INDUSTRIAL PHARMACY-I

UNIT-I

- Preformulation studies
  - ↳ Introduction
  - ↳ Defination
  - ↳ Goals & objective of preformation
  - ↳ Physico-chemical property of preformation

Preformulation studies

- The word "Pre-formation" refers to the steps to be undertaken befor-formation.
- Pre-formulation Include determine Physical and chemical properties of drug Substance with Goal of developing a New drug is "Safe, Stable and effcacious." (Data collect).
- Investigation of "physicochemical properties" of the New drug.

(1) Goals and objective of preformation

- To determine the Physico-chemical property of drug
- To determine the Kinetics and stabily.
- To determine compatibility of New drug with excipient.
- To determine problem that may osise during Preformulation.

Physico-chemical property of drug

(a) Physical properties :-
- Physical form (Crystal & amorphous)
- Particle size, shape
- flow properties
- Solubility profile (PKa, pH, Partition coefficent)
- Polymorphism

(b) chemical properties :-
- Hydralysis
- Polymerization.
- oxidation
- Reduction
- Racemisation

Physical properties of Drug

(a) ORGANOLEPTIC PROPERTIES

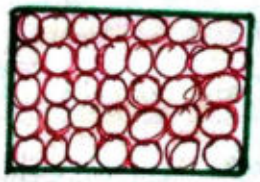
- Organ Means → Sensory
  Leptic Means → Loveing
- It refers evaluation of drug on basis colour, odour, texture and taste.
- Colour of product should be appearing in eye. The odour and taste may be overcome by the use of a less soluble chemical form of the drug.

Purity → Purity studies are essential for further Studies to be carried out safety.

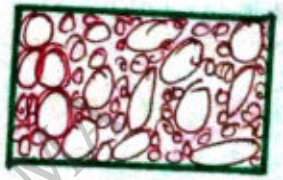
- Some method used to test purity -
- (TLC) Thin layer chromatography.
- (HC) Has chromatography.
- (PC) Paper chromatography

(b) Physical / Bulk form ②

- Drug can be administered therapeutic as "Solid, liquid and gases."
- Solid form are prefered because they can easily converted in to "tablets & capsules"
- A compound can be "crystalline or amorphus" depend on the Internal structure
- Crystalline forms In which the, particles or molecules have the similar shape and they have a fix arrangment.
- It is associated with 3-D assay. high Stability
- Amorphus forms In which the particles or molecules randomly placed as in a liquid. They do not have any fixed Internal structure. Solubility rate is high.



CRYSTALLINE

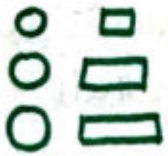


AMORPHUS

(ii) PARTICAL SIZE, SHAPE & SURFACE AREA

These properties of drug affect biopharmaceutical behaviour.

Particle Size → The big difference in the Particle Size, affect flow properties of Powder and cause mixing efficiently [DETERMINE ↓ Microscopy ↓ Sieveing]



Particle shape → The shape and surface charact. also Influence properties like flow and dissolution.

- SHAPE FACTOR is determined which is the ratio of the congest to the shortest dimension

Surface Area → Surface area may be determined by the **BET** Equation.

BET → Graseous absorbtion theory

- The equation states that most substance will absorb a monolayer of gas under certain condition of temp. & pressure.

(iii) Powder flow Properties

- free flowing or cohesive.

factors → Depends on particle size, shape, density, Moisture content, electrostatic charge.

- flow properties of powders is essential for an efficient mixing and tabeletting process.
- Poorly flow powder cause non-uniformly of dose tablet compression.

It can be characterized by

↳ Angle of repose
↳ Compressibility

(A) Angle of repose → It is angle b/w surface of pile of powder and horizontal plane.

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

(B) compressibility

(a) Carr's compressibility Index →

$$\text{Carr's Index}(\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

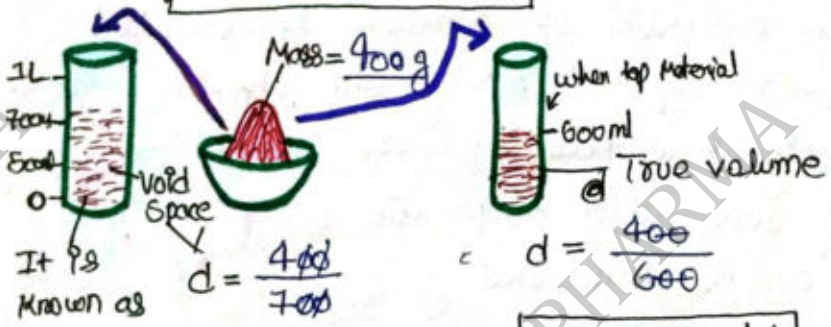
(b) Hausner's ratio →

$$\text{Hausner's ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \times 100$$

(iv) Density of powder (I P)

- Density is a property that provides the characterization of flow ability of powders.

$$\text{Density} = \frac{\text{Mass}}{\text{Volume}}$$



(1) Bulk density = Mass of powder / Bulk volume

(2) Tapped density = Mass of powder / True volume

(v) Solubility Profile

- The amount of the drug (Solute) that dissolve in a given Solution (Solvent) to obtain Saturated Solution.
- Solubility is essential and Important Preformulation parameter before design of dosage form.

(4)

- Sovent system that could occur during drug delivery. for the absorption of drug from dosage form in to systemic circulation. It is necessary that drug should be in solution form.
- Determined in the pH range 1 to 8.

(a) Ionization constant (PKa) ⇒

- Many drugs are either weak acids or weak bases
- It is very Imp. for the study of their Solubility & dissolution rate.
- Gives Handerson Hesselbech

For acidic → $PH = PKa + \log \frac{[\text{Ionized drug}]}{[\text{unionized drug}]}$

For base → $PH = PKa + \log \frac{[\text{unionized drug}]}{[\text{Ionized drug}]}$

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

(b) Common ion effect ⇒ one ion that is already present in solution is added to the solution.

© Partition coefficient → It is also known as distribution.

- The Ratio of unionized drug b/w organic & Inorganic aqueous phase at equilibrium.

$$P_{o/w} = \frac{\text{Drug in octanol}}{\text{Drug in water}}$$

(D) pH solubility →

- By changeing the pH, The solubility of acidic & basic drug will also show a difference solubility.

(E) Polymorphism → "Poly" Means → Many
"Morph" Means → relating to the form drug

- Those solid molecules who do not have fixed structure. Their structure and shape continously changed from one form to another form.

TYPES of Polymorphism

① Enantiotropic → one polymorph can be reversibly changed in to another one by varying temp.

② Monotropic → It is Irreversible. only one polymorph [illegible] at all measurable temp.

CHEMICAL PROPERTIES OF DRUGS

(A) Hydrolysis

- It is the cleavage of chemical bonds by the addition of water.
- The reation of water with with another chemical compound to form two or more Products, Involving the ionization of water molecule using the other compound.
- It is step of degradation of substance.

Ex→ $R-\overset{O}{\overset{\|}{C}}-NH-R' + H_2O \longrightarrow RCOOH + R'-NH_2$

(amide) (Carboxylic acid) (amine)

(B) Oxidation And Reduction

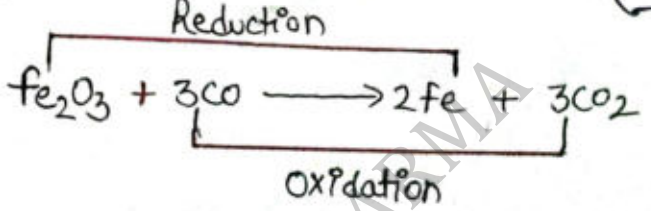
- It is very common pathway for drug degradati in bothe liquid and solid formulation.

Oxidation Mean → Gain of oxygen / loss of electron

Reduction Mean → Gain of ~~Hydro~~ electron

(Redox Reaction)

Ex →

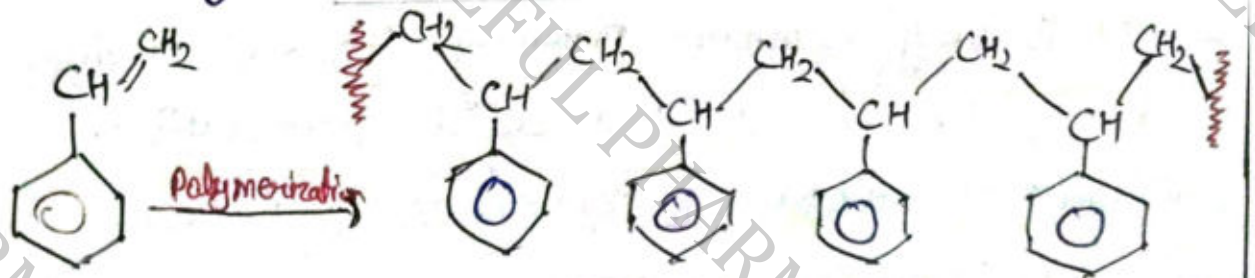


(C) Racemization

- It is a process in which one enantiomer of a compound, such as an L-amino acid, converts to the other enantiomer.
- Optically active compound can racemize depend on the type of grouping attached to asymmetric C-atom. (Chemical Stru. and)

(D) Polymerization

- It is a type of chemical degradation.
- It is a continous reaction b/w molecules.
- More than one monomer reacts to form a polymer.



(Mono) (Poly)

BCS

Biopharmaceutical classification system

- BCS is a system, which is used for classifying drug substance based on its Solubility and permeability.
- This classification system based upon USP.

factor Affecting on BCS

① Solubility → The maximum amount of solute dissolved in a given solvent under standard conditions of temp., pressure and PH.

- The higher single unit dose is completely soluble in 250 ml at PH 1-6.8 (37°C).

② Permeability → Permeability of the drug to pass the biological membrane which is the lipophilic. (absorption).

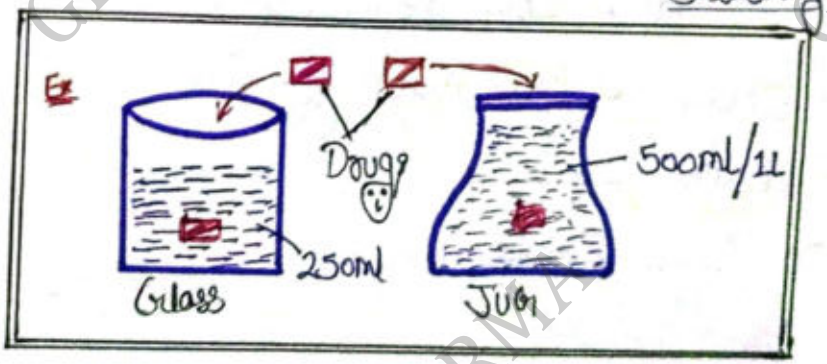
- Highly permable → Exten of absorption in human determine 90%.

Cross

BCS classification system of drugs

CLASS	SOLUBILITY	PERMEABILITY	EXAMPLE
Class-I	High	High	- Metoprolol - Propranolol
Class-II	Low	High	- Nifedipine - Naproxen
Class-III	High	Low	- Cimitidine - Metformin
Class-IV	Low	Low	- Taxal - Chlorthiazole

Dose Number → It is the mass divided by uptake vol. of 250ml and the drug Solubility



[Solubility]

CLASS-I → Both absorption and dissolution number is high/Rapidly.

- Rapid therapeutic effect.
- Make tablets and oral route dosage form.

eg → Paracetamol, Metoprolol.

CLASS-II → Drug absorption rapidly/high but low dissolution and low solubility.

eg → Phenytoin, Danazol.

CLASS-III → These compound have good solubility but low absorption due to low permiability. Ex Cimitidine

CLASS-IV → Drugs are low solubility and low Permeability

- Poor & bioavailability.
- Make Injection

Ex → Taxol & Trihydrate

Application

→ Useful in the Pharmaceutical and biotechnology Industry to formulate dosage forms.
→ used to develop quality control
→ used to study IVIVC

- In Vitro (out side the body) — Solvation
- In Vivo (Inside the body) — absorption

[Correlations]

RREFORMULATION CONSIDERATIONS IN DEVELOPMENT OF SOLID DOSAGE FORMS

—: Solid dosage form are the most widely marketed and administred drug now days.

→: Almost 70% of administered drug are in solid states.

—: It is preferred by the pharmaceutical companies due to its high safety, low cost.

—:— Preformulation studies on solid dosage forms-

- > Organaleptic properties
- > Purity
- > Particle size, shape and surface area.
- > Solubility
- > Stability studies
- > Density
- > Crystal properties and polymorphism

PREFORMULATION CONSIDERATIONS IN DEVELOPMENT OF PARENTERAL DOSAGE FORMS

Parenteral = Para → Outside + Enter → Intestine

Bulk characterization → It include particle size, Powder flow property, polymorphism, crystalline.

Solubility study → It include PKa determination, common ion effect and particial coefficient.

Stability study → It include solution stability and solid state stability.

Spectroscopy → UV spectrophotometry, IR Spectrophotometry and X-rays.

Microscopy → In this method, the substance check / Examined under microscopic for information about shapes, thickness, Particle size etc.