

[REVIEW ON PHARMACEUTICAL PREFORMULATIONS PHYSIOCHEMICAL STUDIES IN FORMULATION AND DEVELOPMENT OF NEW DRUG MOLECULES]

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Abstract—Preformulation commences when a newly synthesized drug shows sufficient pharmacologic promise in animal models to warrant evaluation in man. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form. A thorough understanding of these properties may ultimately provide a rationale for formulation design or support the need for molecular modification. This review article focuses on the various preformulation factors which effect the development of new dosage form like drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability. Every drug has intrinsic chemical and physical properties which has been considered before development of pharmaceutical formulation. This property provides the framework for drug's combination with pharmaceutical ingredients. Preformulation studies carried out by various research scientists are reviewed. Preformulation studies conducted for newly synthesized compounds 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.

I. INTRODUCTION [During the early development of a new drug substance, the synthetic chemist, alone or in cooperation with specialists in other disciplines including reformulation, may record some data which can be appropriately considered as preformulation data. Before starting the preformulation studies we should know the properties of the drug, potency relative to the competitive products and the dosage form, literature search providing stability and decay data, the proposed route of drug administration, literature search regarding the formulation approaches, bioavailability and pharmacokinetics of chemically related drugs. It also includes preliminary investigations and molecular optimization by the drug should be tested to determine the magnitude of each Suspected problem area (Step I), if a deficiency is detected, a molecular modification should be done (Step II). To overcome this deficiency molecular modification is done by salts, prodrugs, solvates, polymorphs or even new analogues.

PHYSICAL CHARACTERISTICS: ^[11,7]

1. Organoleptic properties:

- a) Color
- b) Odor and Taste

2. Bulk characterization studies:

- a) Crystallinity and polymorphism
- b) Hygroscopicity
- c) Fine particle characterization
- d) Bulk density
- e) Powder flow properties
- f) Compression properties
- g) Physical description

3. Solubility analysis:

- a) Intrinsic solubility determination
- b) PKa determination
- c) Partition coefficient
- d) Dissolution studies
- e) Common ion effect

4. Stability analysis:

- a) In toxicology formulations

b) Solution stability

c) Solid state stability

1. Organoleptic properties: [3]

a) Colour: It should be Unappealing to the eye and determined by either instrumental methods or visible method that varies from batch to batch. Record of early batches and establishing “specs” is very useful for later production. Coating of body in variable color can be done if found undesirable.

b) Odour and taste: For unpalatable drug use of less soluble chemical form or suppress it by flavours, excipients, coating etc. Drug substances which irritating to skin should be handle with precautions. Flavours, dyes, excipients used will affect stability and bioavailability. Colour may be off-white, cream yellow, tan, shiny.

Odour may be pungent, sulphurous, fruity, aromatic and odourless. Taste may be acidic, bitter, bland, intense, sweet and tasteless.

2. Bulk characterization studies:

It is needed to identify all the solid forms that may exist as a consequence of the synthetic stage such as the presence of polymorphs. Bulks properties such as particle size, bulk density, surface morphology may be changed during the development process and to avoid mislead predictions of solubility and stability which depends on a particular crystalline form. Bulk characterization testing includes:

a) Crystallinity and polymorphism: The structure of a solid compound refers as crystallinity and these structures disappear in the liquid and vapour states. It can be classified as Internal structures (cubic, tetragonal, hexagonal, rhombic, etc.), Solid habits (platy, needle, tabular, prismatic, bladed, etc.), Changing the internal structures alter the crystal habits, Changing the chemical form (e.g. salt formation) alter both the internal structure and crystal habit. Different polymorphs are obtained by crystallization from different solvents and by solidification after melting. When the incorporated solvent is water, it is called “hydrates”. The compound not containing any water within its crystal structure is called as “anhydrous”. Atoms in crystalline matter are arranged in regular and repeating patterns in three dimensions. e.g. metal and mineral and atoms or molecules randomly placed without a regular atomic arrangement in amorphous solids. Polymorphism is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice and different crystal forms (at different free energy states) of the same compounds. They have different physicochemical properties (melting point, density, vapor pressure, X-ray, color, crystal shape, hardness, solubility, dissolution rate and bioavailability). During preformulation, it is important to identify the polymorph that is stable at room temperature. For examples: Chloramphenicol exist in A, B & C forms, of these B forms is more stable and most preferable. Riboflavin has I, II& III forms, and the III form shows 20 times more water solubility than form I. Enantiotropic polymorphs can be inter converted below the melting point of either polymorph and the conversion is reversible at a define temperature. E.g. sulphur. In Monotonic polymorphs the transition takes place in one direction (irreversible). E.g. glycerol stearate and diamond graphite. Stable polymorph has low free energy, low solubility and high melting point. Metastable polymorph is less stable with higher solubility and bioavailability and lower melting point. Crystals and polymorphs are characterized by Microscopy, Thermal analysis and X-ray diffraction method. Significances of identification of crystal shape and internal structure can influence by Solubility and stability-For example:

Chloramphenicol palmitate exists in 3 crystalline polymorphic forms

(A, B and C) and an amorphous form (D). Increasing the concentration of the form B led to increase the serum level due to its higher water solubility. Melting point-For example: Cacao butter as an oily base for suppositories exists in four polymorphic forms (α , β -prime, γ and β stable). Only the β -stable form can be used as a suppository base due to its higher melting point. Density and Crystal shape influences the flow properties of powders. Tablet hardness influence the compression properties and grinding processes.

Pharmaceutical applications of polymorphism: In suspension phase transformation from unstable form to more stable polymorph can cause changes in crystal size and caking. e.g. Oxyclozanide (anthelmintic). In cream crystal growth as a result of phase transformation can cause grittiness. In suppositories changes in polymorphic forms could cause product with different and unacceptable melting characteristic (failure to melt after administration or premature melting during storage). E.g. Theobroma oil “suppositories base”. It leads characterization of solids that involves verification of solid in expected chemical compound, characterization the internal structure, describing the habit of crystal; determine how many polymorphs may exist for the compound and stability, screening for the presence of an amorphous form etc.

b)Hygroscopicity: Many drug substances exhibit a tendency to absorb moisture. The amount of moisture adsorbed by a fixed weight of anhydrous sample in equilibrium with the moisture of the air at a given temperature. These are classified as Deliquescent (a substance which absorb sufficient moisture from the atmosphere to dissolve itself at higher extreme), Efflorescent (a substance which loses water to form a lower hydrate or become anhydrous at lower level) and Hygroscopic (a substance that exist in a dynamic equilibrium with water). This process depends on the relative humidity of the surroundings. It is characterized by Karl fisher, gravimetric, TGA, or Gas chromatography methods. It is significances as changes in moisture content that affects stability, flow ability, compatibility, etc.

c)Fine particle characterization: Certain physical and chemical properties of drug substances are affected by the particle size distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture colour, and stability. In addition, properties such as flow characteristics and sedimentation rates, among others, are also important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and product efficacy. Methods of evaluation of particle size and distribution includes light microscope with a calibrated grid, Sedimentation techniques, Stream scanning, Coulter counter and Surface area determination by BET nitrogen adsorption method.

d)Bulk density: Knowledge of the true and bulk densities of the drug substance is very useful in forming some idea as to the size of the final dosage form. Obviously, this parameter is very critical for drugs of low potency, which may constitute the bulk of the final granulation or table. Bulk density of a compound varies substantially with the method of crystallization, milling or formulation

once a density problem is identified it is often easily corrected by milling slugging or formulation. It can affect powder flow properties. It affects the size of high dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipients densities.

e) Powder flow properties: The flow properties of powders are critical for an efficient tablet operation. During the preformulation evaluation of the drug substance, therefore, its flow ability characteristic should be studied, especially when the anticipated dose of the drug is large. Powders may be free flowing or cohesive (non-free flowing). Flow properties are affected by changes in particle size, density, shape, electrostatic charges, and adsorbed moisture. It is characterized by Carr's index and Hausner ratio, Angle of repose, rheology and thixotropy etc.⁴

f) Compression properties: The compression properties (elasticity, plasticity, fragment ability and punch filming propensity) for small quantities of a new drug candidate can be established. This property is used in proper selection of the formulation ingredients.

g) Physical description: It is possible to observe on the bases of size, shape, appearance and determined instrumentally or visually.

3. Solubility analysis:

One important goal of the pre-formulation effort is to devise a method for making solutions of the drug. A drug must possess some aqueous solubility for therapeutic efficacy. In order for a drug to enter the systemic circulation to exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete absorption. When a solute dissolves, the substances inter molecular forces of attraction must be overcome by forces of attraction between solute and solvent molecules. This involves breaking the solute-solute forces and the solvent-solvent forces to achieve the solute-solvent attraction. It focuses on drug-solvent interactions that could occur during the delivery of a drug candidate. For example, orally administered drug should be examined for solubility in simulated gastric media. We need to perform solubility analysis of a new drug to provide a basis for later formulation work and can affect drug performance. Drugs with an aqueous solubility less than 1% (10 mg/ml) will suffer from bio absorption problems. Factors affecting the solubility of a drug are temperature, Chemical and physical properties of both the solute and the solvent, Pressure, acidity or basicity of the solution, state of subdivision of the solute and solvent, physical agitation applied to the solution during the dissolving process etc. Methods of Solubility analysis include: Solubility determination, pKa determination, Partition coefficient, Dissolution behaviour, Common ion effect, Membrane permeability. Methods to improve drug solubility are chemical modification of the drug into salt or ester forms, through selection of a different solubilizing agent, use of co-solvents or other techniques such as micronization or solid dispersion and adjustment of the pH of the solvent in which the drug is to be dissolved.⁵

a) Intrinsic Solubility determination: Steps: I All factors that affect the solubility and dissolution should be defined. Steps: II An excess amount of the drug is dispersed in the medium and agitated at constant temperature. Steps: III Withdraw Samples of the slurry as a function of time. Steps: IV Clarify Ampoules by filtration or centrifugation. Steps: V Assay the clear samples for its drug content to establish a plateau concentration and analyse using UV, HPLC, and GC...etc.

b) pKa determination: The interrelationship of the dissociation constant, lipid solubility and pH at the absorption site and absorption characteristics of various drugs are the basis of the partition theory. Dissociation constant or pKa is usually determined by potentiometric titration. The majority of drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers. The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pKa, or dissociation constant, of the drug (whether an acid or base). The concept of pKa is derived from the Henderson-Hasselbalch equation: For acidic compounds $\text{pH} = \text{pKa} + \log (\text{ionized drug} / \text{unionized drug})$ For basic compounds $\text{pH} = \text{pKb} - \text{pKa} + \log (\text{unionized drug} / \text{ionized drug})$ The ideal pH of parenteral products is pH 7.4. If pH is above 9, tissue necrosis may result while below 3, pain and phlebitis in tissue can occur. Buffers are included in injections to maintain the pH of parenteral products e.g., citrates, phosphates etc. 6 Significance: 1. Provided that the intrinsic solubility and pKa are known, the solubility at any pH can be predicted. 2. Henderson equations can facilitate the selection of suitable salt forming compounds and predict salts' solubility. 3. Determination of the ratio of the ionized to the unionized form of a drug molecule. This is useful to predict which form will predominate at different Physiologic pH. Mostly, the unionized form of the drug is the one absorbed. Consequently, acidic drugs will be absorbed in the acidic media of the stomach and vice versa.

c) Partition coefficient: The oil/water partition coefficient is a measure of a molecule's lipophilic characters that is, its preference for the hydrophilic or lipophilic phase. The partition coefficient should be considered in developing a drug substance into a dosage form. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach equilibrium at a constant temperature. The distribution of the solute (un-aggregated & un-dissociated) between the two immiscible layers can be described as follows: it is the ratio of the unionized drug distributed between the organic (upper phase) and aqueous (lower) phases at equilibrium. Determination of partition coefficient: Shake flask method: the drug dissolved in one solvent is shaken with the other partitioning solvent for 30 min. The mixture allowed standing for 5 min. The aqueous solution is centrifuged and then assayed for drug content. It has a number of applications such as: 1. Used in Solubility determination of both in aqueous and mixed solvents. 2. It is applied to a homologous drug series for structure activity relationships in drug absorption in-vivo. 3. Partition chromatography can be helpful for column and stationary phase selection (HPLC), choice of plates for TLC and choice of mobile phases (eluent). 4. This information can be effectively used in the extraction of crude drugs. 5. Recovery of antibiotics from fermentation broths and recovery of biotechnology-derived drugs from bacterial cultures. 6. Extraction of drugs from biologic fluids for therapeutic drug monitoring. 7. Absorption of drugs from dosage forms (ointments, supps, TDDS) and study of the distribution of flavouring oil between oil and water phases of emulsions.

d) Dissolution studies: The speed or rate at which drug substance dissolves in a medium is called dissolution rate. Dissolution rate data when considered along with data on a drug's solubility, dissociation constant and partition coefficient can provide an indication of the drug's absorption potential following administration. The dissolution rate of the drug in which the surface area is constant during dissolution is described by Noyes Whitney equation as follows The equation reveals that the dissolution rate of a

drug may be increased by increasing the surface area (reducing the particle size) of the drug and by increasing the solubility of the drug in the diffusion layer.⁷ Significances: c) Taking into consideration the intrinsic solubility data, dissolution studies can identify potential bioavailability problems. For example: dissolution of solvates and polymorphs can have an impact on the bioavailability and drug delivery. d) It is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed, amount of powdered sample is added to the dissolution medium in a constant agitation system. e) This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent. f) Occasionally, an inverse relationship of particle size to dissolution is noted due to the surface properties of the drug.

e) Common ion effect: The addition of a common ion reduces the solubility of the slightly soluble electrolyte. This salting out (drug precipitation) results from the removal of solvent molecules from the surface of the electrolyte by the hydration of the common ion. Salting in larger anions (hydro tropes) e.g. benzoates, salicylates can open the water molecules allowing an increase in solubility of poorly-water soluble drugs.

Example hydrochloride salts often exhibit lower solubility in gastric juice due to the abundance of the chloride ions. To explore a common ion interaction, the dissolution rate of a hydrochloride salt should be compared in different media: Water and 1.2% w/v NaCl, 0.05 M HCl and 0.9% w/v NaCl in 0.05 M HCl. It is useful in the choice of a suitable salt form for the proper dissolution and accordingly enhanced absorption. Factors affecting degradation rates are temperature, Effect of pH and others such as ionic strength, co-solvent, presence and absence of O₂, presence of antioxidants and presence of chelating agent. The primary goal of this approach is to identify the storage conditions and additives to form a stable solution preparation. For example: Antioxidants (Sod. sulphite, Sod. Thiosulphate, ascorbic acid, BHA and BHT), Chelating agents (EDTA), Replacement of O₂ by CO₂ or N₂, Use of co-solvents (propylene glycol, ethanol) to replace part of the aqueous vehicle for enhancing solubility, stability and Storage at low temperatures.

4. Stability analysis:

a) In toxicology formulations: These studies are advisable to evaluate samples of toxicology preparations for stability and potential homogeneity problems. Usually a drug is administered to the animals in their feed, or by oral gavages of a solution or suspension of drug in an aqueous vehicle. Water, vitamins, minerals (metal ions), enzymes and moisture levels present in feed, which can severely reduce the shelf life of a drug and decrease stability. Solution and suspension toxicological preparation should be checked for ease of manufacture and stored in flame-sealed ampoules at various temperatures. In chemical stability the suspension should be subjected to an occasional shaking to check dispersibility and drug solubility is analysed by pH decomposition. b) Solution stability: These studies include the effect of pH, Ionic strength, Co-solvent, Light, Temperature and Oxygen. Usually these commence with probing experiments to confirm decay at the extremes of pH and temperature e.g., 0.1 N HCl, water and 0.1 N NaOH all at 90°C.

c) Solid state stability: The primary objective of this study is investigation and identification of stable storage condition for drug in the solid state and identification of compatible excipients for a formulation. In all solid dosage formulation there will be some free moisture contributed by excipients as well as the drug and certainly in tablets a significant percentage typically 2% w/w is required for good compression. This free water has ability to act as a vector for chemical reaction between drug and excipients and the absorbed moisture films are saturated with drug compared to the dilute solutions encountered in injectable. Stability Testing of Pharmaceutical Products is first quantitative assessment of chemical stability of new drug. It is defined as the capability of a particular formulation in a specific container or closer system to remain within its physical chemical, microbiological, therapeutic and toxicological specifications throughout its self-life. Stability is officially defined as the time lapse during which the drug product retains the same properties and characters that is processed at the time of manufacture. The stability of a product is expressed as the expiry period or technically shelf life. Stability studies are important for the assurance to the patient, Legal Requirement and Economic Repercussions. Purpose of stability study to ensure the efficacy, safety, quality of active drug substance and dosage forms, to establish shelf life or expiration period and to support label claims, to gain information about its packaging, assess the condition of the product on storage on prolong period of time, determine compatibility of drug with excipients and other additives and to determine the dosage form in which the drug is most suitable.

CHEMICAL CHARACTERISTICS: ^[3,13]

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

1) Hydrolysis

It involves nucleophilic attack of labile groups e.g.: 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 catalyse 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 PH. As most of the potent drugs are weakly acidic or weakly basic in nature. Formulate the drug solution close to its PH of 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.

2) 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 haemolytic bond fission of a covalent bond. These radicals are highly unsaturated and readily accept electron from other substance causing oxidation is called Autooxidation. 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. 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 bisulphate, thioglycolic acid, thioglycerol.

3) 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 do not participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization. Photosensitizer 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.

4) Racemization:

The interconversion from one isomer to another can lead to different P'cokinetic properties (ADME) as well as different P'cological & toxicological effect. E.g. 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.

It follows first order kinetics. It depends on temperature, solvent, catalyst & presence or absence of light.

5) Polymerization:

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer. E.g. Darkening of glucose solution is attributed to polymerization of breakdown product [5- (hydroxyl methyl) furfural].

E.g. Polymerization of HCHO to para-HCHO which crystallizes out from the solution.

6) Isomerization

Reduction is a relatively more common pathway of drug metabolic process. Hepatic microsomes catalyse diverse reductive chemical reaction* and require NADPH for this purpose. Azo and nitro reduction is catalysed by cytochrome P450. Chloral hydrate is reduced to its active metabolite tricolored ethanol by alcohol dehydrogenase. Reduction of prednisolone and cortisone results in the formation of their active metabolites hydrocortisone. Azo dyes used as colouring agents in pharmaceutical products or food are reduced to form amines in the liver and by the intestinal flora.

CONCLUSION

After completion of preformulation evaluation of new drug candidates, it is recommended that a comprehensive report be prepared highlighting the pharmaceutical problems associated with molecules. It helps in developing phase I formulations and in preparing regulatory documents and aid in developing subsequent drug candidates. If, drug is found satisfactory sufficient quantity is synthesized to perform initial toxicity studies, initial analytical work and initial preformulation

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