PHYSICOCHEMICAL FACTORS UNDER PREFORMULATION STUDY

CONTENTS:-

5) Polymerization.
6) Isomerization.
7) Decarboxylation.
8) Enzyme Decomposition.

❑ What Is PREFORMULATION?

It is defined as phase of research and development in which preformulation scientist characterize physical & chemical properties of new drug molecule in order to develop safe, effective, and stable dosage form.

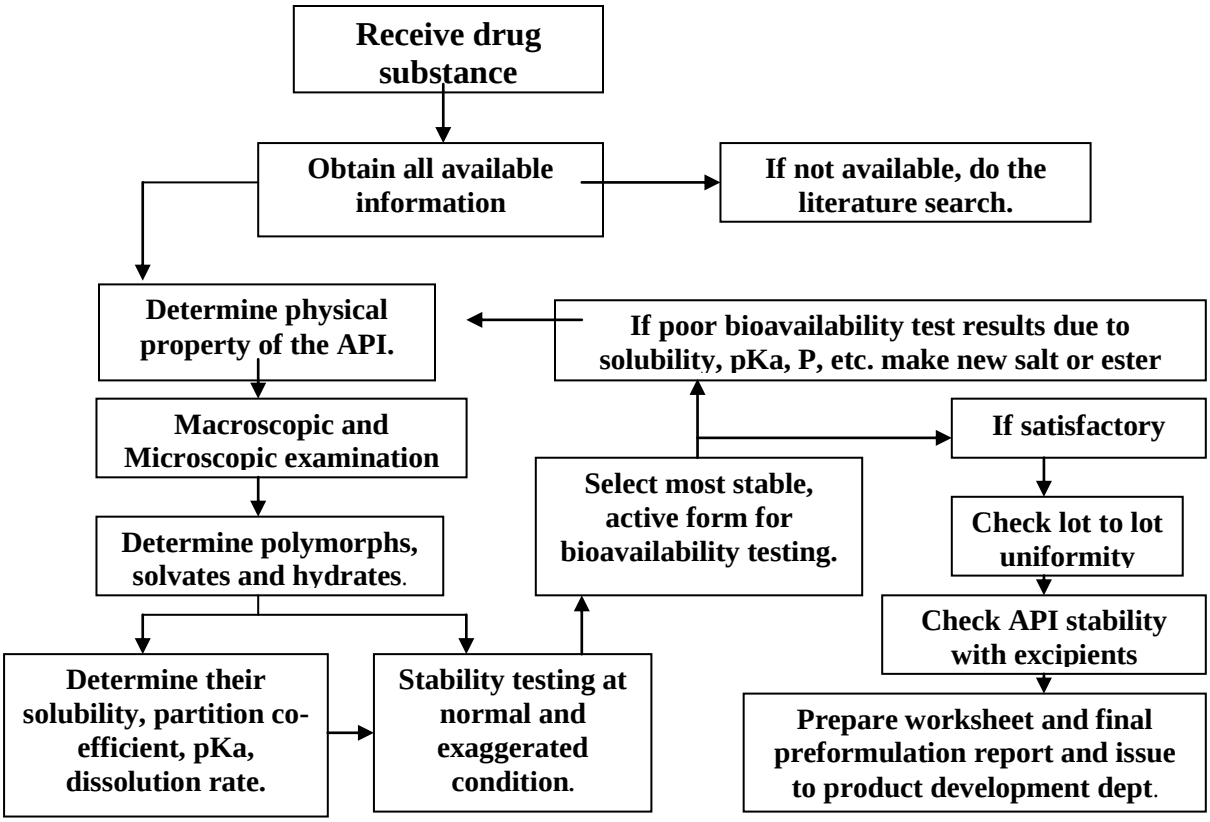
DIRECT BENEFITS:

- ❑ Gives direction for development of formulation in choice of dosage form,excipients,composition,physical structure.
- ❑ Helps in adjustment of Pharmacokinetics and biopharmaceutical properties.
- ❑ Support for process development of drug substance (yield,filtration..).
- ❑ Produce necessary and useful data for development of analytical methods.

According to USFDA it can be characterized as:-

- ➢ Melting point (hot stage microscopy).
- ➢ IR spectroscopy.
- ➢ XRD.
- ➢ Thermal analytical technique.
- ➢ Solid state Raman spectroscopy.
- ➢ Crystalline index of refraction.
- ➢ Phase solution analysis.
- ➢ Solution calorimetery.
- ➢ Comparative intrinsic dissolution rate.

➢ FLOW CHART FOR PREFORMULATION STUDY:



[B] SOLUBILITY ANALYSIS

AQUEOUS SOLUBILITY

- A drug must possess aqueous solubility for therapeutic efficacy in physiological pH range of 1 to 8 at 37 ºC.
- Poor solubility (<10mg/ml) may result into bioabsorption problems.
- If solubility of drug is less than 1 mg/ml it indicates the need for a salt, particularly if the drug will be formulated as a tablet or capsule.
- In the range 1-10 mg/ml serious consideration should be given to salt formation.

- There are **2 fundamental properties** mandatory for a new compd.
  [a] Intrinsic Solubility (Co).
  [b] Ionization Constant (pKa).

[a] INTRINSIC SOLUBILITY(Co):-

- The solubility of weakly acidic & weakly basic drug as a function of pH can be predicted with the help of eqn.

$S = So \{1 + (K_1 / [H^+])\}$ ---------- for weak acids.
$S = So \{1 + ([H^+] / K_2)\}$ ---------- for weak bases.

where, S = Solubility at given pH.
So = Intrinsic solubility of the neutral form.
K_1 = Dissociation constant of weak acid.
K_2 = Dissociation constant of weak base.

- The intrinsic solubility should ideally be measured at 2 temperatures:

a) 4 ºC → To ensure physical & chemical stability.
b) 37 ºC → To support biopharmaceutical evaluation.

<u>Method to determine solubility</u>

(1) Equilibrium solubility method
(2) Turbidometric solubility method
(3) Nephlometric solubility method
(4) Ultrafiltration LC/MS solubility method
(5) Direct solubility method
(6) NRTL – SAC method
[JPS VOL-97 NO-5 May-2008]
(7) COSMO SAC method
[Chemical Abstracts;July-2008 147(05)-568563h]

- **<u>Solubility parameter is used to design dry suspension of cefaclor as a dual pack system</u>. (IJPS):**

BASED ON SOLUBILITY PARAMETER ONE CAN DECIDE WHETHER PARTICULAR SOLUTE WILL SOLUBILIZE IN A GIVEN SOLVENT OR NOT.
SOL. PARAMETER OF CEFACLOR VARIES GREATLY WITH WATER & CEFACLOR IS HIGHLY LIPOPHILIC SO IT IS INSOL. IN WATER WHEN WATER WAS MIXED WITH CO-SOLVENT PEG IN THE RATIO 80:20 THE SOL. PARAMETER OF THE MIXTURE WAS FOUND SIMILAR TO THAT OF CEFACLOR & THEREFORE IT GETS EASILY SOLUBILIZED IN IT…
DUAL PACK SYSTEM IS PREFERRED BECAUSE CEFACLOR BEING A CEPHALOSPORIN CLASS ANTIBIOTIC IS HIGHLY UNSTABLE IN WATER SO…

[b] IONIZATION CONSTANT (pKa):-

- 75 % of all drugs are weak bases,
- 25 % are weak acids and only,

- 5 % are nonionic amphoteric or alcohol.

- The unionized forms are more lipid soluble & more rapidly absorbed from g.i.t.

- The relative conc. of unionized & ionized form of weakly acidic or basic drug in a solution at a given pH can be calculated using the **Henderson-Hasselbalch equation**:-

  pH = pKa + log [unionized form] / [ionized form] ---- for weak bases.

  pH = pKa + log [ionized form] / [unionized form] ---- for weak acids**.**

- **<u>Uses of these equations</u>:-**

1) To determine pka.
2) To predict solubility at any pH provided that Co & pKa are known.
3) To facilitate the selection of suitable salt forming compounds.
4) It predicts the solubility & pH properties of the salts.

- **<u>Limitation</u>:-**
- To fail outside the pH limits of 4-10 or when the solution is very dilute.

- **<u>Method to determine pka</u>:-**
  1) Potentiometric method.
  2) Conductivity method.
  3) Dissolution rate method.
  4) Liquid-Liquid partition method.
  5) Spectrophotometric method.

- **<u>SOLUBILIZATION</u>**

Many different approaches have been developed to improve drug solubility:

1) <u>Micronization</u>:-

- Eg. Griseofulvin shows increased solubility by reducing particle size.

2) <u>Change in pH</u>:-

Eg. Solubility of Nimesulide increases as pH is increased.
[**Chemical Abstracts, 133(6); August 2000: 79182g**]
Eg.Arginine increases solubility of coumarins**.**
[Chemical Abstracts, April 2009; 150 : 290306j]

Eg. Etoposide formulation is difficult because of its poor solubility &

labile chemical stability so its most stable formulation is Etoposide loaded emulsion (ELE) at pH 4-5.
[**JPS July 2007; 96(7): 1791**]

3) **Cosolvency:-**
- Addition of a water miscible solvent can often improve the solubility of a weak electrolyte or nonpolar compound in water by altering the polarity of the solvent.
- The choice of suitable cosolvent is limited for P'ceutical use because of possible toxicity & irritancy.
- Ideally suitable blends should possess values of dielectric constant between 25-80.
- Commonly used cosolvents are ethanol, sorbitol, glycerin, propylene glycol, dimethylacetamide (DMA), DMSO, etc.

4) **Solubilization by surfactant:-**
- Eg. Gelucire 44/14 is a surface active excipient that can solubilize poorly soluble drugs. [**JPS June 2004; 93(6): 1471**]
- Eg. Anionic & cationic surfactants exhibited dramatically higher solubilization for gliclazide, while nonionic surfactants showed significantly lower solubilizing ability. [**JPS April 2003; 92(6): 839**]

5) **Complexation:-**
- Eg. The Complexation of iodine with 10-15% polyvinylpyrolidone (PVP) can improve aqueous solubility of active agent.

6) **Formation of Inclusion Compound:-**
- Eg. The aqueous solubility & chemical stability of Quercetin can be improved via Complexation with β-cyclodextrin.
- Eg. The enhancement of solubilization increased 300 fold for Nimodipine at a polymer conc. 10% by use of water soluble dendrimer based on polyglycerol. (**Chemical Abstracts, July 2007; 147(5): 101548u**)

Eg. Enhanced solubilty of oxicams through inclusion of β- cyclodextrin and its dvts. **(CA-VOL151 Sep2009:107806f)**

7) **Chemical Modification:-**
- Many poorly soluble drugs modified into salt form (water soluble).

8) **Use of Metastable polymorphs:-**
- Eg. B form of Chloramphenicol palmitate is more water soluble than A & C forms.

PARTITION COEFFICIENT:-
- The gastrointestinal membranes are largely lipoidal in character hence the lipid solubility of a drug is an imp. factor in the assessment for its absorption potential.
- When a solute is added to two immiscible liquids it will distribute itself between

the two phases in a fixed ratio, which is referred to as **partition or distribution coefficient**.

- It is independent of concentration of dilute solution of given solute species.
- Various organic solvents used in determination of partition coefficient include Chloroform, ether, amyl acetate, etc.
- Solubility parameter of **n-octanol** (δ=10.24) lies midway in the range for major drugs (δ=8-12). Thus in formulation development the n-octanol-water partition coefficient is commonly used.

- P= (Conc. of drug in octanol) / (Conc. of drug in water) --- For unionizable drugs.
- P= (Conc. of drug in octanol) / (1-α)*(Conc. of drug in water) --- For ionizable drugs. where α = degree of ionization.

- P > 1 ⇨ Lipophilic drug.
- P < 1 ⇨ Hydrophilic drug.

- The value of P at which maximum activity of controlled release dosage forms is observed is approximately 1000:1 in octanol/water.

Methods to determine P:-

a) Shake Flask Method.
b) Chromatographic Method (TLC, HPLC).
c) Counter Current & Filter Probe method.

Applications of P:-

- Measure of Lipophilic character of molecules.
- Recovery of antibiotics from fermentation broth.
- Extraction of drug from biological fluid for therapeutic monitoring.
- Absorption of drug from dosage forms. (Ointments, Suppositories, Transdermal patches).
- Study of distribution of flavoring oil between oil & water in emulsion.

THERMAL EFFECT:-

- Effect of temperature on the solubility of drug can be determined by measuring heat of solution. (ΔHs).

$$\ln S = -\Delta Hs/R*T + C.$$

where, S = Molar solubility at temperature T (ºK).
R = Gas constant.

- Heat of solution represents the heat released or absorbed when a mole of solute is dissolved in a large quantity of solvent.

- Mostly solution process is endothermic (ΔHs = +ve) & thus increasing the solution temperature increase the drug solubility.
- Typical temp. range should include 5ºC, 25ºC, 37ºC & 50ºC.

Importance: Determination of temperature effect on solubility helps in predicting storage condition & dosage form designing.

COMMON ION EFFECT:-

- Addition of common ion reduces the solubility of slightly soluble electrolyte.
- The "**salting out"** results from the removal of water molecules as solvent due to the competing hydration of other ions.
- So weakly basic drug which are given as HCl salts have decreased solubility in acidic solution.
  Eg. Chlortetracycline, Papaverine, Bromhexine, Triamterene, etc.

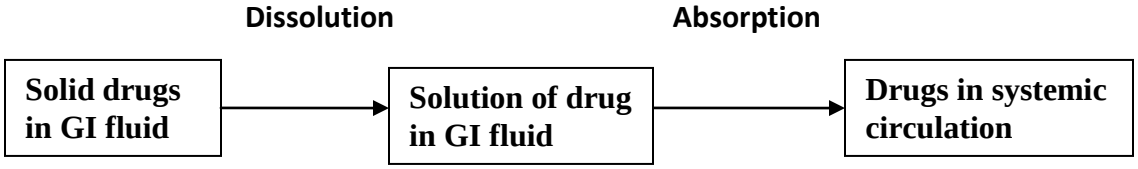
- The reverse process "**salting in"** arises with larger anions. (Eg. Benzoate, salicylate) which can open the water structure.
- These hydrotropes increase the solubility of poorly water soluble compounds.

- To identify a common ion interaction the IDR (Intrinsic dissolution rate) of HCl salt should be compared between
  a) Water & water containing 1.2% W/V NaCl.
  b) 0.05 M HCl & 0.9% NaCl in 0.05 M HCl.

- Both saline media contains 0.2 M Cl^- which is typically encountered in fluids in vivo.

DISSOLUTION

- The absorption of solid drugs administered orally can be understood by following flowchart.



- In many instances, dissolution rate in the fluids at the absorption site is the rate limiting step in the absorption process.
- Dissolution rate can affect
  - Onset of action.
  - Intensity of action.
  - Duration of response.
  - Control the overall Bioavailability of drug form.

- Dissolution is to be considered of 2 types:

[1] Intrinsic dissolution

- The dissolution rate of solid in its own solution is adequately described by **Noyes-Whitney equation:**

$$dC/dt = AD (Cs-C) / hv$$

where, dc/dt = Dissolution rate.
A = Surface area of dissolving solid.
D = Diffusion coefficient.
C = Concentration of drug in solution.
h = Thickness of diffusion layer (at the solid- liquid interface).
v = Volume of dissolution medium.
Cs = Solute concentration in the diffusion layer.

- This equation helps to the preformulation scientist in predicting if absorption would be dissolution rate limited or not.

- **Method to determine intrinsic dissolution:-**
- **Rotating disk method or Wood's apparatus:**
  This method allows for the determination of dissolution from constant surface area, obtained by compressing powder into a disc of known area with a die-punch apparatus.

[2] Particulate dissolution

- This method determines the dissolution of solids at different surface area.
- A weighed amount of powder sample from a particular sieve fraction is introduced in the dissolution medium. Agitation is usually provided by a constant speed propeller.
- It is used to study the influence on dissolution of particle size, surface area & mixing with excipients.

STABILITY ANALYSIS

- Development of a drug substance into a suitable dosage form requires the Preformulation stability studies of drug under the following categories:-
  [1] Solid state stability.
  [2] Solution state stability.

[1] Solid state stability

- Solid state reactions are much slower & more difficult to interpret than solution state reactions because of reduced no. of molecular contacts between drug & excipient molecules & occurrence of multiple reactions.

❁ **Techniques for solid state stability studies:[JPS April 2007; 96(4):777]**

- Solid State NMR Spectroscopy. (SSNMR)
- Powder X-ray diffraction. (PXRD)
- Fourier Transform IR. (FTIR)
- Raman Spectroscopy.
- Differential Scanning Calorimetry. (DSC).
- Thermo gravimetric Analysis. (TGA).
- Dynamic Vapor Sorption. (DSV).

[2] Solution State Stability

- The primary objective is identification of conditions necessary to form a solution.
- These studies include the effects of

- pH.	- Temperature.
- Light.	- Oxygen.
- Cosolvent.	- Ionic Strength.

- Aq. Solution for injection pH 3 containing Irinotecan HCl, phosphate buffer & WFI was stably prepared by dissolving camptothecins without resorting to heating in the course of production. [**Chemical Abstracts, Feb. 2007; 146(9): 169430j**]

- Chitosan hygrogel can change reversibly well at different pH & ionic strength of solution. [**Chemical Abstracts, Sep. 2007; 147(10): 219725c**]

- Solution Stability investigations usually commence with probing experiments to confirm decay at the extremes of pH & temperature.

- If the results of this solution stability studies dictate the compound as sufficiently stable, liquid formulation can be developed.

Stress conditions used in Preformulation stability assessment:-

Test	Condition
SOLID	
Heat (ºC)	4, 20, 30, 40, 40/75 % RH, 50 & 75.
Moisture Uptake	30,40,60,75 & 90 % RH at RT.
Physical Stress	Ball milling.
AQUEOUS SOLUTION	
pH	1,3,7,9 & 11 at RT & 37ºC. Reflux in 1M HCl & 1M NaOH.
Light	UV (254 &366 nm) & Visible (south facing window) at RT.
Oxidation	Sparing with oxygen at RT, UV may accelerate breakdown.

CHEMICAL CHARACTERISTICS

I. OXIDATION

- It is a very common pathway for drug degradation in liquid & solid formulation.

- Oxidation occurs in two ways:-
  1. Auto oxidation.
  2. Free radical chain process.

Auto oxidation:-

- It is **defined as** a reaction of any material with molecular oxygen which produces free radicals by hemolytic bond fission of a covalent bond.
- These radicals are highly unsaturated & readily take electron from other substance causing oxidation.
- For auto oxidation to occur in solid molecular oxygen must be able to diffuse through the crystal lattice to liable sites. Hence crystal morphology & packing are important parameters for determining oxidation kinetics.

Free radical chain process:-

a) INITIATION

$$RH \xrightarrow[\text{Light, Heat}]{\text{Activation}} R^{\cdot} + H^{\cdot}$$

b) PROPAGATION

$$R^{\cdot} + O_2 \longrightarrow RO_2^{\cdot}$$

$$RO_2^{\cdot} + RH \longrightarrow RCOOH + R^{\cdot}$$

c) HYDROPEROXIDE DECOMPOSITION

$$RCOOH \longrightarrow RO^{\cdot} + OH^{\cdot}$$

d) TERMINATION

$$RO_2^{\cdot} + X \longrightarrow \text{Inactive product}$$

$$RO_2 + RO_2 \longrightarrow \text{Inactive product}$$

Functional groups having high susceptibility towards oxidation:-

- Alkenes.
- Substituted aromatic groups. (Toluene, phenols, anisole).
- Ethers.
- Thioethers.
- Amines.

Factors affecting oxidation process:-

1. Oxygen concentration.
2. Light.
3. Heavy metals particularly those having two or more valence state. (Eg. Copper, iron, nickel, cobalt).
4. Hydrogen & Hydroxyl ion.
5. Temperature.

Prevention of oxidation:-

1) Reducing oxygen content.

- Oxidative degradation of drug takes place in an aqueous solution, so the oxygen content can be decreased by boiling water.

2) Storage in a dark & cool condition.

3) Addition of an antioxidant.

a) Reducing agent.
b) Chain inhibitors of radical induced decomposition.

ANTIOXIDANT	
↓	↓
Oil Soluble	**Water Soluble**
↓	↓
Free radical acceptor & inhibit free radical chain process.	Oxidized itself & prevent oxidation of drug.
EXAMPLES	
Hydroquinone	Sodium metabisulphate
Propyl gallate	Sodium bisulphite
Butylated Hydroxy Anisole (BHA)	Acetyl cysteine, Ascorbic acid
Butylated Hydroxy Toluene (BHT)	Sodium thiosulfate, Sulphur dioxide
Lecithin	Thioglycolic acid
α- Tocopherol	Thioglycerol

4) Addition of chelating agent.

- It forms complexes with trace amount of heavy metal ion & inactivate their catalyzing activity.
  Eg. EDTA, Citric acid, Tartaric acid.

5) Adjustment of pH.

- To optimum stability in order to reduce oxidation potential of the system.

6) Changing solvent.

- Solvent other than water may have catalyzing effect on oxidation reaction when used in combination with water or alone.
  Eg. Aldehydes, ethers, ketones may influence free radical reaction.

II. HYDROLYSIS

- It involves nucleophilic attack of labile groups.
  Eg. Lactam > Ester > Amide > Imide.
- When this attack is by a solvent other than water then it is known as **solvolysis.**
- It generally follows 2nd order kinetics as there are 2 reacting species, water and API.
- In aqueous solution, water is in excess, the reaction is 1st order.

Conditions that catalyze the breakdown:-

(1) Presence of hydroxyl ion.
(2) Presence of hydride ion.
(3) Presence of divalent ion.
(4) Heat.
(5) Light.
(6) Ionic hydrolysis.
(7) Solution polarity & ionic strength.
(8) High drug concentration.

Prevention of hydrolysis:-

1) pH adjustment.

- Most of the potent drugs are weakly acidic or weakly basic, which are more soluble when ionized so their instability will increase.
- **Remedy**:-
  - Formulate the drug solution close to its pH of optimum stability.
  - Addition of water miscible solvent in formulation.
  - Optimum buffer concentration to suppress ionization.

2) Addition of surfactant.

- Nonionic, cationic & anionic surfactant stabilizes the drug against base catalysis.

3) Salts & esters.

- The solubility of p'ceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts or ester of drug.
  Eg. Phosphate ester of Clindamycin.

4) Store with dessicants.

5) By use of complexing agent.

III. PHOTOLYSIS

❋ **<u>Mechanism of photodecomposition</u>:-**

- Electronic configuration of drug overlaps with spectrum of sunlight or any artificial light, & thereby energy is absorbed by electron & it goes to the excited state.

- They are unstable & release the acquired energy & come to the ground state & decompose the drug.

- **Photosensitization** means molecule or excipient which absorbs energy but do not participate themselves directly in the reaction but pass the energy to other that will cause cellular damage by inducing radical formation.

Photosensitizer	
↓	↓
Energy transfer	**Electron transfer**
↓	↓
Convert oxygen from its ground state to singlet excited state.	Generate superoxide molecule, which is an anion radical & acts as a powerful oxidizing agent.

❋ **<u>Photodecomposition pathway</u>**

(1) N-Dealkylation.
Eg. Diphenhydramine, Chloroquine, Methotrexate.

(2) Dehalogenation.
Eg. Chlorpropamide, Furosemide.

(3) Dehydrogenation of Ca^{++} channel blocker.
Eg. Solution of Nifedipine → Nitrosophenylpyridine (with loss of water).
↓
Rapidly yellow color → Brown.

(4) Decarboxylation in anti-inflammatory agents.
Eg. Naproxen, Flurbiprofen, Benzoxaprofen.

(5) Oxidation.
Eg. Chlorpromazine & other phenothiazines give N- & S- oxides in the presence of sunlight.

(6) Isomerization & cyclization.
Eg. Noradrenaline, Doxepine.

(7) Rearrangement.
Eg. Metronidazole → Oxidiazine → Yellow color.

Examples:

⇨ Aq. solution of Lincomycin was irradiated with UV light in homogenous & heterogenous systems. Lincomycin disappeared in both systems but the presence of TiO2 noticeably accelerated the degradation of antibiotic in comparison with direct pyrolysis. The degradation pathways involved S- & N- demethylation & propyl dealkylation. [**Chemical Abstracts, April 2007; 146(18): 365263w**]

⇨ The photodegradation behaviour of bisphenol C studied in monochromatic UV irradiation (λ= 254 nm) indicated that phtotodegradation reaction rate constant of bisphenol C in aq. soln. with β- cyclodextrin is higher than that wihtout β-cyclodextrin, mainly due to lower bond energy between some atoms in bispheol C molecule after inclusion interaction with β- cyclodextrin.
[**Chemical Abstracts, Aug. 2007; 147(7): 149559a**]

✵ **Prevention of Photodecomposition:-**

1) Suitable packing.
Eg. Yellow-green glass gives the best protection in U.V. region while Amber confers considerable protection against U.V. radiation but little from I.R.

2) Anti-oxidant.
Eg. Photodegradation of Sulphacetamide solution may be inhibited by an antioxidant such as Sodium thiosulfate or sodium metabisulphate.

3) Protection of drug from light.
[Eg. Nifedipine is manufactured under Na light**]**.

4) Avoiding sunbath. [Eg. Sparfloxacin**]**.

5) Photostabilizer (light absorber).
- Colorant - Curcumine, Azorubine.
- Pigments - Iron oxide, Titanium dioxide.

6) **Coating.**
   - Pigments like TiO_2 / ZnO.
   - Eg. Photostabilization of Sulphasomidine Tab. by film coating containing U.V. absorber (Oxybenzone) to protect color & photolytic degradation. [**JPS Feb. 1978; 67(2): 196**]

IV. RACEMIZATION

- The interconversion from one isomer to another can lead to different P'cokinetic properties (ADME) as well as different P'cological & toxicological effect.
- Eg. L-epinephrine is 15 to 20 times more active than D-form, while activity of racemic mixture is just one half of the L-form. [**JPS April 2004; 93(4): 969**]
- It follows first order kinetics.
- It depends on temperature, solvent, catalyst & presence or absence of light.

V. POLYMERIZATION

- It is a continuous reaction between molecules.
- More than one monomer reacts to form a polymer.
- Eg. Darkening of glucose solution is attributed to polymerization of breakdown product [5- (hydroxyl methyl) furfural].
- Eg. Polymerization of HCHO to para-HCHO which crystallizes out from the solution.

VI. ISOMERIZATION

- It is the process involving change of one structure to another having same empirical formula but different properties in one or more respects.
- Its occurrence is rare.

Examples:-.

(1) Tetracycline & its dvts. can undergo reversible Isomerization at pH range 2-6.
(2) Trans-cis Isomerization of Amphotericin B.
(3) Isomerization of tetrahydrouridine. [**JPS October 2003; 92(10): 2027**]

VII. DECARBOXYLATION

- Evolution of CO_2 gas from –COOH group containing drugs.
- Eg. Solid PAS undergoes pyrolytic degradation to m-aminophenol & CO_2.
- The reaction which follows 1^{st} order kinetics is highly pH dependent & is catalysed by hydronium ions.

VIII. ENZYME DECOMPOSITION

- Chemical degradation due to enzymes induced by drug results into decomposition.

Remedy: -

- Use of buccal tab.
- Use of pro-drug. (L-dopa).

- **ACCORDING TO WHO:**

- Hydrolysis and Oxidation are the most common pathways for API degradation in the solid-state and in solution.

- Photolysis and trace metal catalysis are secondary processes of degradation.

- Temperature affects each of the above chemical degradation pathways; the rate of degradation increases with temperature.

- It is well understood that pH, particularly extremes, can encourage hydrolysis of API when ionised in aqueous solution. This necessitates buffer control if such a dosage form is required.

SUMMARY: **The preformulation evaluation of new drug substances has become an integral part of the development process. Preformulation studies, properly carried out, have a significant part to play in anticipating formulation problems and identifying logical paths in both solid and liquid dosage form. A thorough understanding of the physico-chemical properties of drug substances provides the development pharmacist with the data that are essential in designing stable & efficacious dosage forms.**

- **Comparing physico chemical property with each drug candidate within a therapeutic group, the preformulation scientist can assist the synthetic chemist to identify optimum molecule, pharmacologist to suit the vehicle for electing desired p'cological response and the bulk pharmacist to select and produce best salt with proper p'cle size and morphology for subsequent processing.**

STUDY QUESTIONS

[1] Enlist physical, chemical & pharmaceutical factors affecting preformulation?
→ Discuss chemical decomposition factors with special reference to photodecomposition and methods to retard it? **[April 2006]**

[2] Enlist different chemical degradation pathways in preformulation studies?
→ Explain the various factors influencing degradation pathway?
→ How are the drug subs stabilized against chemical degradation? **[March 2005]**

[3] How is the photo degradation study carried out as per current guidance documents? **[Sept.2004]**

[4] Describe various factors to be considered in preformulation studies? **[Sept.2005]**

[5] Explain any two of the following characteristics that are to be considered before dosage form design?
→ Oxidation → Photo degradation → Hydrolysis **[Jan.2003]**

Different means of arresting hydrolysis of Active P'ceutical Materials? **[May 2003]**

COMMENT:

[6] **IS PREFORMULTION STUDIES APPLICABLE TO NEW DRUGS ONLY?**

[7] How do we control humidity for lab scale purpose?

[8] Occurrence of Degradation pathways according to WHO?

(10)Techniques for the physico-chemical determination acc. to US-FDA?

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