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IN-DEPTH ANALYSIS OF PREFORMULATION METHODS: A SCHOLARLY REVIEW IN DRUG DEVELOPMENT

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ABSTRACT

In the world of pharmacy, individual drug internally has both chemical and physical attributes that have been taken into consideration before creating a pharmaceutical formulation. Preformulation is a topic of study that focuses on the physicochemical attributes of a new drug entity that could affect the development of the drug and the effectiveness of the dose form. Preformulation studies are conducted on newly synthesized or extracted compounds, and they provide information on the drug's toxicity, pharmacokinetics, bioavailability, and formulation of related compounds as well as the process of degradation. These qualities provide the framework for creating dosage forms by mixing drugs with pharmaceutical ingredients. Reformulation studies improve the public safety requirements, the product quality in the manufacture of dosage forms, regulatory relieving, and resource conservation in the improving the development of drug and review process. In this article, certain approaches and properties for preformulation evaluation parameters and medication manufacture are explained.

KEYWORDS: Preformulation, Stability testing, Physio-Chemical properties, Polymorphism.

INTRODUCTION

Preformulation is the process of evaluating a pharmaceutical material's physical and chemical characteristics both on its own and in combination with additional compounds (Excipients). The significant nature of molecular exchange may be adequately justified, and the design of pharmaceutical products can also be properly defended, with a thorough comprehension of all these aspects. It is important to be aware of the properties of the drug, its therapeutic efficacy in comparison to similar products, its dosage form, stability and decay data from literature searches, proposed routes of drug administration, formulation approaches from literature searches, and the bioavailability and pharmacokinetics of drugs with similar chemical combinations before establishing the preformulation studies. After biological screening, when the choice is made to continue the development of the chemical in clinical trials, the official preformulation research should begin prior to starting a formal Programme. The preformulation scientist needs to think about these things.

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- Accessible physicochemical information (including structure of chemicals, and different availability of salts).
- Expected dosage.
- Supplying chain conditions and developing plans (i.e., available time).
- Assays that indicate stability are available.

OBJECTIVES

- It is of the utmost importance to understand how a drug ingredient is physically defined before designing acceptable dosage forms that are stable, safe, and effective.
- Prior to development of dosage form, is the first phase in the logical development of a pharmaceutical dosage form for a drug compound.

GOALS

- Establishment of physicochemical attributes of novel drug entity.
- Establishment of the physical attributes.
- Establishment of the kinetic profiling of rate.
- Determining compatibility with excipients or common side products.

- Choosing of the true form of a drug entity.

Preformulation Parameters

1. Physical properties
   - A) Organoleptic properties
     - •Odour
     - •Colour
     - •Taste
   - B) Bulk characterization
     - •Assay development
     - •Melting point
     - •Flow properties
     - •Characteristics of solid state
     - •Densities
     - •Crystallinity and amorphousness
     - •Polymorphism
     - •hygroscopicity
     - •compressibility
   - C) Solubility analysis
     - •Ionization constant
     - •Dissolution
     - •Common ion effect(ksp)
     - •Common ion effect(ksp)
     - •Solubilization
     - •Effect of temperature
     - •Partition coefficient
   - D) Stability analysis
     - •Stability in solid state
     - •Stability in solution state
     - •Compatibility of drud with excepient
2. Chemical properties
   - •Hydrolysis
   - •Oxidation
   - •Photolysis
   - •Recemization
   - •Polymerization
   - •Isomerization

A) ORGANOLEPTIC PROPERTIES

The proper characterization of the drug material should be the first step in any conventional preformulation operation. Use descriptive terminology to note the new drug's color, smell, and taste. The past batches of the new medication's color must be meticulously documented. It is quite helpful to keep track of the color of the initial batches when creating the right requirements for further production. Clear language should be used to describe the new medication's tone, fragrance, and taste. To avoid confusion in between researchers who use different phrases to explain the same trait, it is crucial to set a standard way of wording these attributes. The past batches of the new medication's color must be meticulously documented.

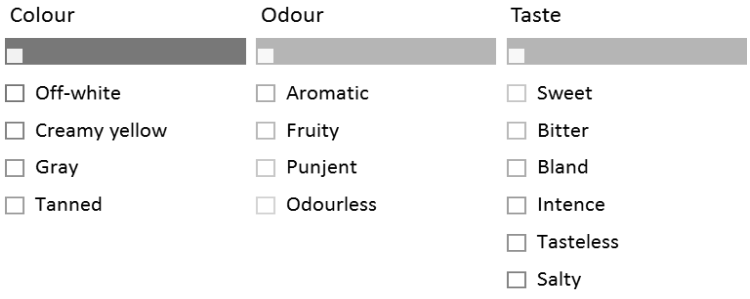

Fig. no.1: Organoleptic attributes of Pharmaceutical Powders.

B) SOLUBILITY ANALYSIS

Fluid solvency is a crucial physiochemical property of a medicinal component. A medication should have some fluid solubility for remedial sufficiency in the pH range A medicine needs to be the first item in the arrangement structure for it to start off on the right foot and have a healing effect. Consideration should be given to enhancing a medicinal substance's solvency if it isn't exactly desirable. Insufficient or unreasonable retention across the pH range between may result in unfortunate solvency (10mg/ml).

For a distinct molecule, however, the disclosure of two significant characteristics is necessary.

a. (Co) Intrinsic solubility.
b. (Pka) Dissociation consistent.

a) Intrinsic solubility (co)

The inborn dissolvability should be evaluated at two temperature of 4 to 5°C, in order to give outstanding real solidity as well as to boost transient stockpiling and synthetic stability until more decisive information is available. 37 degrees Celsius to aid in the assessment of biopharmaceuticals. As a function of PH capacity, the equation can be used to estimate how easily pitifully required and feebly acidic medications will dissolve.

b) Dissociation constant (pka)

Numerous medications are either pitifully basic or acidic substances, and depending on the value of pH, they can exist as an ionised or unionised species. The unionised compounds are more quickly lipid-dissolvable and retained as a result. In this way, the minimal portion of the medicine in the arrangement that is un-ionized is related to the gastro-intestinal retention of pitifully acidic or basic drugs. Retention is favoured by smothering circumstances. The pH found at the site of retention, the ionisation stable, and lipid solvency of the unionized species are the factors that are crucial in the retention of pitifully acidic and fundamental chemicals. Together, these components support the widely accepted pH segment theory. The overall centralizations of an appallingly acidic or basic drug's unionised and ionised kinds [unionized form].

[un-ionized form]

- pH :- pKa + log ---------- for bases.
[ionized form]

[ionized form]

- pH :- pKa + log---------- for acids.
[un-ionized form]

✓ Determination of pka

1. Dissolution rate method.
2. Spectrophotometric Determination.
3. Liquid Liquid Partition method.
4. Potentiometric titration.

c) Partition coefficient

The fraction of the unionised compound that is centralised at harmonisation between the organic and fluid phases is commonly represented as a parcel coefficient, or log P, when describing the lipophilicity of an organic molecule.

- Po/w :- (C oil/water) at equilibrium Or
- logP (unionized compound) in org/ (unionized compound) in aq.

✓ The partition coefficient, sometimes referred to as the dissolving coefficient, is a ratio that is essentially devoid of a grouping of weakly organized configurations of a specific solute animal species. It is implied by logP = 0 that the substance is a comparable solvent in both water and the apportioning dissolvable. The compound is multiplicatively more dissolvable in the apportioning dissolvable if the compound has a value log P = 5 at that point. A log P = - 2 indicates that the substance is very hydrophilic and several times more solvent in water. Drugs classified as lipophilic have P upsides that are significantly greater than 1, while hydrophilic drugs have segment coefficients that are significantly lower than,

Methods for determining partition coefficient

1. Chromatographic methods.
2. Tomlinson’s filter probe method.
3. Shake-flask method.
4. There are now automated instruments readily available.
5. The use of a probe with countercurrent and a filter.
6. Microelectrometric titration method.

✓ Applications of partition coefficient

Percentage of particles that are lipophilic. recovery of anti-infection drugs from outdated inventory. medicine extraction from natural liquid for beneficial testing. medication absorption. distribution in emulsion research.

d) Solubilization

Preformulation research should include limited tests to identify potential solubilization tools for drug components with either bad or poor water solubility or poor dissolvability for predicted arranged dosage shape.

✓ Methods for increasing solubility

1. pH change.
2. Co-Solvency.
3. Solubilization by Surfactant.
4. Dielectric Constant.
5. Complexation.
6. Chemical Modification of drug.

e) Thermal effect

We decide the impact of temperature on the dissolvability of medication applicant. This not set in stone by estimating hotness of arrangement for example HS.

- lnS:- [- ΔHS (1) + C RT].

Where,

dC / dt:- dissolution rate.
Where, S:- molar solubility at temperature T (K), R:- gas constant.

When a mole of solute is broken down into a large quantity of soluble, the amount of heat given or consumed is referred to as the "hotness of the arrangement." An incentive for soaking arrangements equilibrated at regulated temperatures across the range of interest was not totally fixed in stone from solvency. Normally the temperature range should cover 5 °C/25 °C/ 37 °C, and 50 °C. Expanding the arrangement temperature will enhance the drug's solubility if the arrangement is hotter than normal (endothermic cycle).

f) Common ion effect

The normal particle impact is a common relationship with dissolvable that is sometimes overlooked. The solvency of a barely soluble electrolyte is frequently decreased by the expansion of normal particles. Due to the competing hydration of other particles, the water particle that would otherwise dissolve results in this salting out. As a result, sadly basic medications that are administered as salts of HCL have decreased solubility in acidic (HCL) arrangements.

g) Dissolution

Many times, the disintegration rate in liquids at the assimilation site, is the rate restricting strides in the assimilation process. This is valid for the medication managed orally in strong measurement structures such as container, tablet, and suspension and also for medication managed intramuscularly in the type of pellets and suspension. The dissolution method has two kinds.

a. Intrinsic dissolution method.
b. Particulate dissolution method.

a. Intrinsic dissolution

The Noyes-Nernst equation effectively describes the rate of solid disintegration in its own solution

- dC/dt: - [AD (Cs – C)/hv].

Where,
A = surface area of the solid which is dissolving, D = coefficient of diffusion.
C = concentration of solutes in the bulk medium, h = Layer Diffusion Thickness.
V = the dissolving medium's volume.
Cs = concentration of solutes in the diffusion layer.

At the time of beginning stage of disintegration, Cs is greater than C and is basically equivalent to immersion solvency S. Surface region An and volume V can be place constant. Under these circumstances and at steady temperature and tumult,
Equation decreases to dC/dt: - KS
Where, K: - AD/hV: - constant.

b. Particulate dissolution method

It will determine how quickly medicine disintegrates on diverse surfaces. It is used to focus on the impact of surface area, size of molecule, and mixing with an excipient on disintegration. In light of this, alternative strategies, such as surfactant expansion, will be taken into account if molecule size has no effect on disintegration.

C) Bulk characterization

a. Solid state characteristics

A powder is a bulk of solid particulate matter or granules surrounded to the air (another fluid), and after combining of the solid and fluid has a substantial impact on the powder's bulk properties. Given the vast array of factors that might alter their rheological properties, powders are most certainly the least predictable of all materials in terms of stream capacity. Actual particle characteristics, such as size, rakishness, size changeability, shape and hardness, will all affect the characteristics of the stream.

b. Particle size and distribution of size

The particle size distribution and forms of pharmacological compounds have an impact on a variety of chemical and physical properties. In rare cases, the impact also affects the biopharmaceutical behaviour of solid medications in addition to their physical features. Currently, it is widely believed that poorly soluble drugs that have an advancement in the retention cycle that limits the disintegration rate will be more quickly accessible when administered as a finely sub-isolated state rather than as a gritty substance.

Table No. 1: Techniques for Measurement of Particles in Fine Form.

Technique	Particle size (micro meters)
Microscopic	1-100
Sieve	>5
Sedimentation	>1
Elutriation	1-50
Centrifugal	<50
Permeability	>1

c. Densities

Density is the mass-to-volume ratio.

✓ various density types

1. 1. Bulk density is computed using the mass of powder which was known to have been filtered using sieves.
2. Tapped density: By mechanically tapping the measuring cylinder containing the powder, it is obtained.
3. True density: It actually has the density of a solid.

d. Compressibility

A powder's "compressibility" is its capacity to contract under pressure, and its "compatibility" is its capacity to be compacted into a tablet with a specific tensile strength.

Based on the measurement of the density, it can be used to forecast the flow qualities.

- Carr's index (%) =
  [Tapped density–Bulk density] x100
  [Tapped density]

Table no. 2: Criteria for Carr's index approval.

% of Compressibility	Relative Flowability
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

Hausner's ratio

- Hausner's ratio = [Tapped density] X 100
  [Bulk density]

Table no. 3: Acceptance requirements for Hausner's ratio.

Hausner's ratio	Type of flow
1.00–1.11	1.00–1.11
1.12–1.18	1.12–1.18
1.19–1.25	1.19–1.25
1.26–1.34	1.26–1.34
1.35–1.45	1.35–1.45
1.46–1.59	1.46–1.59

e. Powder flow properties

To ensure effective mixing and weight tolerance uniformity for the compressed tablets, It is necessary for the powder or granulation that will be compressed to flow smoothly. By choosing the proper excipients, a problem with a medicine that is "poorly flowable" during the preformulation stage can be resolved. To optimize their flow characteristics, medication powders may occasionally need to be granulated. Compressibility index, shear cell, flow through an aperture, and angle of repose are a few of these techniques. An increased crystal size or a lower angle of repose will be caused by a homogeneous shape and smaller Carr's index; changes in particle size and shape are typically extremely obvious.

✓ Angle of Repose

The maximum angle that is formed between the surface of the pile of powder and the horizontal surface is called the angle of repose.

For most pharmaceutical powders, the angle-of-repose values range from 25 to 45°, with lower values indicating better flow characteristics.

- Tan θ = h / r

Where, h = height of heap of pile, r = radius of base of pile.

Carr's compressibility index.

f. Crystallinity

Drugs and excipients can exist in an array of amorphous or crystalline forms according to their chemical composition and method of separation or crystallization. Molecules may organize themselves geometrically during crystallization, leading to distinct packing arrangements or orientations in the crystal structure.

Based on symmetry, many crystal types are classified into six distinct crystal systems.

1. cubic (Ex. sodium chloride).
2. triclinic (Ex. boric acid).
3. hexagonal (Ex. iodoform).
4. tetragonal (Ex. urea).
5. monoclinic (Ex. sucrose).
6. rhombic (Ex. iodine).
7. trigonal (Ex. crystal meth).

g. Polymorphism

There are a wide variety of pharmacological substances that can exist in different crystalline forms with different spatial lattice configurations. This feature is known as polymorphism. The numerous crystal structures are called polymorphs. When polymorphism happens, molecules arrange themselves in the crystal in two or more distinct ways; alternatively, the molecules' orientation or conformation at the lattice sites may change.

✓ Techniques for identification of polymorphism:

1. Hot stage microscopy.
2. X- Ray Diffraction method.
3. Melting point determination.
4. Thermal methods.
5. Microcalorimetry.
6. Optical crystallography.
7. NMR technique.

h. Hygroscopicity

Many chemicals and salts react negatively to moisture or water vapour. When substances interact with moisture, they retain the moisture by chemical reaction, capillary condensation, bulk or surface adsorption, and, in rare instances, a solution. The process of deliquescence occurs when a solid saturates a thin water film that is present on its surface. The liquid film around the solid is demonstrated to be saturated when moisture is absorbed to the point where deliquescence occurs at a specific critical relative humidity. Heat transport rates and vapour diffusion control this process.

i. Common ion action (Ksp)

The common-ion effect generally describes adding a soluble substance that has the same ion as the ionic

precipitate to a solution can result in a decrease in the precipitate's solubility. This phenomenon was brought into light by Le Chatelier's principle which is known as ionic association /dissociation equilibrium reaction. This effect is prominently felt as a decrease in salt and other weak electrolyte solubility. To see if the solubility equilibrium is reached, increasing the concentration of one of the ions can lead to more precipitation. One ion is present in both the original salt and the extra chemical, which is the cause of the outcome.

j. Thermal Effect

Pharmaceutically, it is possible for a formulation to be more inclined towards endothermic(positive) solutions. In a solution, the heat involved in it can be used to determine how much temperature is influencing a possible therapeutic molecule. Enthalpy of a solution in a formulation is considered to play a crucial role as the heat generated or absorbed when a solute largely dissolves in a sufficient amount of solvent in it. The need to understand temperature as an important parameter in preparing any formulation is because it affects the medical ingredients solubility directly. The solubility of any solute in a solvent mainly depends on the amount of energy needed to break the bonds in the solutes as well as the energy emitted by the solid solvent bond formation(exothermic) to determine whether the enthalpy of solution is positive/endothermic or negative/exothermic.

D) STABILITY STUDIES

General elements of incompatibility: When we combine two or more APIs or excipients, we assume that they are incompatible since they affect each other negatively in terms of welfare, useful viability, appearance, and taste.

a. Solid state stability studies

Due to a decreased number of sub-atomic interactions between drug and excipient particles as well as the occurrence of multiple-stage reactions, solid state responses are much slower and more difficult to interpret than arrangement state responses.

b. Solution state stability studies

Compared to strong state reactions, fluid state responses are easier to recognise. The programme setup is the same as robust measurement structures for the discovery of unknown fluid incompatibility.

- ✓ Following circumstances be assessed in investigations on arrangements or suspensions of mass medication substances
- Acidic or alkaline pH.
- Effect of stress testing conditions
- High Oxygen and Nitrogen atmospheres.

c. Drug-Excipient Compatibility Studies

Compared to strong state reactions, fluid state responses are easier to recognise. The programme setup is the same as robust measurement structures for the discovery of unknown fluid incompatibility.

- ✓ Drug excipient compatibility is determined using the following analytical methods

I. Thermal methods of analysis.
II. DSC- Differential Scanning Calorimetry.
III. DTA- Differential Thermal Analysis.

1. Accelerated Stability Study.
2. FT-IR Spectroscopy.
3. DRS-Diffuse Reflectance Spectroscopy.
4. Chromatography.

I. SIC-Self Interactive Chromatography.
II. HPLC-High Pressure Liquid.
III. TLC-Thin Layer Chromatography.

5. Chromatography.
6. Miscellaneous.

I. Radiolabelled Techniques.
II. Fluorescence Spectroscopy.
III. Vapour Pressure Osmometry.

CONCLUSION

Preformulation studies are essential for anticipating definitional problems and identifying clever solutions in both flexible and robust measurement structure technologies. The Preformulation researcher can assist the engineered scientist in identifying the perfect atom and provide the scholar with the correct vehicles to elicit a pharmacological reaction by analysing the physicochemical qualities of each medicine applicant inside of a healing setting. The validity of parental or other fluid measurements will be shown by soundness studies in arrangement, and they can identify ways for adjustment. The most effective vehicles for a strong measurement structure will be shown to be equally strong state dependability by TLC, HPLC and DSC in the presence of tablet and case excipients. This audit article provides details of earlier investigations about the creation of any supported discharge dosage structures.

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