CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com ***Review Article***

AN OVERVIEW ON PREFORMULATION STUDIES

Prasanna Kumar Desu*, G.Vaishnavi, K. Divya, U.Lakshmi,
Department of Pharmacy, St.Mary's Group of Institutions, Guntur.

Abstract:
Every drug has intrinsic chemical and physical properties which has been consider beforedevelopment of pharmaceutical formulation. This property provides the framework for drug'scombination with pharmaceutical ingredients.Preformulation studies carried out by various research scientists is reviewed. Preformulationstudies conduct for newly synthesiedcompounds or extracted compound and it gives the information regarding the degradation process, any adverse conditions relevant to the drug, bioavailability, pharmacokinetics and formulation of similar compound and toxicity. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product qualityin the fabrication of dosage form.

Key words: *Preformulation, dissolution, oxiadation, computability studies*

Corresponding Author:
D. Prasanna Kumar,
Department of Pharmacy,
St.Mary's Group of Institutions,
Guntur.
Email.id: Prasanna.desu@gmail.com
Mbl.No:9966916329

QR code

Please cite this article in press as ***Prasanna Kumar et al*****, An Overview on Preformulation Studies,** *Indo Am. J. Pharm. Sci, 2015;2(10).*

INTRODUCTION

Preformulation studies were evolved in 1950 & early 1960.Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico- mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials [1,2].

Preformulation during Drug Discovery

Apart from helping formulation development, preformulation studies also help in lead identification during drug discovery phase. A new chemical entity should possess optimal biopharmaceutical properties to become a drug molecule. Mere possession of potency and selectivity does not ensure 'drug ability'. Preformulation studies help in assessing the 'drug ability' of a molecule. Preformulation can thus be considered as critical decision-making tool during both – drug discovery and development phase. A comprehensive understanding of physicochemical properties and its effect on biological performance, allows selection of potential lead molecules and in identification of drug delivery challenges.

Objectives

- ✓ To develop the elegant dosage forms (stable, effective & safe}
- ✓ It is important to have an understanding of the physical description of a drug substance before dosage form development.
- ✓ It is 1st step in rational development of a dosage form of a drug subt before dosage form development.

Goals

- ✓ To establish the physico-chemical parameters of new drug substance.
- ✓ To establish the physical characteristics
- ✓ To establish the kinetic rate profile.
- ✓ To establish the compatibility with the common excipient.
- ✓ To choose the correct form of a drug substance.

3. PREFORMULATIONPARAMETERS:

A. PHYSICAL CHARACTERISTICS.

1) Organoleptic properties
2) Bulk characteristics
a) Solid state characteristics
b) Flow properties
c) densities
d) compressibility
e) crystalline
f) polymorphism
g) hygroscopicity

3) Solubility analysis
a) Ionization constant(P^{ka})
b) Partition co-efficient
c) Solubilization
d) Thermal effect
e) Common ion effect(Ksp)
f) Dissolution

4) Stability analysis
a) Solution-state stability
b) Solid-state stability
c) Drug-excipients compatibility

B. CHEMICAL CHARACTERISTICS

1) Hydrolysis
2) Oxidation
3) Photolysis
4) Recemization
5) Polymerization
6) Isomerization

1. ORGANOLEPTIC PROPERTIES

A typical preformulation program should begin with the description of the drug substance. The color, odour and taste of the new drug must be recorded using descriptive terminology. The color, odour and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property. A list of some descriptive terms to describe the most commonly encountered colors, tastes and odours of pharmaceutical powders is provided in table. The color of all the early batches of the new drug must be recorded using the descriptive terminology. A record of color of the early batches is very useful in establishing appropriate specifications for later production. When the color attributes are undesirable or variable, incorporation of a dye in the body or coating of the final product could be recommended.

Table 1: Terminology to describe organoleptic properties of pharmaceutical powders.

Colour	Odour	Taste
Off-white	Pungent	Acidic
Cream yellow	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic	Intense
	Odouerless	Sweet
		Tasteless

2. BULK CHARACTERISTICS:

a) Solid state characteristics:

Powders are masses of solid particles or granules surrounded by air (or other fluid)and it is the solid plus fluid combination that significantly affects the bulk properties of the powder. It is perhaps the most complicating characteristic because the amount of fluid can be highly variable.Powders are probably the least predictable of all materials in relation to flow ability because of the large number of factors that can change their rheological properties. Physical characteristics of the particles, such as size, shape, angularity, size variability and hardness will all affect flow properties. External factors such as humidity, conveying environment, vibration and perhaps most importantly aeration will compound the problem.

Particle size and size distribution:
Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also in some instances on their biopharmaceutical behaviour.For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drug. It is now generally recognized that poorly soluble drugs showing a dissolution rate- limiting step in the absorption process will be more readily bioavailable when administered in a finely sub divided state than as a coarse material.Size also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipients, mutual sieving (de- mixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps.

Table .2: Common Techniques for Measuring Fine Particles of Various Sizes

Technique	Particle size (micro meters)
Microscopic	1-100
Sieve	>5
Sedimentation	>1
Elutriation	1-50
Centrifugal	<50
Permeability	>1
light scattering	0.5-50

b) POWDER FLOW PROPERTIES :

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the preformulation stage to be "poorly flowable," the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be precompressed or granulated to improve their flow properties. Some of these methods are angle of repose, flow through an orifice, compressibility index, shear cell, etc. Changes in particle size and shape are generally very apparent; an increase in crystal size or a more uniform shape will lead to a smaller angle of repose and smaller carr's index [3,4].

Angle of Repose:
The maximum angle which is formed between the surface of pile of powder and horizontal surface is called the angle of repose.

For most pharmaceutical powders, the angle-of-repose values range from 25 to 45°, with lower values indicating better flow characteristics.

$$\tan \theta = h / r$$

h = height of heap of pile, r = radius of base of pile

c) Densities:
The ratio of mass to volume is known as density
Types of density:

(a) Bulk density: It is obtained by measuring the volume of known mass of powder that passed through the screen.

(b) Tapped density: It is obtained by mechanically tapping the measuring cylinder containingpowder.

(c) True density: It actual density of the solid material.

(d) Granule density: may affect compressibility, tablet porosity, disintegration, dissolution

d) Compressibility:

"Compressibility" of a powder can be defined as the ability to decrease in volume under pressure and "compactability as the ability of the powdered material to be compressed into a tablet of specified tensile strength.

It can be used to predict the flow properties based on density measurement.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{pored density} * 100}{\text{Tapped density}}$$

e) Crystallinity [5-8]:

Generally most of drugs exist in solid state. Very few are in liquid state like valproic acid and even less in gaseous form like some general anesthetics. A crystal structure is a unique arrangement of atoms in a crystal. Physical properties affected by the solid-state properties can influence both the choice of the delivery system and the activity of the drug, as determined by the rate of delivery. Chemical stability, as affected by the physical properties, can be significant. A crystalline particle is characterized by definite external and internal structures. Crystal habit describes the external shape of a crystal, whereas polymorphic state refers to the definite arrangement of molecules inside the crystal lattice. Crystallization is invariably employed as the final step for the purification of a solid. The use of different solvents and processing conditions may alter the habit of recrystallized particles, besides modifying the polymorphic state of the solid.

f)Polymorphism:

Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs.When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecules at the lattice sites.

Methods to identify polymorphism

- ✓ Optical crystallography
- ✓ Hot 0stage microscopy
- ✓ X- Ray Diffraction method
- ✓ NMR technique
- ✓ FTIR technique.
- ✓ Microcalorimetry
- ✓ Thermal methods
- ✓ Melting point determination

g) Hygroscopisity:

Many compounds and salts are sensitive to the presence of water vapour or moisture. When compounds interact with moisture, they retain the water by bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, a solution (deliquescence). Deliquescence is where a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, the liquid film surrounding the solid is saturated. This process is dictated by vapour diffusion and heat transport rates.

Moisture is also an important factor that can affect the stability of candidate drugs and their formulations. Sorption of water molecules onto a candidate drug (or excipient) can often induce hydrolysis.In this situation, by sorbing onto the drug-excipient mixture, the water molecules may ionize either or both of them and induce a reaction. For example, we have found that a primary amine, when mixed with lactose was apparently stable even when stored at 90°C for 12 weeks. However, when the experiment was carried out in the presence of moisture, extensive degradation by way of the well-known Mailliard reaction took place. Other properties such as crystal structure, powderflow, compaction, lubricity, dissolution rate and polymer film permeability may also be affected by moisture adsorption.

Table 2: Different classes of hygroscopic substances

Hygroscopicity Classification		
Class 1	Non-Hygroscopic	Essentially no moisture increases occur at relative humidities below 90%.
Class 2	Slightly hygroscopic	Essentially no moisture in occur at relative humidity below 80%
Class 3	Moderately hygroscopic	Moisture Content does not increase more than 5% after storage for 1 week at relative humidity below 60%
Class 4	Very hygroscopic	Moisture content increase may occur at relative humidity as low as 40 to 50%

3. Solubility Analysis:

An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for therapeutic efficacy in the physiological P^{H} range of 1 to 8. For a drug to enter into systemic circulation, to exert therapeutic effect, it must be first in solution form. If solubility of drug substance is less than desirable, than consideration must be given to increase its solubility. Poor solubility **(< 10mg/ml)** may exist incomplete or erratic absorption over P^{H} rang 1-7 at 37°C. However, knowledge of two fundamental properties is mandatory for a new compound

i) Intrinsic solubility(Co)

ii) Dissociation constant (P^{ka}).

i) Intrinsic Solubility (Co)

The intrinsic solubility should be measured at two temp: **4 to 5°C** to ensure good physical stability and to extend short term storage and chemical stabilityuntil more definite data is available. **37° C** to support biopharmaceutical evaluation. The solubility of weakly acidic and weakly basic drug as function of P^{H} can be predicted with help of equation,

S = So	{1 + (K1/ [H+])}	For weak acid.
S = So	{1+ ([H+]/ K2)}	For weak base.

Where, S = solubility at given $P^{H.}$

So = intrinsic solubility of neutral form.
K1 = dissociation constant for the weak acid.
K2 = dissociation constant for weak base.

a) Ionization Constant(PKA) [9-12]:

Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. The un- ionized species are more lipid-soluble and hence more readily absorbed. The gastrointestinal absorption of weakly acidic or basic drugs is thus related to the fraction of the drug in solution that is un- ionized.The conditions that suppress ionization favor absorption. The factors that are important in the absorption of weakly acidic and basic compounds are the pH at the sit e of absorption, the ionization constant, and the lipid solubility of the un- ionized species. These factors together constitute the widely accepted pH partition theory. The relative concentrations of un-ionized and ionized forms of a weakly acidic or basic drug in a solution at a given pH can be readily calculated using the Henderson-Hasselbalch equations:

$$pH = pKa + \log \frac{[\text{Un- ionized form}]}{[\text{ionized form}]} \quad \text{for bases}$$

$$pH = pKa + \log \frac{[\text{Ionized form}]}{[\text{un ionized form}]} \quad \text{for acids}$$

Weakly acidic compounds (pKa< 4.3) were absorbed relatively rapidly;Those with pKa values ranging between 2.0 and 4.3 were absorbed more slowly; and strong acids (pKa> 2.4) were hardly absorbed.For bases, those with pKa values smaller than 8.5 were absorbed relatively rapidly; those with a pK a between 9 and 12 were absorbed more slowly; and completely ionized quaternary ammonium compounds were not absorbed. In pharmacokinetic area, the extent of ionization is imp. affect of its extent and absorption, distribution, elimination. The extent of P^{ka} , in many cases, highly dependent on P^{H} of the medium containing the drug.

Determination of Pka:

- ✓ Potentiometric Titration
- ✓ Spectrophotometric Determination
- ✓ Dissolution rate method
- ✓ Liquid-Liquid Partition method

b). Partition Coefficient:

The lipophilicity of an organic compound is usually described in terms of a partition coefficient; log *P*, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$P_{o/w} = (\text{C oil/water})_{\text{equilibrium}}$$

Or

$$\log P = \frac{(\text{un ionized compound})_{org}}{(\text{un ionized compound})_{aq}}$$

This ratio is known as the partition coefficient or distribution coefficient and is essentially independent of concentration of dilute solutions of a given solute species. log*P* = 0 means that the compound is equally soluble in water and in the partitioning solvent. If the compound has a log *P* = 5, then the compound is 100,000 times more soluble in the partitioning solvent. A log *P* = –2 means that the compound is 100 times more soluble in water, i.e., it is quite hydrophilic. Drugs having values of P much **greater than 1** are classified as lipophilic, whereas those with partition coefficients much **less than 1** are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the

best predictor of absorption rate, the effect of Must not be neglected. Lipids occurring in living membranes are complex and difficult to obtainin pure form. An indication of the relative lipid solubility, however, can be obtained by determining how a drug substance distributes itself between water and an immiscible organic solvent. When a solute is added to two immiscible liquids that are in contact with each other, it will distribute itself between the two phases in a fixed ratio. This ratio is known as the partitioncoefficient,or distribution coefficient, and is essentially independent of concentration of dilute solutions of a given solute species. Various organic solvents such as chloroform, ether, amyl acetate, isopropylmyristate, carbon tetrachloride, and n - Octanol can be used in the determination of the partition coefficient, with the latter gaining increasing acceptance.

Methods of finding Partition coefficient:

1) Shake-flask method
2) Chromatographic method.
3) Counter current and filter probe method.
4) Tomlinson's filter probe method.
5) Microelectrometrictitratation method
6) Automated instrument is now available.

Applications of Partition coefficient:

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, Transdermalpatches).
Study of distribution of flavouring oil between oil & water in emulsion.

c). Solubilization:

For drug candidates, with either poor water solubility or insufficient solubility for projected solution dosage form, preformulation study should include limited experiments to identify possible mechanism for solubilization.

Methods for Increasing Solubility:

- ✓ Change in pH
- ✓ Co-Solvency
- ✓ Dielectric Constant
- ✓ Solubilization by Surfactant
- ✓ Complexation
- ✓ Hydrotropy
- ✓ Chemical Modification of drug

d) Thermal Effect:

We determine the effect of temp. on the solubility of drug candidate. This can be determined by measuring heat of solution i.e. **H**s

$$\ln S = -\frac{\Delta H_S}{R}\left(\frac{1}{T}\right) + C$$

Where,
dC / dt = dissolution rate
dissolution rate, pKa, and solubility on absorption
Where, S = molar solubility at temp. T (° K)
R = gas constant.

Heat of solution represents the heat released or absorbed when mole of solute is dissolved in large quantity of solvent. It is determined from solubility value for saturated solution equilibrated at controlled temperature over the range of interested. Typically the temperature range should include 5 °C, 25°C, 37°C and 50°C.If heat of solution is positive (endothermic process) thus, increasing solution temp. Increased the drug solubility. For **non-electrolyte and un-ionized** form of weak acid and weak bases dissolved in water, heat of solution range from 4 to 8 Kcal/mol.

e) Common Ion Effect:

A common interaction with solvent, which often overlooked, is the common ion effect. The addition of common ion often reduces the solubility of slightly soluble electrolyte. This salting out results from the removal of the water molecule as the solvent due to competing hydration of other ions. So, weakly basic drug which are given as HCL salts have decreased solubility in acidic (HCL) solution.

Eg.Chlortetracycline, methacyclin, papaverine, cyproheptadine, bromhexine,Triamterene

To identify a common ion interaction, the intrinsic dissolution rate of hydrochloride salt should be compared between, Water and water containing 1.2%W/V NACL 0.05M HCL and 0.9%W/V NACL in 0.05M After this, if solubility is not decreased than we can give drug in chloride salt, otherwise it should be eliminated.

f) Dissolution:

In many instances, dissolution rate in the fluids at the absorption site, is the rate limiting steps in the absorption process. This is true for the drug administered orally in the solid dosage forms such as tablet, capsule, and suspension as well as drug administered I.M. in form of pellets or suspension.Dissolution is of 2 types.

a) Intrinsic dissolution
b) Particulate dissolution

a)Intrinsic Dissolution

The dissolution rate of a solid in its own solution is adequately describedby the Noyes-Nernst equation:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{hv}$$

A = surface area of the dissolving solid
D = diffusion coefficient

C = solute concentration in the bulk medium
h = diffusion layer thickness
V = volume of the dissolution medium
Cs = solute concentration in the diffusion layer
During the early phase of dissolution, Cs » C and is essentially equal to saturation solubility S. Surface area A and volume V can be held constant.Under these conditions and at constant temperature and agitation, Equation reduces to
dC / dt = KS
Where
K =AD/hV = constant.
Dissolution rate as expressed in Equation is termed the intrinsic *dissolution rate* and is characteristic of each solid compound in a given solventunder fixed hydrodynamic conditions. The intrinsic dissolution rate in a fixed volume of solvent is generally expressed as mg dissolved x(min-1 cm- Z). Knowledge of this value helps the preformulation scientist in predicting if absorption would be dissolution rate-limited.

Particulate dissolution:

It will determine dissolution of drug at different surface area.It is used to study the influence on dissolution of particle size, surface area and mixing with excipient. So, if particle size has no influence on dissolution than other method like addition of surfactant will be considered.

4. STABILITY STUDIES:

Incompatibility- general aspects

When we mix two or more API and / or excipient with each other & if they are antagonistic & affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible.

(A). Solid State Stability Studies:

Solid state reactions are much **slower** and more **difficult to interpret** than solution state reactions, due to a reduced no. of molecular contacts between drug and excipient molecules and to the occurrence of multiple phase reactions.

Sample A	Sample B	Sample C
• **Prepare a small mixture of drug and excipient.** • **Place above mix in vial.** • **Palce a rubber closure on vial and dip the stopper in molten carnuba wax to render it hermetically sealed.**	Sample preparation method is same as sample A but 5% moisture is added in mixture.	Drug itself without any excipient is taken as a sample for solid state stability study.

- ✓ All the samples of drug-Excipient blends are kept for 1-3 weeks at specified storage conditions.
- ✓ Then sample is physically observed for (1) caking (2) liquefaction (3) Discoloration (4) odor (5) gel formation.
- ✓ It is then assayed by TLC or HPLC or DSC.
- ✓ Whenever feasible, the degradation products are identified by MASS SPECTROSCOPY, NMR or other relevant analytical techniques.

(B) Solution State Stability Studies [13]:

It is easier to detect liquid state reactions as compared to solid state reactions. For detection of unknown liquid incompatibilities, the program set up is same as solid dosage forms. Now according to ―Stability guidelines‖ by FDA states that:
Following conditions be evaluated in studies on solutions or suspensions of bulk drug substances:

1) Acidic or alkaline pH.
2) Presence of added substances- chelating agents, stabilizers etc.
3) High Oxygen and Nitrogen atmospheres.
4) Effect of stress testing conditions……

Methodology:-

- ✓ Place the drug in the solution of additives.
- ✓ Both flint and amber vials are used.
- ✓ Autoclave conditions are employed in many cases. This will provide information about
  Susceptibility to oxidation.
  Susceptibility to light exposure.
  Susceptibility to heavy metals.
- ✓ In case of oral liquids, compatibility with ethanol, glycerine, sucrose, preservatives and buffers are usually carried out.

(C) Drug-Excipient Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipents, the preformulation scientist must generate the needed information. A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much subject to the discretion of the preformulation scientist.

Importance of Drug Excipient Compatibility Study:-

- ✓ Stability of the dosage form can be maximized. Any physical or chemical interaction between drug and excipient can affect bioavailability and stability of drug.
- ✓ It helps to avoid the surprise problems. By performing DECS we can know the possible reaction before formulating final dosage form.

- ✓ It bridges the drug discovery and drug development. Drug discovery can emerge only new chemical entity. It becomes drug prod uct after formulation and processing with excipients.
- ✓ By using DECS data we can select the suitable type of the excipient with the chemical entities emerging in drug discovery programs. DECS data is essential for IND (investigational new drug) submission. Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

Analytical techniques used to detect Drug-Excipient Compatibility:

1) Thermal methods of analysis
I. DSC- Differential Scanning Calorimetry
II. DTA- Differential Thermal Analysis
2) Accelerated Stability Study
3) FT-IR Spectroscopy
4) DRS-Diffuse Reflectance Spectroscopy
5) Chromatography
I. SIC-Self Interactive Chromatography
II. TLC-Thin Layer Chromatography
III. HPLC-High Pressure Liquid Chromatography
6) Miscellaneous
I. Radiolabelled Techniques
II.Vapour Pressure Osmometry
III. Fluorescence Spectroscopy

B. CHEMICAL CHARACTERISTICS [14]

a) Hydrolysis-It involves nucleophilicattack of labile groups eg: lactam ester amide imide. When the attack is by the solvent other than water, then it is known as solvolysis. It generally follows 2nd order kinetics as there are two reacting species, water and API. In aqueous solution, water is in excess so the reaction is 1st order. Conditions that catalyze the breakdown are Presence of hydroxyl ion, hydride ion, divalent ion and heat, light, ionic hydrolysis, solution polarity and ionic strength, high drug concentration. Hydrolysis can be prevented by Adjusting the P^H.As most of the potent drugs are weakly acidic or weakly basic in nature. Formulate the drug solution close to it'sPHof optimum stability or by Addition of water miscible solvent in formulation or by Using Optimum buffer concentration to suppress ionization or by Addition of surfactant such as non-ionic, cationic and anionic surfactant stabilizes the drug against base catalysis or the solubility of pharmaceuticals undergoing ester hydrolysis can be reduced by forming less soluble salts or ester of drug. eg: phosphate ester of Clindamycin or Store with desiccants, using complexing agents.

b) **Oxidation:**

It is a very commonpathway for drug degradation in liquid and solid formulations. Oxidation occurs in two ways
1. Auto- oxidation
2. Free radical chain process.

Reaction of any material with molecular oxygen producing free radicals by hemolytic bond fission of a covalent bond. These radicals are highly unsaturated and readily accept electron from other substance causing oxidation is called Auto-oxidation. Free radical chain process involves Initiation, Propagation, Hydro peroxide decomposition and Termination. Factors affecting oxidation process are Oxygen concentration, light, heavy metals particularly those having two or more valence state (copper, iron, nickel, cobalt), hydrogen and hydroxyl ion, temperature. Oxidation can be Prevented by Reducing oxygen content-oxidative degradation of drug takes place in an aqueous solution, so the oxygen content can be decreased by boiling water or by storing the formulation in in a dark and cool condition or by addition of an antioxidant/reducing agent /chain inhibitors of radical induced decomposition. Antioxidants are of two types based on Solubility. Oil soluble and Water soluble. Oil Soluble Antioxidants are Free radical acceptors and inhibit free radical chain process eg: hydroquinone, propylgallate, lecithin whereas Water soluble Antioxidants Oxidizes itself and prevents oxidation of drug Eg: sodium metabisulphate, sodium bisulfate, thioglycolic acid, thioglycerol.

c) Reduction: is a relatively morecommon pathway of drug metabolic process. Hepatic microsomescatalyze diverse reductive chemical reaction* and require NADPHfor this purpose. Azo and nitro reduction is catalyzed by cytochrome P-450.Chloral hydrate is reduced to it's active metabolite trichloroethanol by alcohol dehydrogenase. Reduction of prednisolone and cortisone results in the formation of their active metabolites hydrocortisone. Azo dyes used as coloring agents in pharmaceutical products or food are reduced to form amines in the liver and by the intestinal flora.

d)Photolysis: Mechanism of photodecomposition: Electronic configuration of drug overlaps with the spectrum of sunlight or any artificial light where energy is absorbed by the electron resulting in excitation. As they are unstable, they release the acquired energy and return to the ground state by decomposing the drug. The phenomenon where molecules or excipients which absorb energy but donot participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization. Photosentizer Convert oxygen from its ground state to singlet excited state and Generate superoxide molecule which is an anion radical and acts as a powerful oxidizing

agent.

Photo Decomposition Pathway

1. N-dealkylation: eg:Dipenhydramine, Chloroquine, Methotrexate
2. Dehalogenation: eg:-Chlorpropamide, Furesemide
3. Dehydrogenation of ca++ channel blockers
4. Decarboxylation in anti-inflammatory drugs: Naproxen, Flurbiprofen, Benzoxaprofen
5. Oxidation:- Chlorpromazine and other phenothiazines give n- oxides in the presence of sunlight.
6. Isomerization and cyclization:- Noradrenaline, Doxapine
7. Rearrangement: Metronidazole and oxidiazine yellow color Photodecomposition canbe Prevented by-suitable packing, antioxidant, protection of drug from light, avoiding sunbath, photostabilizer, coating [6].

e) 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.

f) 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 ofracemic mixture is just one half of the L-form.
- ✓ It follows first order kinetics.
- ✓ It depends on temperature, solvent, catalyst & presence or absence of light.

CONCLUSION

Preformulation studies have a significant part to play in anticipating formulation problems and identifying logical paths in both liquid and solid dosage form Technology. By comparing the physicochemical properties of each drug candidate within a therapeutic group, the Preformulation scientist can assist the synthetic chemist to identify the optimum molecule, provide the biologist with suitable vehicles to elicit pharmacological response. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization. In parallel solid-state stability by DSC, TLC and HPLC in the presence of tablet and capsule excipient will indicate the most acceptable vehicles for solid dosage form. This review article gives details of above studies with respect to any sustained release dosage forms can be developed without preformulation studies.

REFERENCES

1. Albert,A.A. and Serjeant,E.P(1984) ionization constants of Acids and Bases.Wiley,Newyork.
2. Yalkowiski,S.H.andRoseman,T.J(1981) Techniques of solubilisation of Drugs,Chapter3,ed.S.H.Yalkowski Marcel Dekker,Newy.
3. Kaplan,S.A.(1972)Drug Metab.Rev,1,15 -32.
4. Davies,S.S and Higuchi,T. (1970) j. Pharm Sci.,59-137.
5. Leon Lachman , Herbart liebeman. The theory and practice of industrial pharmacy .Indian Edition CBS publishers.2009.
6. LoyolV.Allen.Jr.Nicholas,G.Popovich Howard C.Ansel. pharmaceutical forms and drug delivery system. 8th Edition 2005. BI.Publications.
7. Michael E Aulton. Pharmaceutics,The Science of Dosage form Design. 2nd Edition.,2005.
8. Jens T. Cartstensen,C.TRhodes.Drug Stability Principles and practices. 3rd Edition Replica Press Ltd.,2000.
9. Guy RH, Hadgraft J, Bucks DA. Transdermal drug delivery and cutaneous metabolism, Xenobiotica 1987, 7, 325-343.
10. Aulton ME, Pharmaceutics-The science of dosage form design,1st(Internatoinal student) Edn., Churchill Livingstone , New yok,1996.p,113-138.
11. Kandavilli S, Nair V, Panchagnula R. Polymers in transdermal drug delivery systems, Pharmaceutical Technology 2002, 62-78.
12. Guy RH. Current status and future prospects of transdermal drug delivery, PharRes1996, 1765-1769.
13. Baker RW, Heller J. Material selection for transdermal delivery systems; In: Hadgraft J, Guys RH, editors. Transdermal Drug Delivery:Development Issues and Research Initiatives. New York, Marcel Dekker Inc. 1989; 293-311.
14. D.Swathi, Sowjanya et al, Various aspects of Pharmaceutical Preformulation: A Review, PHARMANEST: An International Journal of Advances in Pharmaceutical Sciences. ISSN: 2231-0541, Vol(4),Issue(2), Pages:171-190, Mar 2013.