International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Preformulation

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Abstract:
Each and every drug has physical and chemical properties which is consider before development of pharmaceutical formulation. Preformulation study is carried out for the newely synthesized drug.It gives the information regarding the Bioavailibility, Pharmacokinetics and Toxicity.

Keywords: Preformulation, Physicochemical Property, Oxidation, Dissolution.

Introduction: Preformulation studies were evolved in 1950 & early 1960.Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico- mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials.
Preformulation during Drug Discovery Apart from helping formulation development, preformulation studies also help in lead identification during drug discovery phase. A new chemical entity should possess optimal biopharmaceutical properties to become a drug molecule. were possession of potency and selectivity does not ensure ‘drug ability’. Preformulation studies help in assessing the ‘drug ability’ of a molecule. Preformulation can thus be considered as critical decision-making tool during both – drug discovery and development phase. A comprehensive understanding of physicochemical properties and its effect on biological performance, allows selection of potential lead molecules and in identification of drug delivery challenges.

Objectives:

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

Goals:

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

Study of Physicochemical Characteristics of Drug Substances

Following are the major physicochemical characteristics of drug substances evaluated in the pre-formulation research:

1) Physical properties:

i) Bulk characterisation:

a) Physical form,
b) Polymorphism,
c) Particle size,
d) Particle shape,
e) Flow properties.

ii) Solubility analysis:

a) Ionisation constant – pKa,
b) Ph solubility profile,
c) Partition coefficient.

iii) Stability analysis

a) Stability in toxicology formulations,
b) Solution stability – pH rate profile,
c) Solid state stability.

2) Chemical properties:

i) Hydrolysis,
ii) Oxidation,
iii) Reduction,
iv) Racemisation,
v) Polymerisation.

1) Physical properties:

i) Bulk characterization:

a) Physical form:

Solid is one of the three classical states of matter (the others being gas and liquid). It is characterised by structural rigidity and resistance to changes in shape or volume. A solid molecule is made up of atoms tightly bound to each ot her either in a regular geometric lattice (crystalline solids that include metals and ordinary water ice) or irregularly (amorphous solid, such as a common window glass).

Crystal: The bulk and physicochemical properties of a drug (ranging from flowability to chemical stability) are affected by its crystal habit and internal structure. The outer appearance of a crystal is known as habit and the arrangement of molecules within the solid is termed as internal structure. The internal structure of a compound can be either crystalline or amorphous. The compound is said to be crystalline if its atoms or molecules are arranged repetitively in a 3-D array.

Amorphous:

Amorphous solids are the ones in which the atoms or molecules are arranged in a random manner (as in a liquid). In these solids, different bonds have different strength, there is no regularity in their external

structure, and also they do not have sharp meltin g points (due to the variable strength of bonds present between the molecules, ions, or atoms).

b)Polymorphism:

The ability of a substance to exist in more than one crystalline form is polymorphism and the various crystalline forms are termed as polymorphs. There are two types of polymorphs:

1. Enantiotropic Polymorphs: By altering the temperature or pressure, the enantiotropic polymorph s can be changed into another in a reversible manner, e.g., sulphur.
2. Monotropic Polymorphs: Under all the conditions of temperature and pressure, the monotropic polymorphs remain unstable, e.g., glyceryl stearate.

C)Particle Size:

The term particle size is used to compare the dimensions of solid particles (flakes), liquid particles (droplets), or gaseous particles (bubbles). Size, shape, and surface morph ology of the drug particles put a direct effect on the bulk flow, formulation homogeneity, and surface -area controlled processes , such as dissolution and chemical reactivity. Preparation of homogeneous samples is facilitated and surface area of drug for in teractions is enhanced during pre-formulation when each new drug candidate is tested with the smallest particle size.

D)Particle shape:

The term particle shape is used to express the geometrical shape and surface regularity (rugosity) of the material (figure 1.2). Moreover, particle shape affects the surface area, flow, packing, and compaction properties of the particles. The particle shape, either spherical or asymmetrical can be determined. In order to differentiate the shape of spheric al or asymmetrical objects, it is necessary to know that the sphere has minimum surface area per unit volume.

e)Flow properties:

Free-flowing or non-free-flowing/cohesive are the two types of pharmaceutical powders. Changes in particle size, density, shape, electrostatic charge, and adsorbed moisture (arising from processing or formulation) significantly affects the flow properties of a powder.

ii)Solubility analysis:

a)Ionisation constant – pKa

Solubility and absorption undergo change by the orders of magn itude with change in pH, therefore, dissociation constant of a drug that can ionise within a pH range of 1 -10 should be determined. At a particular pH, an estimate of the ionised and unionised drug concentration can be obtained by the Henderson-Hasselbalch equation.

b)pH solubility profile:

The pKa of the ionising functional group and the intrinsic solubilities for both the ionised and unionised forms of acidic or basic drug influence their solubility

c)Solid state stability:

Identifying stable storage conditions for solid state drug and compatible excipients for a formulation is the major objective of this pre-formulation study. Changes in purity and crystallinity (resulting from process

improvements) affect these stability studies. The reactions of solid state are slow and their interpretation is difficult than the reactions of solution state. This is because of the reduced number of molecular contacts between the drug and excipient molecules and occurrence of multiple-phase reactions

2)Chemical properties:

i) Hydrolysis:

Hydrolysis is the most common degradation pathway since water plays an important rol e in many processes, especially in solution and also in solids (in which water may be present in low concentrations). Hydrolysis occurs via nucleophilic attack of the water molecule on labile bonds with susceptibility dependent on the bond type and decreas ing from lactam > ester > amide > imine.

ii) Oxidation:

The environmental phenomenon of oxidation requires oxygen (or an oxidising agent), light, and trace metals that can catalyse the reaction. If molecular oxygen is involved, the reaction is rapid and termed auto-oxidation. Chemically, oxidation involves loss of electrons, which requires an electron acceptor or an oxidising agent [for example , iron converting from ferric (Fe3+) to ferrous (Fe2+)].

iii) Reduction:

Reduction is a relativel y common pathway of drug metabolic process. Hepatic microsomes catalyse diverse reductive chemical reactions with the use of NADPH. Cytochrome P450 catalyses the azo and nitro reduction reaction. The enzyme alcohol dehydrogenase catalyses the reduction of chloral hydrate into trichloroethanol (its active metabolite). Prednisolone and cortisone reduces to hydrocortisone (their active metabolites). The intestinal flora reduces the azo dyes (used as colouring agents in pharmaceutical or food products) into amines in the liver.

iv) Racemisation:

Racemisation involves the conversion of one enantiomer of a compound, such as an L - amino acid, into the other enantiomer. The compound then alternates between each form while the ratio between the (+) and (–) groups approach es the ratio 1:1, at which it becomes optically inactive.

v) Polymerisation:

Polymerisation is a continuous reaction occurring between molecules. A polymer is formed by the reaction between more than one monomer. For example, glucose solution darkens due to polymerisation of the breakdown product [5 -(hydroxyl methyl) furfural]; HCHO polymerises into para-HCHO that crystallises out from the solution.

CONCLUSION:

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

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