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Review Article

VARIOUS ASPECTS OF PHARMACEUTICAL PREFORMULATION: A REVIEW

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ABSTRACT

Elaborated interpreting of drug substance is requisite to minimize formulation problems in later stages of drug development in order reduce drug development costs and diminish the products time to market. Goals of Preformulation is to demonstrate the physico-chemical properties of new drug substances, to set up the kinetic rate profile of drug, to lay down the physical characteristics and to build compatibility with the excipients. The present review focuses on the various aspects in setting the Preformulation study that helps to understand the concept of Preformulation and its role in assistance of Preformulation scientist to identify the optimum molecule in providing the biologist with suitable vehicles to elicit pharmacological response.

Key words: Preformulation, Charecteristics, Drug-Excipient Compatibility Study.

INTRODUCTION:

Preformulation can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Almost all new drugs are commercialized as tablets, capsules or both. Only few are marketed as an injection. I.V route is compulsory for early toxicity, metabolic, bioavailability and clinical studies to furnish a accurate drug and dose deposition.Before developing this major dosage forms, it is necessary that certain fundamental physical and chemical properties of drug molecule and other derived properties of powder are checked. The objective case of Preformulation examination is to engender valuable information to the formulator to formulate a stable and bioavailable dosage form.

Table.1. Data required for setting Preformulation Study

To examine	**process**
Spectroscopy	UV simple assay
Solubility purity	Phase solubility
a) Aqueous	intrinsic and PHeffect
b) Pka	solubility control and salt formation
c) Salt	solubility, hygroscopicity, stability
d) Solvents	vehicles and extraction
e) Ko/w	Lipophilicity, structure activity
f) Dissolution	biopharmacy
Melting point	DSC- Polymorphism, hydrates, solvates
Assay development	UV, TLC, HPLC
Stability	
a) In solution	thermal hydrolysis, PH
b) In solid state	oxidation, photolysis
Microscopy	particle size and morphology
Bulk density	Tablet and capsule formation
Powder flow	Tablet and capsule formation
Angle of repose	Tablet and capsule formation
Compression properties	Tablet and capsule formation
Excipient compatibility	Preliminary screening by DSC, confirmation by TLC
Analytical Preformulation	
Attributes such as identity, purity, assay and quality	
Identity: NMR, IR, UV, DSC, Optical Rotation	
Purity: moisture (water and solvents), heavy metals, inorganic elements, organic impurities	
Assay: titration, UV, HPLC	
Quality : appearance, odour, solution, color, PHof slurry, melting point	

The first step in Preformulation is to build a simple analytic method. Most drugs assimilate light in UV (190-390nm) due to presence of aromatic and double bonds. Acidic/ basic nature of molecule is noticed from functional groups. Using UV spectrum of drug, it is possible to choose a wavelength suitable to measure the quantity of drug in particular solution. Excitement of molecule in solution causes loss in energy. Net change from intensity of incident light and transmitted light can be measured. The amount of light absorbed by the drug solution is proportional to the concentration and pathlength (c) and pathlength of the solution (l) through which light is passed. In pharmacy, doses of drugs and concentration are in unit weights rather than in molarity.

Thus specific absorption coefficient can be given as

E= AF/ X

Where A = Absorbance

F = Dilution factor E=Molar Extinction Coefficient

X = Weight of drug in mg

It is now possible to determine concentration of drug in any solution by measuring absorbance[1]

C= AF/ E

PREFORMULATION CHARECTERISTICS

I) PHYSICAL - Physical-Particle size, shape, Surface area, melting point, Pka & solubility, partition coefficient, salt formation, polymorphism, crystal form, interfacial tension, wetting of solids, flow characteristics, compressibility

II) CHEMICAL - degradation pathways

A. Hydrolysis
B. Oxidation
C. Reduction
D. Photolysis
E. Drug excipients compatibility study

III) BIOPHARMACEUTICAL- lipid solubility, dissolution constant, dissolution rate, drug stability in GIT, Complexation

I) PHYSICAL CHARACTERISTICS:

a) Particle size: bulk flow, formulation homogeneity, dissolution

Various (chemical and physical properties) of drug substances are effected by their particle size, distribution, shape and morphology. Particle size determined by sieving, microscopy, sedimentation. Coulter-counter is also used for particle size analysis. Particle size not only effects physical properties of solid drugs but also on their biopharmaceutical behavior. Generally poorly soluble drugs showing a dissolution rate limiting step in the absorption process will be more readily bioavailable when administered in a finely divided state than on course material. Very fine materials are difficult to handle but many difficulties can be overcome by creating solid solution of interest in a carrier such as water soluble polymer. It

represents size and shape influence the flow and mixing efficiency of powders and granules. Size can also be a factor in stability. Fine materials are more open to attack from atmospheric oxygen; humidity. Size also plays a role in homogeneity of final tablet. Particle size considerations in suspensions: Drug particle size comprises a crucial element tempting product appearance, settling rates, drug solubility, in vivo absorption re dispersibility and overall constancy of pharmaceutical suspensions. Ostwald ripening is the growth of large particles at the expense of small ones, owing to a difference in solubility rates of different size particles. The effect may be expressed by the relationship.

Particle size considerations in parenterals: The particle size of a water soluble drug is not of concern unless it exists in large aggregates and an increase in rate of solution is desired to reduce manufacturing time. Under such circumstances milling through an appropriate size sieve may be sufficient. Slightly soluble drugs such as diazepam is know to precipitate in body fluids following injection because although sufficiently soluble in their co-solvent dosage form, they are not soluble in aqueous body fluids. The precipitated particles may dissolve eventually, but the rate of dissolution is slow.

Particle size distribution in suppositories: The particle size of the suspended drug and the presence of surfactants are factors that affect drug release from suppositories.

Particle size distribution in aerosols: Particle size distribution is probably one of the most important characteristic of an (MDIC) metered dose inhalers. To be effective, the particles emitted from the spray must be below 10µ and in most cases between 2-8µ in diameter.

b) Pka and solubility: Pka determination of a drug molecule will help to predict the Fate of the drug in physiological conditions**,** Pharmacokinetic parameters of a drug and Tendency of a drug molecule to form a salt.

Procedure for determination of Pka: If d rug is Water soluble then dissolve the Drug in 0.25M Kcl water titrated with 0.01N NaOH in 0.25M Kcl water. Plot PHVs Titer volume. Determine the Half Neutralization Point (HNP). HNP gives aqueous Pka. If drug is not Water soluble. Dissolve the Drug in Organic Solvent water mixture [ACN or Methanol+ DMSO+0.25M Kcl water] titrated with 0.01N HCL and 0.01N NaOH (0.25M Kcl water). Plot PHV_S Titer Volume. HNP gives Pka. Determine the Pka's in Different concentrations of Organic solvents. Plot concentration of organic solvent Vs Pka. Extrapolate to zero concentration of organic solvent. It gives the value of aqueous Pka.

b) Solubility: Solubility is defined in quantitative terms as the concentration of a solute in a saturated solution at a certain temperature. The availability of a

drug is always limited and initially Preformulation studies have only 50mg. As the compound is new, the quality may be invariably poor, large number of impurities may be present and often first crystals come down as metastable polymorph. Thus the solubility and Pka values are determined. Solubility dictates the ease with which formulation for oral garage & I.V injection studies are obtained. Pka allows the informed use of PHto maintain solubility and to choose salts required to achieve good bioavailability from solid state and improve stability and powder properties. A drug substance administered by any route must possess same aqueous solubility for systemic absorption and therapeutic response. Solubility is of two types- Aqueous solubility and intrinsic solubility

Aqueous solubility: Poorly soluble compounds i.e. aqueous solubility less than 10mg/ml PHrange (1-7) at 37 degrees Celsius may exhibit incomplete erratic & slow absorption and thus produce minimal response at desired dosage. A solubility < 1mg/ml indicates the need for salt (tablets & capsules).When solubility cannot be manipulated in this way, glycosides, sterols, alcohols, where Pka <3 for base, >10 for acid, then liquid filling in soft or hard gelatin capsules may be necessary. Enhanced aqueous solubility can be achieved by preparing More derivative (salts, esters) of parent compounds or By chemical complexation or By reducing particle size.

Intrinsic solubility: The solubility of the drug is determined in solvents such as 0.1N Hcl, 0.1NNaOH and water. Most commonly the solubility is determined by analyzing the samples with UV Spectrophotometric method. An increase in both acid and alkali suggests either amphoteric or zwitter ions will have 2 Pka's one in acidic and in basic. No change in solubility suggests non-ionizable neutral molecules with no measurable Pka**.** Purity of a substance can also be determined by phase solubility diagrams. Desired drug solubility for good oral absorption depends on the permeability of compound & required dose.

Table.2. Desired solubility correlated to therapeutic doses

Dose(mg/kg) permeability	**Solubility values(mg/kg) for drugs with**		
	high	medium	low
0.1	1	5	21
1	10	52	207
10	100	520	2100

Table.3.Approximate solubilities of pharmacopeial and national formulary substances are indicated by descriptive terms

Terms	part of solvent required for 1part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	32-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Insoluble	>10000

The solubility should be ideally measured at 2 temperatures

1) **40⁰ C** -To ensure physical stability and extend short term storage. Chemical stability until more definite data becomes available. Maximum density of water occurs at 40C. It leads to minimum aqueous solubility.

2) **37 ⁰ C** - To support biopharmaceutical evaluation however absolute purity is often doubt and crucial solubility can be accurately determined by using phase solubility diagram. The data obtained from series of experiments in which ratio of amount of drug to the dissolving solvent is varied. Any deviation from the horizontal is an indicative of impurities in which higher drug loading and it's inherent impurities either promotes or suppresses solubility.

Determination of solubility: It is ascertained by equilibrium solubility method. Extra material is dissolved in solvent and agitated for extended time until equilibrium is reached.

Different solvents utilized are - water, ethanol, methanol, castor oil, peanut oil, sesame oil, benzyl alcohol and buffers at various PH.

Pka from solubility data

75% of drugs are weak bases

20% of drugs are weak acids

5% of drugs are non ionic, Amphoteric / alcohol

It is appropriate to consider Henderson-Hasselbalch equation for weak bases/acids.

For weak bases PH= Pka+log10[B]/[BH+]

Weak acids PH= Pka+log10[A-]/[HA]

Equations are used to determine Pka. If intrinsic solubility & Pka are known,solubility at any PHcan be predicted. Equations are useful to select suitable salt forming compounds and predict the solubility and P H properties of the salts.When the PHis 2units either side of Pka then the drug will be either completely ionized or unionized.To have

any chance of significant PHsolubility manipulation, the Pka for a base must be greater than 3 and for an acid less than 11. If the solubility of the drug is measured in 0.1N Hcl (A) or 0.1N NaOH (B) then the intrinsic solubility (C0) will be solely due to the unionized free acids or bases. If the solubility is then measured at $P^{H}4$ and 6 for bases, the resultant saturated solubility (Cs) can be used in equations to calculate Pka.

Table.4.Examples of drug salt forms

Salt counterion	Pka	drug (base)	Pka
Hydrobromide	-8.0	dextromethorphan	8.3
Hydrochloride	-6.1	numerous	-
Nitrate	-1.44	mionazole	6.7
phosphate	2.15	codeine	8.2

The Pka value of the drug substance decides the aqueous and lipophilic solubility of the drug and hence alters the reactivity and permeability of the drug through various biological membranes[2].

c) Partition coefficient: The Partition coefficient P is a measure of lipophilicity of a compound. It is measured by determining the equilibrium concentration of a drug in an aqueous phase (generally water) and an oily phase (generally octanol or chloroform) held in contact with each other at a constant temperature .Various organic solvents such as CHcl3, ether, amyl acetate, isopropyl myristate, Carbon tetrachloride and n-octanol can be used in the determination of Partition coefficient with the later gaining increasing acceptance. In the determination of Partition coefficient, both the aqueous and organic phases are presaturated with respect to each other. The drug is then dissolved in either the aqueous or the organic phase and the known volumes of the two phases are equilibrated by shaking. The phases are separated by standing or via centrifugation. Partition coefficient has a number of applications which are relevant to Preformulation Solubility can be estimated in Both aqueous and in mixed solvents, Drug absorption invivo: Applied to a homologous series for Structural Activity Relationship (SAR), Partition chromatography: choice of column (HPLC) or plate (TLC) and choice of mobile phase (eluant). Relative polarities of solvents can be scaled using Dielectric constant, Solubility parameter, Interfacial, Hydrophilic-liphiophilic balance (HLB) .The best solvent is its polarity matches with the solute. This can be obtained by determining solubility maxima using dielectric constant. Ko/w is the most useful scale of solute polarity. The equation used to relate solvent solubility to partition coefficient ie.,Log Ko/w = log P

Yalkowsky & Roseman(1981) derived the expression for 48 days in propylene glycol.

Effect of partition coefficient on formulation: In case of parenteral emulsions, P values may provide an indication of the duration of activity that a drug is likely to achieve. If the partition coefficient is high, a depot effect can be expected for the drug dissolved in oily phase.

Effect of partition coefficient on suppository formulation: The partition coefficient of a drug is an important consideration in the selection of the suppository base and in anticipating drug release from that base. A lipophilic drug that is distributed in a fatty suppositary base in low concentration has fewer tendencies to escape into the aqueous fluids than would a hydrophilic substance present in a fatty base to an extent approaching its saturation.

Partition coefficient in transdermal drug delivery system: The partition coefficient is important in establishing the flux of a drug through the stratum corneum.The magnitude of the partition coefficient can differ by a factor of 108 drug - drug or vehicle – vehicle eg: Topical steroids provide a good example of the importance of partition coefficient. Triamcenelone acetonide with a more favorable K value shows a 100 fold increase in cutaneous activity[3].

d) Polymorphism: It is defined as the ability of substance to exist as two or more crystalline phases that have different arrangements or confirmations of the molecules in the crystal lattice. Only one crystalline form is stable and all other forms found under these conditions are called "metastable polymorphs" The metastable polymorPHwill tend to transform into the most stable form at rates that depends on the energy difference between the metastable and stable forms. The metastable polymorPHis higher energy form of a drug and usually has a lower melting point, greater solubility and dissolution rate than the stable crystal form.

Eg: Chloramphenicol palmitate which exists in 3 crystalline forms designated as A,B,C

PolymorPH'A' is the stable form

Polymor^{PH}'B' is the metastable form

PolymorPH'C' is the unstable form under normal conditions of temperature and pressure

Properties of polymorphism:

Polymorphs show the same properties in liquid or aqueous state but they behave differently in solid state. Polymorphs differ from each other with respect to physical properties like melting point and sublimation temperature, vapour pressure, solubility and dissolution rate, stability, optical and electrical properties, crystal habbit, hygroscopicity, heat capacity, solid state reactions, conductivity, compression characteristics.

Types of polymorphism: Enantiotropic and Monotropic

Phase transition: The process of transformation of one polymorPHinto another (which may also occur on storage or during or processing) is called phase transition. If One form is stable over certain pressure and temperature range, while other polymorPHis stable over different pressure and temperature range called Enantiotrophs eg:sulphur. If Only one polymorPHis stable at all temperatures below the melting point while all other polymorphs being unstable called Monotrophs. eg: Glyceryl stearate, chloramphenicol palmitate. Temperature at which both stable and metastable forms exist in equilibrium with each other is called Transistion temperature.

Pseudo polymorphism: The term pseudo means false phenomenon in which solvent molecules get incorporated into crystal lattice of solid are known as solvates. This exists in different crystal forms called pseudo polymorphs and the phenomenon is called pseudo polymorphism. Psuedopolymorphs can be differentiated from true polymorphs by observing melting behavior in silicon oil using hot stage microscopy. Here in this technique, psuedopolymorphs evolve gas causing bubbling of the oil, while true polymorphs merely melts, forming second globular phase.

Methods to identify polymorphism are Optical crystallography- It is used in the identification of polymorphs. Crystal exist in isotropic and anisotropic forms. When isotropic crystals are examined, the velocity of light is same in all directions while anisotropic crystals have 2 or 3 different light velocities or refractive indices. Video recording systems have made it possible to record the events visualized during the heating and cooling stages. It is useful to know the degree of stability of metastable form, Transition temperature, Melting point, Rates of transition under various thermal and physical conditions, whether to preserve polymorphism as a route to an improved dosage form.

Hot stage microscopy: Using this technique, fluid phase transformation as a function of temperature is observed. Generally silicon oil hot stage microscopy is used for detection of pseudo polymorphs.

X-ray diffraction method: Using Bragg's equation

$$n\lambda=2d\sin\Theta$$

d = distance for different planes of crystal

λ= wavelength of x-ray used

Θ = angle of incoming beam

n = order of spectrum

NMR technique: In this technique, powder sample must be rotated at a specific angle with respect to magnetic field.

FT-IR technique: It has been used to quantify binary mixtures of polymorphs. In identification of polymorphs, only solid samples can be used. In solutions polymorphs of a compound have identical spectra. Advantages are Rapid and technique is qualitative and quantitative.

Dilatometry: Using dilatometry, the melting behavior of Theobroma oil was studied. Extremely accurate but tedious, time consuming and not widely used.

Microcalorimetry: Used to characterize thermodynamic properties of different molecules

Thermal methods:

a) DSC(Differential Scanning Calorimetry)

b) DTA(Differential Thermal Analysis)

c) TGA(Thermo Gravimetric Analysis)

This method measures heat loss or gain from physical or chemical changes occuring in sample which is recorded as a function of temperature as substance is heated at uniform scale. Advantages are Thermodynamic parameter can be evaluated.Heat of transition from one polymorPHto the other can be monitored.

Parameters to be checked Preformulation while doing polymorphism study: Number of polymorphs**,** Relative degree of stability, Presence of glassy state, Stabilization of metastable form, Temperature stability range, Solubility of each polymorph, Method of preparation, Effect of micronization,Excipients incompatibility, Formation of metastable polymorphs.

Preparation of metastable polymorphrequi res: Supersaturating conditions for the metastable state and Crystallization of the metastable state before the stable polymorPHforms Providing Stable conditions for the metastable polymorphs so that conversion to the stable form is prevented.

Factors affecting polymorphism: temperature and humidity, photostability, effect of solvent, effect of grinding, effect of tablet compression.Crystal have definite internal and external structure.Habit is the external shape of crystal. Many physico-chemical properties vary with the internal structure of the solid drug including melting point, density, hardness, crystal shape, solubility and dissolution rate. Crystal habit and the internal structure of a drug can affect physicochemical properties which range from chemical stability to bioavailability. Different habit crystals are Tabular-moderate expansion of two parallel faces, Platy – plates, Prismatic – columns, Acicular - needle like Bladed - flat acicular

Internal structure is classified as crystalline compound and amorphous compound

Crystalline compound: repetitious spacing of constituent atoms / molecules in 3D array. Amorphous forms prepared by rapid precipitation or lyophilization / rapid cooling of metals

Crystal habit can be modified by Excessive super saturation, which tends to transform a prism or isodiametric (granular) crystals to a needle shape or Cooling rate and agitation which changes habit as it changes the degree of supersaturation eg: naphthalene. The crystallizing solvent affects habit by preferential absorption onto certain faces, inhibiting their growth. Resorcinol produces needles from benzene and squat prisms from butylacetate. The addition of cosolvents or other solutes and ions which change habit by poisoning crystal growth in one or more directions. eg: Sodium chloride is usually cubic, but Urea produces an octahedral habit.Techniques used to determine the structure of compound are Chemical crystallography and X-ray diffraction.[4]

e) Wetting of solids: Wetting is the displacement of either a liquid or gas from a surface by a second liquid. The wetting of a solid during the manufacture of a suspension or the dissolution of a tablet in the gastro intestinal tract, involves the displacement of air from the solid surface. The angle that includes the liquid at the point where the drop and solid meet can vary from 0-180^{0}C and is termed the contact angle.The contact angle can be measured directly by the use of a microscope fitted with a goniometer or indirectly by measuring height (h) and diameter (d) of a droplet and using the Barfell relationship given by the equation**.**

Wetting in formulations: Suspensions-During the preparation of physically stable pharmaceutical suspensions, wetting agents are employed to lower the interfacial tension and contact between solid particles and liquid vehicle. A wetting agent that is suitable surfactant with a HLB value between 7 and 9 is used.They are employed at low concentration (0.05-0.5%) to allow the displacement of air from hydrophobic material and permit the liquid and usually water to surround the particles and provide a proper dispersion.Sometimes alcohol, glycerine or other polyols such as PEG or propylene glycol are used in the initial stages to disperse the solid particles there by allowing the vehicle to penetrate. Two simple tests have been devised for wetting agent evaluation**.** They are Wet point method and Flow point method. Wet point method measures the amount of suspending vehicle required to just wet all of the powder which is expressed as millimeters/100g and may, for example have values of 15-45 with a 10% additive concentration. Flow point method measures the amount of suspending vehicle used to achieve pourability. This method has values at a 10% additive level in the range of 50-250 with the better wetting agents producing lower values.

Tablet dosage forms: Wetting agents have been used in tablets with poorly soluble drugs to enhance their rate of dissolution. Surfactants are often choosen for this purpose with Sodium Lauryl Sulphate (commonly used) or Tween 80(an uncharged surfactant which has less

likelihood of interacting with charged molecules)

Wetting and bioavailability: If hydrophobic compounds have to be included in formulation because of filling machine requirements, their deleterious effect on drug release can be overcome by the addition of wetting agents, surfactants at levels of 0.1-0.5%**.** The effective surface area of hydrophobic drug particles may be increased by the addition of wetting agent to the formulation.

f) Flow characteristics:

Bulk density- The flowability of the powder can be evaluated by comparing the poured (fluff) density and tapped density of a powder and the rate at which it is packed down. A useful empirical guide is given by Carr's compressibility index. Carr's index is one point determination and does not always reflect the ease or speed with which the powder consolidates.

Angle of repose: A static heap of powder with only gravity acting upon it will tend to form a conical angle, the angle to the horizontal cannot exceed certain value and this is known as the angle of repose.If any particle temporarily lies outside this limiting angle, it will slide down the adjacent surface under the influence of gravity until the gravitational pull is balanced by the friction caused by interparticulate forces.When only the small quantities of powder are available, an alternative is to determine the angle of spatula by picking up a quantity of powder on a spatula and estimating the angle of triangular section of the powder heap viewed from the end of the spatula.

g) Compressibility: is the ability of powder to decrease in volume under pressure. Compression of a powder means reduction in the bulk volume of a material as a result of displacement of the gaseous phase under pressure. In pharmaceutical tablet manufacturing an appropriate volume of granules in a die cavity is compressed between an upper and lower punch to consolidate the material into a single solid matrix which is subsequently ejected from the die cavity as an intact tablet. The events that occur in the process of compression are Transitional repacking, deformation at point of contact, fragmentation, bonding, deformation of the solid body, decompression, ejection. Properties significantly affected by compression pressure are density and porosity, hardness and tensile strength, specific surface, disintegration, dissolution and friability

Density and porosity: As the porosity and apparent density are inversely proportional, the plot of porosity against the logarithm of applied pressure is linear with negative slope.

Hardness and tensile strength: The ability of a tablet to withstand mechanical handling and transport has been evaluated by various types of test -

Abrasion, bending, indentation, hardness, diametral crushing.

Effect of binders on tensile strength: A blend of powders may be granulated with a granulating solution to increase the adhesiveness of a formulation. eg: The radial strength is little effected by the concentration of Povidone but axial tensile strength is increased by increased concentration of providone to strength greater than the radial strength.

Specific surface: Specific surface is increased to a maximal value indicating the formation of new surfaces due to fragmentation of the granules. Further increase in applied pressure produce a progressive decrease in specific surface as the particles bond.

Disintegration: Usually as the applied pressure used to prepare a tablet is increased, the disintegration time.

Dissolution time: The effect of applied pressure on dissolution rate may be deliberated from the point of view of non-disintegrating and disintegrating tablets.

If the fragmentation of the granules happens during compression, the dissolution is faster as the applied pressure is increased.

If the bonding of the particles is the predominant phenomenon in compression, the increases in applied pressure cause a decrease in dissolution[5].

II) **CHEMICAL PROPERTIES:**

Degradation pathways

a) Hydrolysis-It involves nucleophilic attack 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's PHof 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 common pathway 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 Intiation, Propagation, Hydroperoxide 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 more common pathway of drug metabolic process. Hepatic microsomes catalyze 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 photo decomposition: 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. **Photodecomposition 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 ? oxidiazine ? yellow color

Photodecomposition canbe Prevented by- suitable packing, antioxidant, protection of drug from light, avoiding sunbath, photostabilizer, coating [6].

e) Drug- excipient compatibility study: Incompatibility- When two or more API's and or excipients with each other affect adversely the safety, efficacy, appearance or elegance, then they are said to be incompatible. Types of Incompatibility-

a. Physical incompatibility- It involves the change in the physical form of the formulation which involves color changes, liquefication, phase separation and immiscibility.

b. Chemical Incompatibility- It involves undesirable change in formulation which is due to the formation of new chemical compound with undesirable activity or formulation undergoes oxidation, hydrolysis, reduction, precipitation, decarboxylation, racemization

c. Therapeutic Incompatibility- It involves the change in the response of the formulation which is undesirable to the patient as well as physician.

Compatibility tests- 2 Aspects of Compatibility tests are

1. Identification of compatible excipients for formulation

2. Identification of stable storage conditions

Steps in Compatibility study- 1.Sample preparation 2.Storage 3.Method of analysis. Sample preparation for solid state reactions: Sample A: mixture of drug and excipient

Sample B: sample A + 5% Moisture

Sample C: drug itself without excipients

All the samples of drug - excipient blends are kept for 1-3 weeks at specified storage conditions. Then the sample is physically observed. It is then analyzed by TLC or HPLC or DSC. Whenever feasible the degradation products are identified by mass spectroscopy, NMR or other relevant techniques. To determine solid state stability profile of new compound:- Weighed sample is placed in screw cap vials and exposed directly to a variety of temperatures, humidity, light intensities for upto 12 weeks. For liquid state reaction: The drug is placed in the solution of additives. Both flint and amber

colored vials are used. This provides information about susceptibility to oxidation, susceptibility to light exposure, susceptibility to heavy metals. In case of oral liquids, compatibility with ethanol, glycerin, sucrose, preservatives and buffers are usually carried out. Storage condition: The storage conditions used to determine compatibility can very widely in term of temperature (50^0C) and humidity are considered appropriate. Some compounds may require high temperature to make reaction proceed at a rate than can be measured over a convenient time period.

Analytical techniques used to detect Drug-excipient compatibility are

1. Thermal methods of analysis- DSC(Differential Scanning Calorimetry), DTA (Differential Thermal Aanalysis)
2. Accelerated Stability Study
3. FT - IR Spectroscopy
4. DRS (Diffuse Reflectance Spectroscopy)
5. Chromatography- Self Interactive Chromatography(SIC), TLC, HPLC
6. Miscellaneous-

a) Radio labelled techniques

b) Vapor pressure Osmometry

c) Fluorescence spectroscopy

Differential Scanning Calorimetry: Method-Preformulation screening out drug- excipient interaction require 5mg of drug in 50% mixture(1:1) with excipient to maximize the likelihood of observing an interaction. Mixture should be examined under N2 to eliminate oxidative and pyrrolytic effects at heating rate (2.5 or 100C/min) on DSC apparatus. Identify chemically compatible excipient using DSC with confirmatory TLC. Advantages of DSC over traditional methods- fast, reliable, requires little sample

Differential Thermal Analysis-Thermal analysis is useful in solid state interactions and in the detection of eluetics. Thermograms are generated for pure components and their physical mixtures with other components[7].

Accelerated stability study: Different formulations of the same drug are prepared and kept at 400C/ 75% RH. Chemical stability is assessed by analyzing the drug content at regular interval. Amount of drug degraded is calculated. % drug decomposed vs time(month) is plotted and determined with excipient combination in which drug attains maximum stability.

Diffuse Reflectance Spectroscopy: Principle- incursion from a position of an incident radiation flux into the interior of the solid sample, bring back of some portion of radiation to the surface of sample following partial absorption and multiple scattering at boundary of individual sample particles. DRS detect the decomposed products along with physical and chemical absorption of excipients onto API and vice versa.The

diffuse reflectance depends upon the packing density of the solid, it's particle size and crystal form. DRS can be used to investigate physical and chemical changes occurring on solid surface. A shift in the diffuse reflectance spectrum of the drug due to the presence of the excipient indicates physical absorption whereas the appearance of a new peak indicates chemisorption or formation of a degradation product. DRS is more useful than HPLC assay to detect surface discoloration due to oxidation or reaction with excipients.

Chromatography- TLC is generally used as verificatory test of compatibility after performing DSC as if sample undergoes negligible thermal changes it will be difficult to detect by thermal method. In TLC stationary phase consists of powder adhered onto glass plastic or metal plate. Powders commonly used are silica, alumina, polyamide, cellulose, and ion exchange resin. Solution of drug excipient and drug excipient mixture are prepared and spotted on the same base line at the end of the plate. The plate is then placed upright in a closed chamber containing the solvent which constitutes the mobile phase. As the solvent moves up the plate, it carries with it the materials and those that have strong affinity will move at a slower rate. The material is identified by it's Rf value. The position of the material on the plate is indicated by spraying the plate with certain reagents or exposing the plate to UV radiation. If and there is no drug interaction between drug and excipient the mixture will produce two spots. The Rf values which are identical with those of individual drug and excipient. If there is interaction the complex formed will produce a spot. The Rf value which is different from those of the individual components.

SIC-This is useful for proteinous products with excipients. Eg: INF- Tau a new anti-viral drug. Interaction of it with different types of buffers were studied by SIC. Here buffer is used to prevent aggregations. Method- SIC is a modified type of affinity chromatography. The drug is made immobilized as the stationary phase and the solution to be tested acts as mobile phase. Retention time is measured and compared with non- retained marker. Principle- For different mobile phases (i.e different excipients) the injected drugs have different interactions (either repulsive or attractive) with the stationary phase of drug leading to shift in retention time. When the interaction is repulsive, a sharper peak is obtained at shorter retention time. When no net interaction between the immobilized drug Rt = dead volume of the column.When attractive interactions, it will have longer retention time and wider peak High Performance Liquid Chromatography (HPLC): The API's and model compounds of diversified chemical structure were studied. Elution rate is at 7.5ml/ hr at ambient temperature. HPLC allows the detection and quantification of impurities, which span a wide range of polarities including non polar compounds.

Fluorescent measurement: This technique is restricted to those compounds which can generate fluorescence. So this method is used in analysis and not in preformulation.

Vapor pressure Osmometry and Equilibrium dialysis- Principle - Sample of solution and pure solvent are introduced into a temperature controlled enclosure which is saturated with solvent vapor. Since the vapor of the solution is lower than that of solvent, solvent vapor condenses on solution sample causing it's temperature to rise. The temperature rise is predicted by Clausis Clapceyon equation.

Radio labelled techniques- This is important when the API has radio activity. This technique is highly sensitive but due to the cost of carrying out the method and the availability of well established techniques, it is not preferred[8].

III) BIOPHARMACEUTICAL CHARACTERISTICS

a) Dissolution and lipid solubility: PHpartition theory- The interrelationship of dissociation constant, lipid solubility, PHat the absorption site and the absorption characteristics of various drugs throughout the GIT is known as PHpartition theory. The theory explains the process of drug absorption from the GIT and it's dissolution across all biological membranes. The theory states that for the drug compounds of molecular weight greater than 100 which are primarily transported across the biomembrane by passive diffusion, the process of absorption is governed by

a. The dissociation constant (Pka) of the drug

b. Lipid solubility of the unionized drug

c. PHat the absorption site

Drug absorption by passive diffusion across the GIT membrane is limited essentially to lipid- soluble drugs and the rate of absorption is proportional to the concentration of the drug at the site of absorption. The absorption rate of the drug that exist in ionized and unionized form in the biological fluids is proportional to the concentration of the absorbable form and not on the total concentration of the drug. The concentration of the absorbable species is a function of both the dissociation constant (Pka) of the drug and PHof the environment. The dissociation constant of weakly acidic and basic drugs is important as it determines their aqueous solubility, dissolution rates in the GIT and the rate of transport across lipoidal layers. The concentration of the unionized form is a thermodynamic parameter which is constant at given temperature and pressure conditions. The fraction of the ionized form in the solution changes as a function of solution PH. The relation between PH and Pka and the extent of ionization is described by Henderson Hasselbalch equation. The PH of the body fluids varies, PH in the stomach range from 1-3, PHin small intestine(mostly drug absorption occurs)

range from 5.5 - 7.0. Weakly acidic compounds will therefore generally dissolve faster in the gastric fluids and weakly basic compounds dissolve faster in intestinal fluids. The relative equilibrium concentration of ionized and unionized forms of Aminopyrine in the gastric fluid compartment is in the ratio of 6310.6 and 1.004. At equilibrium, the total concentration of the weakly basic drug in the stomach is approximately 6300 times greater than in the blood. Thus according to P^H partition hypothesis, drug which are predominantly ionized at gastric $P^H$are poorly absorbed from the stomach.

Dissolution rate: Dissolution is a process in which a solid substance solubilizes in a given solvent i.e mass transfer from the solid phase to the liquid phase.

Theories of dissolution rate:

1. Diffusion layer model / film theory
2. Danckwort's model / penetration or surface theory
3. Interfacial barrier model / double barrier or limited salvation theory

Table.5.Dissolution apparatus types and their applications

Apparatus	Name	Drug formulation
Apparatus I	Rotating basket	conventional tablets, chewable tablets, controlled release formulations
Apparatus II	Rotating paddle	Orally disintegrating tablets, chewable tablets , capsules, controlled release products, suspensions
Apparatus III	Reciprocating cylinder	controlled release formulations, chewable tablets
Apparatus IV	Flow through cell	Formulations containing poorly soluble drugs, powders and granules, implants
Apparatus V	Paddle over disc	Transdermal formulations
Apparatus VI		Transdermal formulations
Apparatus VII	Reciprocating disc	controlled release formulations (non - disintegrating oral formulations, Transdermal formulations)

b) Complexation: Complexation of a drug in gastro intestinal fluids may alter the rate and in some cases, the extent of absorption. The drug may form complex with the components of a formulation, regular components of GIT, components of diet. The influence of the complexation of the drug on it's rate and the extent of absorption depends on whether the complex formed is soluble or insoluble in

the GI fluids. Further the soluble complex of a drug should dissociate to liberate the parent drug for absorption. Thus it appears that, it is not the magnitude of the association of the complex but the rate at which the complex dissociates that determines whether the absorption of the drug is rapid and/or as complete as in the absence of complex formation. Mucin is a viscous muco polysaccharide that lines the mucosal surfaces of the stomach and the intestine. It forms complexes with the drugs. Streptomycin, dihydroStreptomycin quarternary ammonium compounds bind strongly to the mucin forming un absorbable complexes. Thus their complexation with mucin reduces the bioavailability of each of these drugs. Bile salts in the small intestine interact with certain drugs including Neomycin, Kanamycin, Tubocurarine to form insoluble, non- absorbable complexes. Tetracyclines provide an example of drug whose bioavailability are reduced by the formation of poorly soluble complexes with the dietary components. Tetracyclines form insoluble complexes with calcium ions and other polyvalent metal ions present in milk, certain foods or other sources such as antacids. Tetracyclines bioavailability is reduced on concomitant administration with Ferrous sulphate due to complexation. Dialkylamides improves the absorption of Prednisone by forming lipid soluble complexes with Prednisone. Digoxin absorption from GIT is improved when it is administered as Hydroquinone- Digoxin complex. Hydroquinone forms a water soluble rapidly dissolving complex with Digoxin. The complex is quickly and completely dissociated when dissolved[8].

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.

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