



Review On Preformulation Studies.

Avhad Prafulla Raosaheb ^{1*}, Tekade Gaurav Vinayak ², Patil Gaurav Anil ³,

Patharwat Vinayak Dattatray ⁴, Chandankhede Aniket Vilas ⁵.

Department of Pharmaceutics, PDEA's Seth Govind Raghunath Sable College of Pharmacy Saswad, Pune.

Abstract

Preformulation refers to a collection of research that concentrate on a novel drug candidate's physicochemical characteristics that might influence the drug's performance and the creation of a dosage form. This can support the necessity for molecular change or offer crucial information for formulation design. Before developing a pharmaceutical formulation, consideration was given to each drug's inherent chemical and physical qualities. This characteristic offers a framework for combining medications with pharmaceutical components to create dosage forms. The goal of the preformulation study is to create a dosage form that is beautiful, stable, safe, and effective by determining the kinetic rate profile, compatibility with other ingredients, and physico-chemical parameters of new therapeutic compounds. Drug solubility, partition coefficient, dissolving rate, polymorphic forms, and stability are among these qualities, and they all play significant roles in preformulation studies. 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.

Keywords: Preformulation , Physiochemical Properties ,Compatibility , Methods.

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 earliest programmes that might be called "preformulation" were inspired by advancements in analytical techniques. Preformulation testing's main goal is to collect data that the formulator can use to create stable, bioavailable dosage forms that can be mass-produced. The synthetic chemist may gather information that can be suitably categorized as preformulation data during the early stages of the creation of a new therapeutic molecule, either alone or in collaboration with experts in other disciplines,

including preformulation. The drug's properties, potency in comparison to comparable products, dosage form, stability and decay data from literature searches, proposed route of drug administration, formulation approaches from literature searches, and the bioavailability and pharmacokinetics of medications from chemically related classes should all be considered before beginning the preformulation studies¹. Preformulation developed in the late 1950s and early 1960s as a result of a shift in the emphasis on industrial pharmaceutical product development. The first projects that may be referred to as "preformulation" were motivated by developments in analytical methods. The primary objective of preformulation testing is to gather information that will be used by the formulator to develop stable, bioavailable dosage forms that can be mass manufactured. When developing a novel pharmaceutical molecule, synthetic chemists, either alone or in collaboration.

Preformulation studies support lead identification throughout the drug discovery phase in addition to aiding formulation development. To become a therapeutic molecule, a novel chemical entity must have the best biopharmaceutical qualities. 'Drug ability' is not necessarily implied by the mere presence of potency and selectivity. Preformulation studies aid in determining a molecule's "drug ability." Preformulation can therefore be viewed as a crucial instruments for decision-making both- the phase of drug discovery and development. A thorough knowledge of physicochemical qualities and how they affect biological function enables the selection of possible lead compounds and the detection of drug delivery problems.². When the choice is taken to continue the development of the chemical in clinical trials, a formal preformulation should be started once the medicine has undergone biological screening. The preformulation studies were advised by the IND, NDA, and ANDA guidelines released by the US FDA and ICH.

Fundamental studies in preformulation

These studies focus on candidate drug molecules and include permeability studies, solubility analysis (e.g., ionization constant, partition coefficient, solubilization, thermal effect, common ion effect, dissolution, etc.), solid state properties (e.g., polymorphism, solvated forms, and amorphous forms), stability analysis (e.g., solution-state stability, solid-state stability), and stability analysis (e.g., solid-state stability). The chemical makeup of the potential therapeutic molecule is what drives these studies.

Derived Preformulation Studies:

The characterization of particle characteristics, such as particle size and shape, bulk density, powder flow characteristics, compaction behavior, etc., is all included in this research. They are done using the prescribed dose form⁴.

Objective of Preformulation:

- To give the formulator crucial information.
- To reduce excipients compatibility issues.
- To make medications more bioavailable.
- To design beautiful dosage forms (that is reliable, efficient, and secure).
- It's important to understand the physical description of the medication material development before selecting a dose form.
- Prior to dosage form development, it is the initial stage in the logical formulation of a drug dosage form.

Advantage of preformulation studies:

- Preformulation studies help the drug development and evaluation process save resources while bolstering the scientific basis of the guidelines
- Raise the bar for public safety.
- Improve the caliber of the product
- Assist in the adoption of new technology

Disadvantage of preformulation studies:

- Ionosphere is incorrect because resistance results from a spherical particle.
- Crystals with needle-like shapes have a tendency to obstruct the aperture hole.
- Compound dissolution in an aqueous conducting media.
- Particle stratification within the suspension³.

Preformulation Parameter:

1. Solubility Studies:

- a) pKa determination
- b) Common ion effect
- c) Effect of Temperature
- d) Solubilization

1. Solubility Studies:

Solubility is defined as the concentration at which the solution phase and the solid phase are in equilibrium at standard temperature and pressure. The solubility of the drug has a big effect. The drug's in-vivo absorption is referred to as "dissolution".

One of the most important factors in achieving desired NDM plasma concentrations in the systemic circulation is solubility, or the phenomenon of a solute dissociating in a solvent to form a homogeneous system, which has a significant impact on achieving the specific pharmacological goal.

a) PKa Determination:

A PH electrode is used in a potentiometric titration to monitor the progress of the titration by adding acid or base to a sample. The pK_a value is determined by comparing the shape of the titration curve with a blank titration that has no sample present. By titrating a strong base with a weak acid and constructing a titration curve that displays PH as a function of the amount of titrant added, it is possible to estimate the pK_a value of the weak acid.

Methods of pK_a determination

- a) Potentiometric titration
- b) UV spectroscopy
- c) HPLC technique
- d) Capillary Zone Electrophoresis
- e) Foaming activity

b) Common ion effect:

The solubility of the ionic medicine reduces as the concentration of the same ionic species in solution rises. In gastric juice, the chloride ion concentration ranges from 0.1 to 0.15 M. The hydrochloride salt of the medication is not readily soluble.

c) Effect of temperature:

When a drug-containing solution's temperature is increased, its solubility increases if the process is endothermic and the solution's heat is positive, as it does in the case of NaCl in water.

When chloride and other HCl salts are employed, the process is exothermic. Solubility decreases because the heat of solution is negative. The solubility values used to calculate the heat of solution at 5, 25, 37,

and 50°C. Fusion heat ranges from 4 to 8 kcal per mol for weak acid and base unions involving non-electrolytes.

d) Solubilization:

Limited experiments should be included in the preformulation research for drug candidates with poor water solubility or insufficient solubility for the intended solution dosage form in order to uncover potential solubilization mechanisms⁴.

2. Organoleptic Properties

Any preformulation endeavour should start with a description of the drug substance. Color, flavour, and aroma of the new medicine must be uniform. Documented with illustrative terminology It is necessary to report the new drug's color, flavour and odour. Utilizing illustrative language Building a shared vocabulary to define them is essential to preventing misunderstandings.

The phenomenon is described by scientists in a variety of ways. Identical quality the most popular colors are described using a list of apt adjectives. The aromas and smells of pharmaceutical powders are distinctive. A table is offered. The initial batches were all the same color. The new medication's efficacy must be supported by terminologically descriptive early batches' color records are very helpful in creating the right kind of⁵.

Preformulation Technique Used For Characterization of Solid:

Method:

- 1) Microscopy
- 2) Differential scanning Calorimetry
- 3) Infrared spectroscopy
- 4) X-ray powder diffraction
- 5) Scanning electron microscopy
- 6) Thermo gravimetric analysis

1. Microscopy:

When viewed via a microscope with crossed polarizing filters, almost all transparent materials are either isotropic or anisotropic. Organic non-crystalline solids and amorphous solids are both isotropic materials with a single refractive index. These isotropic materials appear black when the ordinary polarized filter passes through

them because they do not transmit light. Materials with multiple refractive indices are anisotropic and stand out against the polarized black background.

The thickness of the crystals and their refractive indices affect how colors interact. Biaxial or uni-axial anisotropy exists. Crystallographic axes are necessary to produce or describe the full crystal shape. A good tool for examining polymorphism, melting points, transition temperatures, and rates of transition at regulated heating rates is the polarizing microscope equipped with a hot stage. The two techniques of microscopy used to characterize the drug's crystallinity are as follows:

SEM stands for scanning electron microscopy.

TEM stands for transmission electron microscopy⁶.

2. Differential Scanning Calorimetry (DSC/DTA):

"A technique in which a difference in the heat flow (power) to the sample (pan) is monitored against time or temperature," according to the definition of DSC. The plot of heating rate vs. temperature or time that the DSC device produces can be understood. Comparative Scanning Calorimetric has developed from the Differential Thermal Analysis (DTA) method; however it does not take into account the fundamental shift in the method's operation. It entails making a few adjustments to the position of the thermocouple sensor and maintaining a steady heat flow to the sample⁷.

3. Crystallinity & Polymorphism:

Physical and chemical characteristics, like as flow capacity and chemical stability, can be influenced by a drug's crystal habit and internal structure. Habit refers to a crystal's description of its external look. Internal structure specifies how the solid's molecules are arranged, although changes to internal structure typically modify crystal habit.

A. Crystalline:

Crystals are distinguished by the repetitive spacing of their component molecules or atoms in a three-dimensional array. Preformulation activities such as evaluating crystal structure, polymorphism, and solvate form are crucial. Changes in crystal properties may have an impact on bioavailability, chemical and physical stability, and the operation of the dosage form process. For instance, due of flow and compaction behavior, among other things, it may be a significant factor in tablet formulation⁸.

B. Amorphous / non crystalline:

Atoms or molecules are arranged haphazardly as liquid in this form.

4. Polymorphism (Crystal forms):

The drug's crystalline or amorphous shape is a crucial element that affects formulation. MP and solubility are just a couple of the physicochemical characteristics that polymorphic form demonstrates. Drugs that take on polymorphic forms are rather prevalent; it has been estimated that at least one-third of all chemical substances do so. The term "Polymorphism" refers to the phenomenon of a substance existing in more than one crystalline form, each of which is labelled as a separate polymorph⁹.

Conclusion

Preformulation studies are essential for predicting formulation issues and establishing logical directions in both liquid and solid dosage form technology. The Preformulation Scientist can help the Synthetic Chemist find the best molecule and give the Biologist suitable vehicles to elicit pharmacological response by analyzing the physicochemical features of each drug candidate within a therapeutic group. Studies on stability in solutions can pinpoint stabilization techniques and show whether or not parental administration or another liquid dosage form is feasible. The most suitable vehicles for solid dosage forms will be determined concurrently by solid-state stability as measured by DSC, TLC, and HPLC in the presence of tablet and capsule excipient. This review article provides information on the aforementioned studies about the development of sustained release dosage forms without preformulation experiments.

References

1. Yalkowiski, S. H., & Roseman, T. J. (1981). Techniques of solubilisation of Drugs, Chapter 3, ed. *SH Yalkowski Marcel Dekker, Newy.*
2. Sahitya, G., Krishnamoorthy, B., & Muthukumaran, M. (2013). Importance of preformulation studies in designing formulations for sustained release dosage forms. *International Journal of Pharmacy and Technology*, 4(4), 2311-2331.
3. Chaurasia, G. (2016). A review on pharmaceutical preformulation studies in formulation and development of new drug molecules. *International journal of Pharmaceutical sciences and research*, 7(6), 2313.
4. Aulton, M. E., & Taylor, K. (2002). *Pharmaceutics-The Science of Dosage Form Design*. Churchill Livingstone. London, England, 340, 348.
5. Kesharwani, R., Ansari, M. S., & Patel, D. K. (2017). Novel technology used in the preformulation study: a review. *Journal of Drug Delivery and Therapeutics*, 7(4), 20-33.
6. Kesharwani, R., Ansari, M. S., & Patel, D. K. (2017). Novel technology used in the preformulation study: a review. *Journal of Drug Delivery and Therapeutics*, 7(4), 20-33.
7. Liberman, H. A., & Kanig, J. L. (1970). *The theory and practice of industrial pharmacy*.
8. Brahmankar, D. M., & Jaiswal, S. B. (1995). *Biopharmaceutics and pharmacokinetics. A Treatise* Vallabh Prakashan. New Delhi.
9. Vilegave, K., Vidyasagar, G., & Chandankar, P. (2013). Preformulation studies of pharmaceutical new drug molecule and products: An Overview. *The American Journal of Pharmacy*, 1(3), 1-20.