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A REVIEW ARTICLE ON THE PROCESS AND DEVELOPMENT OF NEW DRUG DOSAGE FORM

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ABSTRACT

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. Every drug has intrinsic chemical and physical properties which has been consider before development of pharmaceutical formulation. This property provides the framework for drugs combination with pharmaceutical ingredients in the fabrication of dosage form. Objective of Preformulation study is to develop the elegant, stable, effective and safe dosage form by establishing kinetic rate profile, compatibility with the other ingredients and establish Physico-chemical parameter of new drug substances. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability are plays important role in Preformulation study. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule. This article explains some properties and techniques for Preformulation evaluation parameters of drug.

KEYWORDS: Preformulation, Partition coefficient, Dissolution-Rate, Polymorphic.

INTRODUCTION

Preformulation developed in As a result of the shift in the late 1950s and early 1960sFocus on industrial pharmaceuticals development. improved analysis How I spurred the first program We named it "pre-formulation". Total Pre-blending check goals are generated Useful information for formulators during development Stable and bioavailable dosage form mass production Early stage of drug development Substances, synthetic chemists, alone or in collaboration with experts in other fields Includes pre-formulation and can record some data can reasonably be regarded as Pre-prescription data. Before starting a pre-prescription study, It is necessary to know the nature and potency of the drug Comparing to Competitive Products and Dosages Literature survey on morphology, stability and disintegration data, proposed route of drug administration, Literature survey for formulation Approach, bioavailability and pharmacokinetics of chemically related drugs. Also included preliminary research and molecules Optimization with drugs should be tested Determine the size of each suspected problem area (Step I). If defects are found, molecular modification should be performed (Step II). To overcome this shortcoming, molecular modifications are made in the form of salts, pro drugs, solvates, polymorphs and even new analogues. The dissolution rate of salt forms of drugs is generally quite different from that of the parent compound. Sodium and potassium salts of weak organic acids and hydrochloride salts of weak organic bases dissolve much more readily than the corresponding free acids or bases. For example, ephedrine-based water is very bad soluble molecules characterized by low solubility and dissolution rate. As such, it is ionized and modified in the form of the salt ephedrine HCL, which provides higher water solubility and dissolution rate. Pro drug formation is the formation of synthetic derivatives (eg, esters or amides) of drugs that release the active drug in vivo. A pro drug may or may not have pharmacological activity. the active substance is released via an acidic medium, Pro drug formation can enhance absorption due to its lipophilicity (passive) or water solubility (active). Pro drug formation can prolong the duration of action. Pro drug formation can improve drug stability, solubility, crystalline, taste and odor, and reduce pain during injection. For example, erythromycin base It has a bitter taste and is rapidly hydrolyzed in the stomach to inactive products. Erythromycin Estolate (a pro drug of erythromycin) is inactive and tasteless. 4 times more absorption. Hydrolyzed by acid in the stomach to release the active free base.[1] Table 1 shows some evaluation parameters used in pre-formulation drug development..

Table 1: Evaluation Parameters Used In Preformulation Of Drug Development.

S.NO	Parameters	Evaluation parameter
1	Stability, Solid State, Solution	Temperature, Light, humidity Solvent, Ph
2	Solid State Compatibility	TLC and DRS Analysis
3	Physico-chemical Properties Color, odor, particle size, shape crystalline	Molecular Structure and Weight, melting point
4	Thermal Analysis Profile Solubility Water and other solvent, pH	DTA, DSC,TGA Salt forms, co-solvent, Complexation, pro-drug
5	Absorbance Spectra	UV-IR
6	Other properties Hygroscopicity	Potential Bulk characterization Volatility, optical activity, solvate formation Crystalline and polymorphism
7	Physico-mechanical Properties Bulk and tapped-density	compressibility Photomicrograph
8	In Vitro Availability Properties Rat Everted Gut technique	Dissolution and analysis of Drug Crystal, pallets
9	Other Studies Plasma Protein-Binding, ionization constant	Effect of Compatible Excipients on dissolution, Kinetic Studies of Solution Degradation, Use of Radio-labeled Drug

Physicochemical parameters[2]

1. Organoleptic properties

2. Bulk characterization studies

a) Crystalline and polymorphism

b) Hygroscopicity

c) Fine particle characterization

d) Bulk density

e) Powder flow properties

f) Compression properties Physical description

3. Solubility Analysis

a) Intrinsic solubility determination

b) PKa determination

c) Partition coefficient

d) Dissolution studies Common ion effect

4. Stability Analysis

a) In toxicology formulations

b) Solution stability

c) Solid state stability

1. Organoleptic properties

Colour

It must be invisible, by instrumental methods or Visible way different from batch to batch. Recording an early batch and creating a 'specification' is very useful for subsequent production. If this is considered undesirable, the body can be coated with another color.

Odor and taste

For non-edible drugs used in poorly soluble chemical forms or suppressed by flavors, excipients, coatings, etc. Drugs that irritate the skin should be handled with caution. Flavors, colors and additives used affect stability and bioavailability. Colors can be cream, cream yellow, brown, or glossy. The aroma is sharp, sulphureous, fruity, aromatic and odorless. Taste can be sour, bitter, mild, strong, sweet or tasteless.

2. Bulk characterization studies

Fixed forms that may exist as a result of synthetic steps, such as the presence of polymorphs, should be identified. Bulk properties such as particle size, bulk density, and surface morphology can be altered during the development process, avoiding misleading predictions of solubility and stability that depend on specific crystal forms. Mass property testing includes.

a) Crystalline and polymorphism

The structure of a solid compound refers as crystalline and these structures disappear in the liquid and vapor states. It can be classifies 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, vapour pressure, X-ray, colour, crystal form, hardness, solubility,

dissolution rate and bioavailability). in the meantime In pre-formulation, it is important to identify a stable crystalline polymorph at room temperature. for example: Chloramphenicol comes in A, B, and C forms, but the B form is the most preferred because it is more stable. Riboflavin comes in Forms I, II, and III, with Form III being 20 times more water soluble than Form I. Transformed below the melting point of each polymorph, the transformation is reversible at defined temperatures. Example: Sulphur. Transitions occur in monotropic polymorphs One-way (irreversible). For example, glyceryl stearate and diamond graphite. Stable polymorphs have low free energy, low solubility, and high melting points. Metastable polymorphs are less stable, have higher solubility and bioavailability, and lower melting pointspoint.3 Crystals and polymorphs are characterized by microscopy, thermal analysis and X-ray diffraction. The implications of identifying crystal forms and internal structures can be influenced by solubility and stability. For example: Chloramphenicol palmitate exists in three crystalline polymorphs (A, B, and C) and one amorphous form .Form (D). Increasing concentrations of Form B increased serum levels due to its increased water solubility. Melting point - example: Cocoa butter as an oily base for suppositories exists in four polymorphs: α, β-prime, β, and β-stable. Due to its high melting point, only the β-stable form can be used as a base for suppositories. Density and crystal shape affect the flow properties of powders. Tablet hardness affects the pressing properties and crushing process.[3]

Pharmaceutical applications of polymorphism

In the slurry phase, crystal size changes and caking can occur due to the conversion of unstable forms to more stable polymorphs. For example oxyclozanide (an anthelmintic). In the case of creamy crystal growth, grain coarsening can occur as a result of phase transformation. In suppositories, polymorph variation can result in products with different and unacceptable melting characteristics (no melting after administration or premature melting during storage). Example: Theobroma oil "suppository base". Perform solid characterization including: Verification of solids in expected chemicals Compounds, characterization of internal structure, description of crystal forms. Determine how many polymorphs can exist for connectivity and stability, and screen for the presence of amorphous forms.

a) Hygroscopicity

Many medicines tend to absorb water. The amount of moisture adsorbed by a specified weight of an anhydrous sample in equilibrium with the humidity of the air at a specified

temperature. These are called deliquescent (deliquescent substances). Effluent (substances that lose water to form less hydrates or become anhydrous at a lower level), and hygroscopic (with water). substances in dynamic equilibrium).This process depends on the relative humidity of the environment. Characterized by Karl Fischer method, gravimetric method, TGA or gas chromatography method. The importance of changes in water content that affect stability, fluidity, compatibility, etc.

b) Fine particle characterization

Certain physical and chemical properties of drugs are influenced by particle size distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture colour, and stability. Properties such as flow properties and settling velocity are also important factors related to particles size. It is important to determine as soon as possible how the particle size of the active ingredient affects formulation and product efficacy. Methods to assess particle size and distribution include optical microscopy using calibrated grids, sedimentation, stream scanning, Coulter Counter, and surface area measurements by BET nitrogen adsorption.

c) Bulk Density

Knowing the true density and bulk density of the drug substance is very useful in knowing the size of the final dosage form. Clearly, this parameter is very important for low potency drugs that may dominate the final granulation or table. Bulk densities of compounds vary greatly depending on the method of crystallization, grinding, or compounding. Once a density problem is identified, it can often be easily fixed with a bang or a concoction. It can affect the flow properties of the powder. affects size Homogeneity of high-dose capsule products or low-dose formulations with large differences in active ingredient and excipients densities.

d) Powder flow properties

Powder flow properties are important for efficient tableting operations. Therefore, during pre-prescription evaluation of a drug, its mobility should be considered, especially if the expected dose of the drug is large. Powders may be free-flowing or cohesive (not free-flowing). Flow properties are affected by changes in particle size, density, shape, static charge, and adsorbed moisture. It is characterized by Kerr index and Hausner ratio, angle of repose, theology, thixotropy, etc.[4]

e) Compression properties

Compression properties (elasticity, plasticity, fragment ability, and punch-filming propensity) of low-volume drug candidates can be determined. This property is used in correct selection of formulation components.

f) Physical description

It is possible depending on the size and shape look and definitely instrumental or Visually.

3. Solubility analysis

A key goal of pre-formulation efforts is the development of processes for preparing drug solutions. The drug must have a certain water solubility for therapeutic effect. In order for a drug to enter the systemic circulation and exert its therapeutic effect, it must first be dissolved. Relatively poorly soluble compounds often exhibit incomplete absorption. When a solute dissolves, the intermolecular attraction of the substance must be overcome by the attraction between the solute and solvent molecules. This involves breaking the solute and solvent-solvent forces to attract the solute to the solvent. Focuses on drug-solvent interactions that may occur during dosing drug candidates. For example, drugs administered orally should be tested for solubility in a simulated gastric medium. need to dissolve Analyzes of new drugs provide the basis for later formulation work and can influence drug performance. Drugs with a water solubility of less than 1% (10mg/ml) suffer from bio absorption problems. Factors that affect drug solubility include temperature, chemical and physical properties of both solute and solvent, pressure, acidity or basicity of the solution, partitioning conditions between the solute and solvent, and effects on the solution during dissolution. physical agitation. and so on. Solubility analysis methods include: solubility measurements, pKa measurements, partition coefficients, dissolution behaviour, common ion effects, membrane permeability. Chemical Modification is a Way to Improve Drug Solubility of the drug in salt or ester form Selection and use of alternative solubilizersco-solvents or other techniques Coordination with micronization or solid dispersion pH of the solvent in which the drug is present Resolved.[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 agitate 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 analyze using UV, HPLC, and GC…etc.

b) pKa determination

Relationship between dissociation constant, lipid solubility, and pH value Absorption sites and absorption characteristics of various drugs are the basis of the pH distribution theory. The dissociation constant or pKa is usually determined by potentiometric titration. Most of today's drugs are weak organic acids or weak bases. It is important to know their individual ionization or dissociation properties. Their absorption is largely determined by the degree of ionization presented to the membrane barrier. The degree of drug ionization depends on both the pH of the solution in which the drug is presented to the biological membrane and the pKa or dissociation constant (acid or base) of the drug. Henderson-Hassel batch equation.

For acidic compounds pH=pKa + log (ionized drug/ unionized drug)

For basic compounds pH= Pkw- pKb + log (unionized drug/ionized drug)

The ideal pH for parenteral products is pH 7.4. A pH above 9 can cause tissue necrosis and below 3 can cause tissue pain and phlebitis. Buffers are included in injectable to maintain the pH of parenteral products. citrate, phosphate, etc.[6]

Significances

1. If you know the intrinsic solubility and pKa, you can predict the solubility at any pH.

2. Henderson's equation facilitates the selection of suitable salt-forming compounds and can predict salt solubility.

3 Determination of the ratio of ionized and non-ionized forms of drug molecules. This helps predict which forms will predominate at different physiological pH values. Most often the unionized form of the drug is absorbed. As a result, acidic drugs are absorbed into the acidic medium of the stomach and vice versa.

Partition coefficient

The oil/water partition coefficient is a measure of a molecule's lipophilicity, its preference for hydrophilic or lipophilic phases. Partition coefficients should be considered when developing drug substances into dosage forms. When a solute is added to a mixture of two immiscible liquids, the solute will partition into the two phases and reach equilibrium at a certain temperature. The distribution of solutes (unagglomerated and undissociated) between two

immiscible layers can be described as follows. Tt 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

Shake the drug dissolved in one solvent with the other partitioning solvent

For 30 minutes the mixture was left for 5 minutes. The aqueous solution is centrifuged and analyzed for drug content. It has many uses such as.

1. Used to determine solubility in both aqueous and mixed solvents.
2. Applied to homologous drug series for structure-activity relationships in drug absorption in vivo.
3. Partition chromatography helps in column and stationary phase (HPLC) selection, plate selection for TLC, and mobile phase (eluent) selection.
4. Four. This information can be used effectively when extracting herbal medicines.
5. Recovery of antibiotics from fermentation broths and recovery of biotechnological agents from bacterial cultures.
6. Extraction of drugs from biological fluids for therapeutic drug monitoring.
7. Investigation of drug uptake from dosage forms (ointments, nutraceuticals, TDDS) and the distribution of aromatic oils between the oil and water phases of emulsions.

d) Dissolution studies

The rate at which the active ingredient dissolves in the medium is resolution rate. Dissolution rate data, when considered in conjunction with drug solubility, dissociation constant, and partition coefficient data, can indicate the absorption capacity of a drug after administration. The dissolution rate of a drug with constant surface area during dissolution is described by the Noyes-Whitney equation as follows.

This formula indicates that the dissolution rate of a drug can be increased by increasing the drug's surface area (reducing the particle size) and increasing the drug's solubility in the diffusion layer.[7]

Significances

1. Taking into account intrinsic solubility data, dissolution studies can identify potential bioavailability issues. Example: Dissolution of
2. solvates and polymorphs can affect bioavailability and drug delivery.

3. Helps predict absorption problems due to dissolution rate. In articulated dissolution, a weighed amount of powder sample is added to the dissolution medium in a constant stirring system.
4. This method is often used to investigate the effects of particle size, surface area, and excipients on active substances.
5. In some cases, an inverse correlation between particle size and solubility is observed due to the surface properties of the drug.

e) Common ion Effect

Addition of normal ions reduces the solubility of sparingly soluble electrolytes. This salting out (drug precipitation) results from the removal of solvent molecules from the surface of the electrolyte by hydration of common ions. Salting out to larger anions (hydrotropes) such as benzoic acid and salicylic acid can open water molecules and thus increase the solubility of poorly water soluble drugs. Exemplary hydrochloride salts often exhibit lower solubility in gastric fluid due to the abundance of chloride ions. To study general ionic interactions, it is necessary to compare hydrochloride dissolution rates in different media. This helps in choosing the right salt form for proper dissolution and corresponding enhancement of absorption. Factors that influence the rate of degradation are the effects of temperature, pH, and other factors such as ionic strength, co-solvents, presence of O2, presence of antioxidants, and presence of chelating agents. The primary objective of this approach is to identify storage conditions and additives to form stable solution formulations. Examples: antioxidants (sodium sulfite, sodium thiosulfate, ascorbic acid,BHA and BHT), chelating agents (EDTA), replacing O2 with CO2 or N2, usingco-solvents (propylene glycol, ethanol) Replace parts. Improves solubility, stability, and cryopreservation of in aqueous vehicles.

4. Stability analysis

a) In toxicology formulations

These studies are recommended for random sample evaluation Preparing Toxicology for Stability and Potential problem of homogeneity. Typically, animals are administered drug with food or by oral gavage of a solution or suspension of drug in an aqueous vehicle. Water, vitamins, minerals (metal ions), enzymes, and moisture levels in the diet can significantly reduce drug shelf life and reduce stability. Toxic solution and suspension formulations should be tested for ease of manufacture and stored in closed ampoules at various temperatures. For

chemical stability, suspensions are occasionally shaken to check dispensability, and drug solubility is analyzed by pH decomposition.[8]

b) Solution stability

These studies include the effects of pH, ionic strength, co-solvents, light, temperature and oxygen. These typically start with a probing experiment to confirm attenuation extreme pH and temperature; B. 0.1N HCl, water, and 0.1N NaOH, all at 90°C.[9,10]

c) Solid state Stability

Main goal of this research Stable Storage Conditions for Solid State Drugs identification of formulation compatible excipients. All solid dosage forms contain free water, which includes excipients as well as the drug, and a significant proportion (typically 2% by weight) of tablets is required for good compression. This free water has the ability to act as a vector for chemical reactions Between drug and excipients, the absorbed water film is saturated with drug compared to dilute solutions encountered in injections. Pharmaceutical stability studies are the first to quantitatively assess the chemical stability of new drugs. This means that a particular formulation in a particular container or closed system will have the same properties and characteristics as it was treated during manufacture and will remain within physicochemical, microbiological, therapeutic and toxicological specifications throughout its life. Defined as the ability to stay. The stability of a product is expressed in terms of its shelf life or technical shelf life. Stability testing is important for safety Patients, Legal Requirements, and Economic Impact.[11] Stability to check efficacy, safety and quality of active substances and dosage forms, determine shelf life or expiry date, support label claims, obtain information on packaging, assess product status In research purpose extended storage determine the compatibility of pharmaceutical products with excipients and other additives; Determine the dosage form in which the drug is most suitable. Table 2 shows the types of stability and states maintained throughout the product's shelf life.[12]

Table 2: Types of Stability and The Condition Maintained During The Shelf Life of The Product.

Types of stability	Conditions maintained during the shelf life of the product
Chemical	Retains its chemical integrity and labeledpotencyl
Physical	Retains appearance, palatability, uniformity, dissolution and suspend ability
Microbiological Retains sterility	effectiveness of antimicrobial agents

Therapeutic	Drug action remains unchanged
Toxicological	No significant increase in toxicity

CONCLUSION

Once the pre-prescription evaluation of a new drug candidate is completed, it is recommended to produce a comprehensive report highlighting the pharmacological issues associated with the molecule. It supports the development and regulatory writing of Phase I formulations and supports the development of subsequent drug candidates. If the drug proves satisfactory, it will be synthesized in sufficient quantity to cause initial toxicity Research, first analytical work, and first Preformulation. Beyond initial toxicity, Phase I(Clinical Toxicology) starts with the actual formulation. Phase 2 and 3 clinical trials will then begin, at which stage the size formula will be finalized. After completing all the steps above, an NDA will be submitted and once the NDA is approved, production will begin.

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