PRE-FORMULATION STUDIES IN THE DEVELOPMENT OF NOVEL DRUG MOLECULES

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ABSTRACT

A category of studies called "preformulation" concentrate on the physical and chemical characteristics of a potential new medication the performance of a drug and the creation of a dosage form. These investigations ought to concentrate on the characteristics of a novel substance that might influence the drug performance and the creation of a potent dosage form. A detailed comprehension of these features may ultimately justify the necessity for molecular alteration or offer a justification for formulation design. Therefore, for any initially implemented, the Preformulation research of any API should be finished before choosing excipients. The drug molecule's polymorphism, which includes crystal and amorphous forms, reveals many chemical, physical, and medicinal descriptions. This article describes a few characteristics and methods for medication preformulation evaluation parameters. Preformulation studies were investigated and reported on, including solubility, pKa, dissolution, melting point, stability in solid state, bulk density, and flow parameters.

Keywords: *Preformulation, API, Novel substances, Phyical properties, chemical properties*.

INTRODUCTION

A change in the focus in industrial pharmaceutical product development led to the evolution of preformulation in the late 1950s and early 1960s. The first programmes that might be called preformulation were inspired by improvements in analytical techniques. Preformulation testing's main goal is to collect data that will help the formulator create stable, bioavailable dosage forms that can be mass-produced. The synthetic chemist may gather information that can be suitably categorised as preformulation data during the early stages of the creation of a novel medicinal molecule, either alone or in collaboration with experts in related fields, including preformulation.
A literature search that includes information on stability and decay, the suggested method of administration, formulation strategies, and the bioavailability and pharmacokinetics of medications with similar chemical compositions.

It also entails initial research and molecular optimization by the drug should be tested to gauge the size of each suspected problem area (Step I), and if a deficiency is found, a molecular alteration should be made (Step lI). Molecules are modified using salts, prodrugs, solvates, psolymorphs, or even new analogues to make up for this shortcoming[1].

Although paracetamol has antipyretic and analgesic qualities, it does not have any practical anti-inflammatory characteristics. Easily absorbed from the digestive system is paracetamol. Tablets, which are solid dosage forms

containing one or more medicines with or without excipients and are made by compression, fall under the bcs classification ii for paracetamol. It offers the lowest content variability and the highest dosing precision.

EVALUTION PARAMETER USED IN PREFORMULATION OF DRUGS

Physicochemical parameters[2,3]

1. **Organoleptic properties:**
2. **Bulk characterization studies:**
- Crystallinity and polymorphism
- Hygroscopicity
- Fine particle characterization
- Bulk density e) Powder flow properties
- **(** Compression propertiesg) Physical description
3. **Solubility analysis:**
- Intrinsic solubility determination
- PKa determination
- Partition coefficient
- Dissolution studiese) Common ion effect

4. **Stability analysis:**

In toxicology formulations
- Solution stability
- Solid state stability

1. Organoleptic properties

Color: It should be unappealing to the eye and determined either by instrumental means or by visible methods that differ from batch to batch. For subsequent production, keeping track of early batches and creating "specs" is particularly helpful. If it is thought to be undesirable, the body might be coated with a variety of colours.

Odor and taste: Use a less soluble chemical version of an unappealing medicine or mask it with flavours, excipients, coatings, etc. Drug compounds that are irritant to the skin should be handled carefully. Excipients including flavours, colours, and dyes will impact stability and bioavailability. Off-white, cream yellow, brown, or glossy are possible colours. Odors might be strong, weak, fruity, fragrant, sulphurous, pungent, or odourless. Acidic, bitter, bland, strong, sweet, and tasteless flavours are all possible.

2) Bulk Characterization studies: All solid forms that might exist as a result of the synthetic step, such as the presence of polymorphs, must be identified. During the development process, bulk parameters such as particle size, bulk density, and surface morphology may be altered to prevent inaccurate predictions of solubility and stability, which depend on a certain crystalline structure.

3) Crystallinity and polymorphism: In the liquid and vapour states, a compound's crystallinity refers to its structure, which vanishes. It falls within the category of internal structures (cubic, tetragonal, hexagonal, rhombic, etc.), strong habits (platy, needle, tabular, prismatic, bladed, etc.), Altering the chemical form (for example, salt production) affects both the internal structure and crystal habit. Altering the internal structures affects the crystal habits. Different polymorphs are created through melting and solidification after crystallisation using various solvents. It is referred to as "hydrates" when water serves as the included solvent[3,4].
Crystalline matter has its atoms arranged in three dimensions in predictable and recurring patterns. For instance, amorphous materials can contain metal, mineral, and atoms or molecules randomly arranged without a normal atomic configuration. They differ in their physicochemical characteristics (melting point, density, vapour pressure, X-ray, color, crystal shape, hardness, solubility, dissolution rate and bioavailability). It's crucial to find the polymorph that is stable at room temperature during preformulation. For instances: There are three different forms

of chloromphenicol: A, B, and C; the B form is the most stable and ideal. There are three different forms of riboflavin: I, II, and III. Form III has a 20-fold higher water solubility than form I. Below either polymorph's melting point, enantiotropic polymorphs can be interconverted, and the conversion is reversible at a specific temperature. as in sulphur.

Pharmaceutical applications of polymorphism:

Crystal size and caking changes during the suspension phase can result from the transformation from an unstable form to a more stable polymorph. e.g. Oxyclozanide (anthlemintic) (anthlemintic). Grittiness in cream can come from crystal development brought on by phase change. Changes in polymorphic forms in suppositories could result in a product with an unsatisfactory melting characteristic (failure to melt after administration or premature melting during storage). Like the "base" for Theorem oil suppositories. It leads to the characterization of solids, which entails confirming that the solid contains the anticipated chemical compound, describing the internal structure, and describing the crystallographic habit; figuring out how many polymorphs might be possible for the compound and stability; and checking for the presence of an amorphous form, among other things.

a) **Hygroscopicity:** A lot of medication ingredients have a propensity to absorb moisture. the volume of water absorbed by a fixed weight of anhydrous material that is in moisture equilibrium with the air at a specific temperature. These fall into three categories: Efflorescent (a substance that loses water to form a lower hydrate or become anhydrous at lower level), Deliquescent (a substance that absorbs enough moisture from the atmosphere to dissolve itself at higher extreme), and Hygroscopic (a substance that exist in a dynamic equilibrium with water). The relative humidity of the environment affects this process. Karl Fisher, gravimetric, TGA, or gas chromatography methods can be used to describe it. Changes in moisture content have implications for stability, flowability, compatibility, etc.
b) **Characterization of fine particles:** The particle size distribution affects the bioavailability, homogeneity, taste, texture, colour, and stability of medicinal substances as well as the rate at which they dissolve in the body. Particle size is affected by a number of different parameters, including flow characteristics and sedimentation rates, among others. It is crucial to determine as early as possible how the drug substance's particle size may influence the formulation and efficacy of the finished product. A light microscope with a calibrated grid, sedimentation techniques, stream scanning, a Coulter counter, and the calculation of surface area using the BET nitrogen adsorption method are some of the methods used to assess particle size and distribution.
c) **Bulk density:** Having a general notion of the drug substance's true and bulk densities is highly helpful in determining the size of the final dosage form. This parameter obviously plays a crucial role for medications with modest potency, which may make up the majority of the final granulation or table. When a density issue is found, it is frequently quickly fixed by milling, slugging, or formulation. Bulk density of a product varies significantly with the method of crystallisation, milling, or formulation. The properties of powder flow may be impacted. It has an impact on the size of high-dose capsule products or the homogeneity of a low-dose formulation where there are significant variations in the densities of the medication and excipients.
d) **Powder flow characteristics:** For effective tablet operation, powder flow characteristics are essential. Therefore, it is important to study the drug substance's flow ability property during the preformulation evaluation, especially if a big drug dose is predicted. Powders can be cohesive or free-flowing (non free flowing). Changes in particle size, density, shape, electrostatic charges, and adsorbed moisture have an impact on the flow properties. Carr's index, Hausner ratio, angle of repose, rheology, and thixotropy are some of the characteristics.
e) **Compression properties:** It is possible to determine a new drug candidate's compression properties (elasticity, plasticity, fragment ability, and punch filming tendency) in small quantities. This characteristic is utilised to choose the ingredients for formulations properly.
f) **Physical characteristics:** They can be measured, determined instrumentally or visually, and observed based on their size, shape, and appearance.
g) **Solubility analysis**: Finding a way to make medication solutions is a key objective of the pre-formulation work. A drug's therapeutic effectiveness depends on its ability to dissolve in water. A drug must initially be in solution in order for it to enter the systemic circulation and have a therapeutic impact. Compounds that are relatively insoluble frequently show inadequate absorption. In order for a solute to dissolve, forces of attraction between the molecules of the solute and the solvent must outweigh those between the molecules of the substance.

h) Pka Determination: The pH-partition theory is based on the interactions between the dissociation constant, lipid solubility, pH at the absorption site, and the properties of different medications' absorption. Potentiometric titration is typically used to determine the dissociation constant or pKa. Nowadays, most medications are weak organic bases or acids. Understanding each substance's unique ionisation or dissociation characteristics is crucial because the degree of ionisation to which substances are exposed to membrane barriers greatly influences how readily they are absorbed. The degree of a drug's ionisation is determined by the drug's pKa, or dissociation constant, as well as the pH of the solution in which it is delivered to the biologic membrane (whether an acid or base). The term "pKa" is derived**.**

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

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

Partition coefficient: A molecule's lipophilic characteristics, or preference for the hydrophilic or lipophilic phase, are indicated by the oil/water partition coefficient. The partition coefficient should be taken into account when creating a dosage form for a pharmacological ingredient. A solute will disperse between the two phases and reach equilibrium at a steady temperature if it is added to a combination of two immiscible liquids.

4) Dissolution studies: The dissolution rate is the speed or rate at which a drug substance disintegrates in a medium. When taken into account combined with information on a drug's solubility, dissociation constant, and partition coefficient, dissolution rate data can give an indicator of the drug's potential for absorption after delivery. Noyes' equation describes the drug's dissolving rate when the surface area remains constant. Whitney's equation is as follows:[5-7]

$$\frac{dc}{dt} = \frac{D\,A\,(Cs-C)}{h\,V}$$

D: diffusion coefficient
h: thickness of the diffusion layer at solid liquid interface.
A: the surface area of the drug in contact with the dissolution medium.
V: volume of media.
Cs: saturated solubility of the drug in the dissolution medium at exp. Temp.
C: the concentration of the drug at time t.

Fig. 1 Whitneys Equation describing Dissolving Rate.

e) Common Ion effect: The presence of a common ion decreases the solubility of the hardly soluble electrolyte. This salting out (drug precipitation) happens when the common ion is hydrated, which removes solvent molecules from the electrolyte's surface. Larger anions (hydro tropes), such as benzoates and salicylates, can open the water molecules, increasing the solubility of medications that aren't very water soluble. Due to the high concentration of chloride ions, example hydrochloride salts frequently show reduced solubility in gastric juice. A hydrochloride salt's dissolving rate in various mediums should be studied in order to investigate a common ion interaction: 1.2% by weight NaCl, 0.05 M HCl, and 0.9% by weight NaCl in 0.05 M.

2. **Stability analysis:** These investigations are advised to assess samples of toxicological preparations for stability and possible homogeneity issues. Animals are typically given medications through their feed or by oral gavages of a solution or suspension of medication in an aqueous medium. The presence of water, vitamins, minerals (metal ions), enzymes, and moisture levels in feed can significantly shorten a drug's shelf life and decrease stability. Toxicological preparations in the form of solutions and suspensions should be examined for ease of manufacturing before being kept in flame-sealed ampoules at varied temperatures. Drug solubility is assessed by pH decomposition, and for chemical stability, the suspension should occasionally be shaken to check for dispersibility[8].

b) Solution stability: The impact of pH, ionic strength, cosolvent, light, temperature, and oxygen is studied in this area. These often start with probing studies to verify degradation at the pH and temperature extremes, for example, 0.1 N HCl, water, and 0.1 N NaOH all at 90^0C.

c) Solid state stability: The exploration and identification of stable storage conditions for drugs in the solid state, as well as the identification of compatible excipients for a formulation, are the main goals of this study. Excipients and the medicine will both provide some free moisture to all solid dose formulations, and tablets definitely need a large amount—typically 2% w/w—to achieve adequate compression. In contrast to the dilute solutions seen in injectables, this free water has the ability to act as a vector for chemical reactions between the drug and excipients, and the absorbed moisture sheets are saturated with the medicine. The initial quantitative evaluation of a new drug's chemical stability is done through stability testing of pharmaceutical products.

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. Once past initial toxicity, phase I (clinical toxicology) begins for actual formulations. After that phase II and III clinical testing begins, and during this phase an order of magnitude formula is finalized. After completion of all above, an NDA is submitted and after approval of NDA, production can start[9-12].

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