



INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

PREFORMULATION STUDIES

Suraj R. Magar¹, Prof. Vaibhav P. Gote², Dr. Swati Deshmukh³,

Aniket R. Bhutkar⁴, Ankita D. Haral⁵

¹Student Shraddha Institute of Pharmacy, Kondala Zamre, Washim 444505

² Assistant Professor, Shraddha Institute of Pharmacy, Washim

³Principal, Shraddha Institute of Pharmacy, Washim

^{4,5}Student Shraddha Institute of Pharmacy, Kondala Zamre, Washim

Abstract

It is group of studies that before the formulation and development of any dosage form. In The preformulation mainly studied the Physiochemical properties and nature of API & excipient. In preformulation studied provide important information for design formulation. & need for molecular modification. Every drug has their intrinsic / different physical and chemical properties which are consider before the development of the drug. study of drug - excipient compatibility is an important phase in pre-formulation stage in drug development main objective of the preformulation is to The develop elegant safe stable and effective dosage form. Also studied the physical properties such. As physical form (crystalline , Amorphous) particle size, shape, flow properties, solubility profile, polymorphism. chemical properties such are Hydrolysis, oxidation, reduction. Racemization polymerization. In this review we also studied about the biopharmaceutical Classification system ,in BCS we studied the Solubility and permeability profile for absorption of drug and also the rate of absorption of drug. This Review Also explain the different properties & technique for preformulation parameter evaluation parameter of drug

Keywords

Preformulation studies ,stability testing, physical Properties, chemical properties .polymorphis

Introduction

The overall goal of preformulation is to create useful information for the formulation developer in developing a stable, safe and effective dosage form. Before starting the production of the dose, it is necessary to study / know the properties of the drug effectiveness and the effectiveness of the dosage form. A literature search providing data on disintegration, stability, intended route of administration, bioavailability and pharmacokinetics of a chemically related drug. The study of Preformulation that developed from the late 1950s to the 1960s led to an emphasis on pharmaceutical product development.

A preformulation study is used to overcome the deficiency and molecular modification within the drug. It should be done with prodrug, polymorphs and salts. They are mainly used as a prodrug / this formulation may be prolonged due to the duration of their effect. Absorption of the prodrug is increased due to their lipophilicity. Prodrug formulation can increase the nature of solubility, stability of the drug, taste, smell, crystallinity and reduce pain due to injection.

Definition Preformulation can be defined as → A research and development process where a Scientist studied the physical, chemical, biopharmaceutical and mechanical properties of a new drug substance in order to develop a safe, stable and effective dosage form.

The active drug is released by an acidic environment, action of enzymes etc. Prodrug formation can increase the rate of absorption due to its lipophilicity (passive) or its solubility in water (actives). Prodrug formation may prolong the duration of action. Prodrug formation can improve drug stability, solubility, crystallinity, taste, smell and reduced pain on injection. For example, erythromycin base it has a bitter taste and hydrolyzes quickly stomach for inactive products. Erythromycin Estolate (prodrug of erythromycin) is inactive and tasteless. It has 4 times the absorption rate. It is hydrolyzed by acid in the stomach to release its free base that is active, 'Table 1 describes some evaluation parameters used in preformulation drug development .

Physicochemical parameters:

1. Organoleptic properties:.

2. Bulk characterization studies:

- a) Crystallinity and polymorphism
- b) Hygroscopicity
- C) Fine particle characterization
- d) Bulk density
- e) Powder flow properties

D) Compression properties 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

- **Organoleptic properties**

Color :

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

Order and taste:

For an unpalatable drug, the use of a less soluble chemical form or suppress with flavors, auxiliaries, coating etc. Medicinal substances that irritate the skin should handle with care. Flavorings, colorings, the excipients used will affect the stability and bioavailability. The color can be off-white, cream yellow, tan, shiny. The smell can be pungent, sulphurous,fruity, aromatic and odorless. The taste may be sour, bitter, bland, intense, sweet and tasteless.

- **. Bulk characterization studies:**

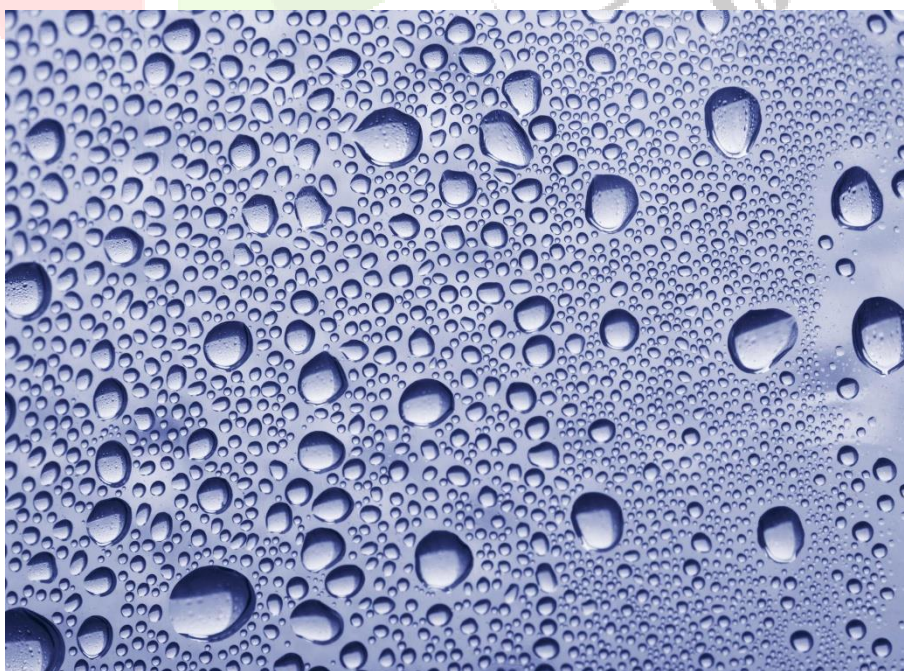
It is necessary to identify all solid forms that can exist as a consequence of the synthetic phase eg .gas the presence of polymorphs. Mass properties such as particle size, bulk density, surface area morphology can be changed during development process and avoid deception solubility and stability predictions which depends on the particular crystalline form. In bulk

Characterization testing includes:**a) Crystallinity and polymorphism:**

The structure of a solid compound denotes as crystallinity and these structures disappear in liquid and vapor state. It can be classified as Internal structures (cubic, tetragonal, hexagonal, diamond-shaped, etc.), fixed habits (salary, noodle, tabular, prismatic, vane, etc.), Change interm structures change crystalline habits, change the chemical form (e.g. formation of salts) changes both internal structure and crystal habitus. Different polymorphs are obtained by crystallization from of various solvents and solidification after thaw. When the incorporated solvent is water, it is called "hydrates". The compound does not containing water in its crystal structure is called as anhydrous "Atoms in crystalline matter are arranged regularly and repeating patterns in three dimensions. e.g. metal and mineral and atoms or molecules randomly placed without a regular atom arrangement in amorphous solids. Polymorphism is the ability of a compound to crystallize as more than one distinct crystallic species with various internal grid and various crystal forms (at different free energy states) of the same compounds. They have different physicochemical properties (melting point, density, vapor pressure,)

Pharmaceutical applications of polymorphism:

In suspension phase transformation from unstable form to a more stable polymorph may cause changes in crystal size and sintering. eg Oxyclozanide (an anthelmintic). When cream crystals grow as a result phase transformation can cause sand. In suppositories changes in polymorphic forms could cause a product with different and unacceptable melting characteristics (non-melting after administration or premature melting storage space). E.g. theorbo oil "suppose leads the characterization of solids variation fixed in

a) Hygroscopicity:

Mandy medicinal substances tend to be absorbed humidity. The amount of moisture adsorbed a fixed weight of the anhydrous sample at equilibrium with air humidity at a given temperature. These are classified as Moisturizing (substance which absorb sufficient moisture from it for the atmosphere to dissolve at the higher extreme) Efflorescent (substance that loses water and forms lower hydrate or become anhydrous at lower level) and hygroscopic (substance that exists in a dynamic equilibrium with water). This process depends on the relative humidity of the air Surroundings. It is characterized by Kat fisher. Gravimetric. TGA or gas chromatography methods. It is as important as changes in humidity content that affects stability. flow ability. Compatibility etc.

b) Characterization of fine particles:

Some physical and chemical properties of the drug substances are affected by particle size distribution, including drug dissolution rate, bioavailability. uniformity of content. taste. Texture color and stability. n addition features such as flow characteristics and sedimentation rates, among others are also important particle-related factors size. It is essential to establish as soon as possible as the particle size of the medicinal substance can be affect the composition and effectiveness of the product. Methods evaluation of particle size and distribution includes a light microscope with a calibrated grid, Sedimentation techniques, Stream scanning. Blade counter and determination of surface area by BET nitrogen adsorption method.

c) 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 method of he 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.

d) Powder flow characteristics:

The flow properties of powders are critical efficient operation of the tablet. During the pre-evaluation of the medicinal substance formulation. There for its flow capability characteristic should be studied especially when the expected dose the drug is large. The powders can be loose or cohesive (loosely flowing). The properties of the flow are affected by changes in particle size, density, shape, electrostatic charges and adsorbed moisture. It is characterized by the Carry index and the Hausner ratio, Angle of repose, rheology and thixotropic, etc.

e) Compression properties: Compression properties (elasticity. plasticity. Fragmentation ability and propensity to hit shoot) for small amounts of a new drug candidate may be established. This feature is used correctly selection of formulation components. With

F) Physical Description:

It can be observed based on size, shape, appearance and determined instrumentally or visually.

3. Solubility Analysis:

One important goal of the pre-formulation effort is propose a method for creating a solution medicine. The drug must have some solubility in water for therapeutic efficacy. To get the drug there systemic circulation to exert a therapeutic effect, must first be in the solution. Relatively insoluble compounds often show incomplete absorption. When a solute dissolves, the substance is intermolecular forces of attraction must be overcome by the pulling forces between the sol

and solvent molecules. This involves breaking down the solute forces and solvent-solvent forces to achieve solute-solvent attraction. It focuses on the drug-solvent interactions that could occur during

. 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 centrifugation.

Steps: V Assay the clear samples for its drug content to establish a plateau concentration and analyze using UV, HPLC determination .

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 pH-partition theory. Dissociation constant or pKa is usually determined by potentiometric titration The majority of drugs today are weak organic acids or International Journal of Pharmaceutical

C) Partition coefficient-

The oil and 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

d) Dissolution studies:

Rate or rate at which the medicinal substance dissolves in the medium is the so-called dissolution rate. Dissolution rate data when together with drug solubility data, dissociation constant and partition coefficient can provide an indication of drug absorption potential after administration. Dissolution

e) Common ion effect- :

common ion decreases solubility slightly soluble electrolyte. This salting out (precipitation of drug) results from ear removal of solvent molecules from the surface electrolyte by hydration common ion. Salting into larger anions (hydrotropic) eg benzoates, salicylates can open water molecules allowing an increase in water solubility of poorly soluble drugs.

4. Stability analysis:**a) In toxicology formulation**

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 . 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 dispensability and drug solubility is analyzed by pH decomposition

b) Solution stability:

These studies include the effect of pH, ionic strength, Co-solvent, Light. of the product temperature and oxygen. Usually these start with probing experiments to confirm the decay to extreme values of pH and temperature, e.g. 0.1 N HCl, water and 0.1 N NaOH all at 90 °C 910

C) Solid phase stability:

Primary objective this study is an exploration and identification stable storage conditions for the drug in the solid state and identification of compatible excipients for a formulation. In all fixed dose formulations out there some free moisture will contribute excipients and medicine and certainly in tablets represent a significant percentage, typically 2 wt.% f needed for good compression. This free water has the ability to act as a vector of chemical reactions between drug and excipients and absorbed wet films are saturated with drug compared to diluted solutions encountered in injectable preparations. The first is stability testing of pharmaceutical products quantitative assessment of chemical stability a new drug.

- **Chemical parameters**

Hydrolysis

Oxidation

Reduction

Racemization

polymerization:

Hydrolysis

Many pharmaceuticals contain ester or amide functional groups, which undergo hydrolysis in solution. Examples of drugs that tend to degrade by hydrolytic cleavage of an ester or amide linkage are anesthetics, antibiotics, vitamins, and barbiturates.

eg. Ester Hydrolysis

The hydrolysis of an ester into a mixture of an acid and alcohol essentially involves the rupture of a covalent linkage between a carbon atom and an oxygen atom. Although some of these hydrolyses can be effected in pure water, in the majority of cases, the presence of a catalyst is needed to promote the reaction. These catalysts are invariably substances of polar nature, such as mineral acids, alkali, or certain enzymes, all of which are capable of supplying hydrogen or hydroxyl ions to the reaction mixture. In practice, the general scheme employed to denote ester hydrolysis is as follows:

Amide Hydrolysis

Pharmaceutical compounds containing an amide group can undergo hydrolysis in a manner similar to that of an ester-type compound. Instead of the acid and alcohol that form as a result of ester hydrolysis, hydrolytic cleavage of amide results in the formation of an acid and an amine.

Oxidation

The oxidative decomposition of pharmaceutical compounds is responsible for the instability of a considerable number of pharmaceutical preparations. For example, steroids, vitamins, antibiotics, and epinephrine undergo oxidative degradation. The most common form of oxidative decomposition occurring in pharmaceutical preparations is autoxidation, which involves a free radical chain process. In general, autoxidation may be defined as the reaction of any material with molecular oxygen. Free radicals are produced by reactions involving homolytic bond fission of a covalent bond so that each atom or group involved retains one of the electrons of the original covalent bond. To test whether a compound is sensitive to oxygen, simply bubble air through the solution, or add hydrogen peroxide, and assess the amount of degradation that takes place.

Reduction

Reduction involves a half-reaction in which a chemical species decreases oxidation number, usually by gaining electrons. The other half of the reaction involves oxidation, in which electrons are lost. Together, reduction and oxidation form redox reactions (reduction-oxidation redox). Reduction may be considered the opposite process of oxidation

Racemization

In such a reaction, an optically-active substance loses its optical activity without changing its chemical composition. This reaction can be important to the stability of pharmaceutical formulations since the biological effect of the dextro-form can be considerably less than that of the Levo form. For example, levo-adrenaline is 15 to 20 times more active than dextro-adrenaline. Solutions of levo-adrenaline form a racemic mixture of equal parts of levo-and dextro-adrenaline with a pharmacologic activity just over half that of the pure Levo-compound.

The primary objective of this phase of pre formulation research is the identification of conditions necessary to form a stable solution. These studies should include the effects of pH, ionic strength, cosolvent, light, temperature, and oxygen. Solution stability investigations usually commence with probing experiments to confirm decay at the extremes of pH and temperature (e.g. 0.1N HCl, water, and 0.1 N NaOH all at 90°C). These intentionally-degraded samples may be used to confirm assay specificity as well as to provide estimates for maximum rates of degradation. This initial experiment should be followed by the generation of a complete pH-rate profile to identify the pH of maximum stability. Aqueous buffers are used to produce solutions over a wide range of pH values with constant levels of drug, cosolvent, and ionic strength.

Since most solution pharmaceuticals are intended for parenteral routes of administration, this initial pH-rate study should be conducted at a constant ionic strength that is compatible with physiologic media. The ionic strength (μ) of an isotonic 0.9% sodium chloride solution is 0.15, and several compendia contain formulae for isotonic buffer solutions. Ionic strength for any new buffer solution may be calculated from the following equation:

where, m_i (is the molar concentration of the ion having a valiancy, Z_i . Note that all ionic species (even the drug molecules) in a buffer solution must be considered in computing ionic strength.

Once the stability solutions are prepared, aliquots are placed in flint glass ampules, flame-sealed to prevent evaporation, and stored at a constant

Polymerization

: Is a process through which a large number of monomer molecules react together to form a polymer. The macromolecules produced from a polymerization may have a linear or a branched structure. They can also assume the shape of a complex, three-dimensional network. There exist several categories of polymerization reactions; the most important ones are step-growth polymerization, chain-growth polymerization (both fall under the category of addition

- 9, Beaker GS and Rhodes CT Modern Pharmaceutics Revised and expanded. Marcel Dekker. Inc. New York Edition 4, vol. 121, 2008:167-1RS
10. Vincent HK LL Vincent HK Lech and Robinson JR:Influence of drug properties and drug administration or the design of sustained and controlled release system. Controlled drug delivery fundamental and applications. Marcel Dekker, New York Edition 2. 1987: 3-61.. Kulkarni G T. Gotha Mahajan B and Suresh B:
- 11)Stability testing of pharmaceutical products-An overview. London Journal of Pharmaceutical Education 2004 38(4): 194-198.
12. Jain NK and sharma SN: A text book of Vallabh Prakashan Pins pharmacy.317-333.
- 13.Leon Lachman, Liberman. The theory and practice of Industrial pharmacy, edition 4. CBS publishing house, NewDelhi.2013 p:217-307.
- 14.Banker GS, Rhodes CT. Modern pharmaceutics, edition 4. Marcel Dekker, New York. 2002 p:167-184.
- 15.Loyd V. Allen, Nicholas G.popovich, Howard C. Ansel's pharmaceutical Dosage forms & Drug delivery systems, Edition 8. B.I. Publication pvt. Ltd, p:187-193,42 & 43,126-133.
16. Brahmankar D.M, Jaiswal BS. Biopharmaceutics and pharmacokinetics a Treatise, Edition 2. Vallabh Prakashan, Nagpur. 2009; p: 37-45.05/122015 NGSMIPS

