	Example
Class I	High	High	Metaprolol
Class II	Low	High	Aceclofenac
Class III	High	Low	Cimetidine
Class IV	Low	Low	Bifonazole

i) Class I → These compounds are well absorbed and their absorption rate is usually higher than excretion. eg. Paracetamol.
- make tablets or oral dosage form easily.

ii) Class II → These compounds have good absorption but slow dissolution and low solubility. (Solution rate ↓)
eg. Phenytoin, Bicalutamide etc.

iii) Class III → These compounds have good solubility but low absorption due to low permeability.

iv) Class IV → These compounds have low absorption, low solubility.
- Poor bioavailability.

- Criteria →
- Solubility class boundaries are based on the highest dose strength of an immediate

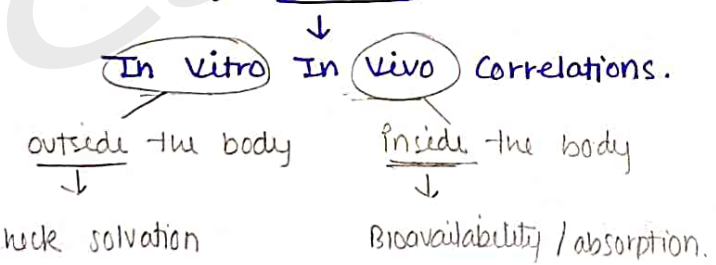
release product.

- A drug is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5.

- A drug substance is considered highly permeable when absorption is 90% or more.

- Significance →

- Useful in formulation of dosage form.
- Used to develop quality control.
- Stimulate food effects on bio-availability.
- Used to study IVIVC.



Stability Analysis

→ The state / quality being steady and not changed.

- But there are many factors which can affects the stability of ~~many factors~~ drug substances.
- factors such as temperature, humidity, light etc influence the quality of drug product over time.
- some physical, chemical and microbiological changes influence the effectiveness, safety and stability of final drug products.

- Physical change → change in appearance of drug products, and also their, M.P, B.P, purity, clarity, and other physical factors.

- Chemical changes → degradation of drug substances. eg. oxidation, hydrolysis etc.

• Microbial changes → drug substance can be decompose due to micro-organism.
↳ microbial contamination.

– The physical, chemical, microbiological, therapeutical, toxicological properties of any drug is remain constant form as per begining → Stability

• These studied are conducted to recommend storage conditions, establish shelf life of drugs.

– Stability analysis includes

a) Solid-state stability analysis
b) Solution-state stability analysis
c) Compatibility studies.

a) Solid-state stability Analysis →

In this, we study about the physical or chemical properties of the drug molecules that may affects the stability of a drug products.

• In this we study about solid dosage form.
• In this we study about those factors which affects solid dosage form such as temperature, pH, humidity, hydrolysis, oxidation etc.

b) Solution-state stability Analysis →

• Degradation in solution form is more rapid than solid form.
• In this, we study about the stability of drug substance at various factors which affects stability such as pH, temp etc..
• The effect of pH on stability is important in the development of both oral and parenteral dosage form.

c) Compatibility studies →

In this, we study about the drug-excipients interaction and how they affects the stability of drug substances.

A + B + C

Preformulation Consideration in development of dosage forms.

Before development of dosage form, we have to consider preformulation studies
physiochemical properties

- Mostly used solid dosage form
  - stable, high safety, low cost
- Considerable points :-
  - Drug substance selection (API)
  - Identify of API
  - Selection of other formulation components
  - Manufacturing processes
  - Most appropriat container closure system
  - Analytic methods
  - Toxicological strategy
- Properties :-
  - Physical and Chemical
    - Organoleptic, purity, particle size + shape, solubility, solubility profile, flow property.
    - Stability of drug substance
- Some techniques :-
  - Spectroscopy - UV spectrophotometry, X-ray diffraction methods are used to characterize the substance
  - Microscopy - Helps to check the particle size, shape and thickness etc of drug molecules
  - Chromatography - TLC (thin layer chromatography) GC (Gas chromatography) and HPLC (High pressure Liquid chromatography) are used to obtain analytical data.