INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Research Paper

Recent Advances in Preformulation Studies and Pharmaceutical Development

Sandhya Malekar*, Akshata Birajdar, Pruthviraj Mali, Archana Pawar, Asif Mulani

Department of Pharmacy, Nootan College of Pharmacy, Kavathe Mahankal, Dr. Babasaheb Ambedkarb Technological University, Lonere 402103, Maharashtra, India.

ARTICLE INFO

Published: 18 May 2026
Keywords:
Preformulation, Stability testing, Physicochemical properties, Polymorphism
DOI:
10.5281/zenodo.20267800

ABSTRACT

Preformulation studies are a critical stage in pharmaceutical development, providing essential information on the physicochemical and biopharmaceutical properties of drug candidates. These investigations guide the selection of suitable dosage forms and delivery systems, ensuring stability, safety, and therapeutic effectiveness. Key parameters such as solubility, permeability, partition coefficient, polymorphism, and excipient compatibility influence formulation design and clinical performance. Recent advances highlight innovative approaches to enhance solubility, improve stability, and optimize drug delivery through modern excipients and nanotechnology-based systems. This review summarizes current strategies in preformulation research, outlines challenges encountered during early development, and emphasizes the importance of regulatory compliance. By integrating contemporary techniques with traditional evaluation methods, preformulation studies continue to play a pivotal role in reducing development costs and accelerating the transition of new drug molecules from discovery to clinical application

INTRODUCTION

Before initiating preformulation studies, it is essential to understand the fundamental properties of a drug candidate, including potency, dosage form, stability, pharmacokinetics, and bioavailability. These characteristics provide the foundation for rational formulation design and help anticipate potential challenges during development. Once a pharmacologically active molecule is identified, researchers must ensure that it enters the development process in its optimal form. At this stage, multidisciplinary teams conduct probing experiments to identify limitations and, if necessary, introduce molecular

***Corresponding Author:** Sandhya Malekar
Address: *Department of Pharmacy, Nootan College of Pharmacy, Kavathe Mahankal, Dr. Babasaheb Ambedkarb Technological University, Lonere 402103, Maharashtra, India..*
Email ✉: sandhyamalekar6@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

modifications such as salts, prodrugs, solvates, or analogs to enhance drug performance [1]. Preformulation is a critical step in pharmaceutical development where the physicochemical and biopharmaceutical properties of a drug are systematically evaluated. These studies guide the selection of appropriate dosage forms and delivery routes by assessing solubility, stability, polymorphism, dissolution rate, and partition coefficient [2]. Understanding these parameters ensures compatibility with excipients and supports the design of formulations that are stable, effective, and safe.

Drugs often exist in both crystalline and amorphous forms, each exhibiting distinct physicochemical and therapeutic properties. Preformulation research provides insights into these variations, enabling the development of robust dosage forms with adequate shelf life and resistance to environmental stress. Effective preformulation reduces formulation difficulties, lowers development costs, and improves the likelihood of clinical success. Furthermore, preformulation studies contribute to patient safety and therapeutic efficiency by enabling precise dosage administration, protecting drugs from environmental degradation, and overcoming challenges such as gastric acidity through specialized formulations like enteric coatings [3].These investigations begin once a newly synthesized drug demonstrates sufficient pharmacological activity in animal models, ensuring that its physicochemical profile supports rational formulation design and clinical evaluation [4].

✓ NECESSITY OF DOSAGE FORMS

At several phases of the drug development process, formulation development is necessary. Drugs are rarely administered on their own, as we already mentioned. Including the medication in a formulation has several benefits, including increased stability or bioavailability, convenience of handling, and simplicity of administration. For the different phases of the aforementioned clinical research, different formulations are required. Preclinical usage of animals necessitates simple liquid formulations that are easy to provide to the animals [5].A thorough preformulation investigation helps to understand the pharmaceutical molecule's physicochemical characteristics. It offers the basis for creating a sturdy dosage form with a long shelf life and resistance to processing. By lowering difficulties during formulation development, preformulation activities result in long-term cost reductions.

- To provide a method for administering a precise dosage in a safe and easy manner.
- To protect against environmental elements, such the harmful effects of oxygen or moisture.
- To prevent the harmful effects of stomach acid after oral administration for example, an enteric coated pill.
- To cover up the medicine's salty, bitter, and sickening fragrance. Coated pills and capsules are two examples.
- To deliver liquid formulations that are unstable or insoluble in a carrier. For instance, suspension
- To administer drugs in clear dosage forms. Syrups and solutions, for instance.
- To deliver pharmacological activity that is rate-controlled. For instance, tablets with controlled and sustained release
- To deliver the best possible medication activity when applied topically. For instance, ointments, creams, and patches [6].

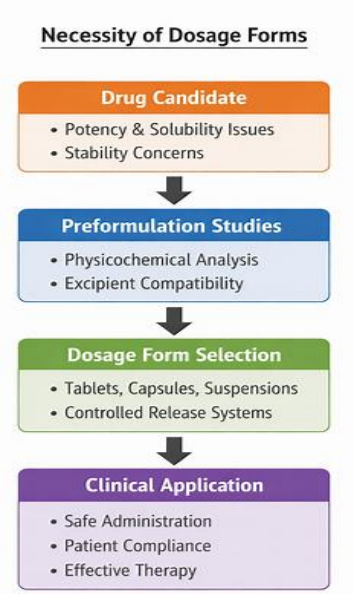


Figure 2: Stages in Preformulation and Formulation Design [7]

✓ OBJECTIVES

Preformulation studies aim to generate essential information about drug candidates that guides rational dosage form design and ensures successful pharmaceutical development. The key objectives include:

- To determine physicochemical properties such as solubility, pKa, and partition coefficient.
- To evaluate stability under environmental conditions (temperature, humidity, light, oxygen).
- To assess compatibility with excipients used in formulation.
- To identify polymorphic forms and their impact on bioavailability.
- To establish dissolution and absorption characteristics.
- To generate data that supports dosage form selection and regulatory submission [8].

✓ GOALS:

The present work was undertaken with the following goals:

- To compile a structured black book with uniform botanical drug profiles, images, and Vancouver-style references.
- To adapt nanoparticle-based anti-acne gel formulation to available lab-scale reagents (zinc oxide, copper sulfate).
- To calculate reagent quantities and optimize synthesis procedures for reproducibility at laboratory scale.
- To prepare plagiarism-free, journal-style manuscript sections (abstract, introduction, methods, results, discussion) for publication.
- To achieve high performance in cosmetic science examinations through concise, highlighted answers.
- To align manuscript quality with international journal standards (grammar, formatting, referencing) [9].

Figure 2 show the stepwise process of drug formulation and its entry into the market

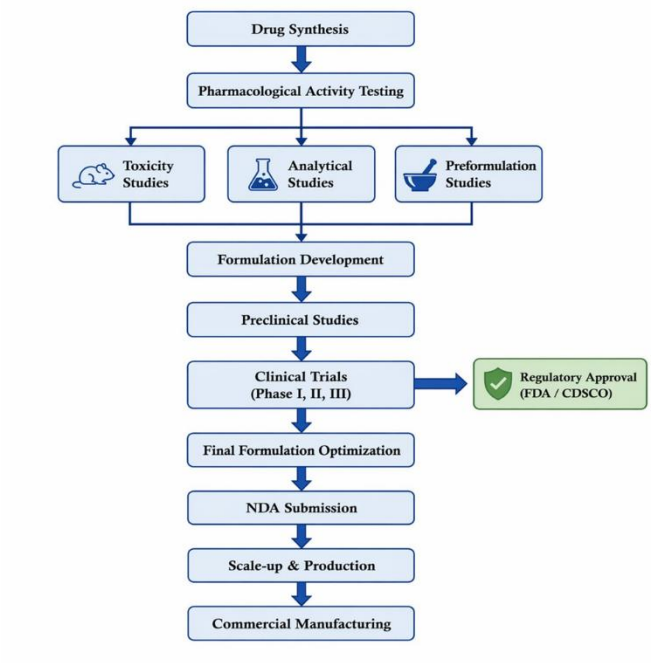


Figure 2: Drug formulation and its entry in to market stepwise representation [10].

THE FOLLOWING ARE THE MAIN AREAS OF PREFORMULATING RESEARCH:

1. **Characterization of bulk**
   - Polymorphism and Crystallinity
   - Hygroscopicity
   - Size of particles
   - Density of bulk
   - Properties of powder flow
2. **Analysis of Solubility**
   - Ionization constant-pKa pH solubility profile
   - Common Ion Effect: Ksp
   - Thermal Impacts
   - Solubilization
   - Dissolution of Partition Coefficient
3. **Analysis of Stability**
   - Analysis of Stability
   - Formulation Stability and Solution Stability
   - Solid State Stability pH Rate Profile
   - Compatibility of Bulk Stability [11]

1. Characterization of bulk

Not all of a drug candidate's solid forms have yet been found, and there's a good probability that new polymorphs will emerge. Particle size, bulk density, and surface morphology are examples of bulk characteristics for the solid forms that are likely to alter during process development.

A] polymorphism and Crystallinity

The phrase "allotropes" describes the two or more different forms that an element can take. Carbon: diamond in cubic (tetrahedral lattice arrangement) and graphite in hexagonal lattice sheets. Polymorphs have the same properties while they are liquid or gaseous, but they behave differently when they are solid. Similar to how two different compounds' crystals differ from one another, different polymorphs of a chemical typically have different structures and characteristics. Additionally, polymorphism is very prevalent, especially within specific structural groups.
Polymorphism is common in organic molecules, and many drugs can crystallize into a variety of polymorphic forms.

Molecules Polymorphic forms of pharmaceuticals may be of interest to drug developers since they may offer an improvement over the original form due to their thermodynamic and physicochemical properties, such as melting point, density, stability, and particularly solubility. Since their solubility is usually kinetically higher than that of a thermodynamically more stable polymorph, metastable polymorphs may theoretically resolve bioavailability problems. In actuality, it has been demonstrated that differences in a polymorph's solubility are typically smaller than a factor of two or, less frequently, five. Therefore, there may be no benefit to choosing a polymorph over the original, even if it is marginally more soluble than the original molecule. This is because the polymorph is also less stable than the original. Actually, the more thermodynamically stable form usually transforms into the more soluble and metastable form quite quickly [12].

B] Hygroscopicity

Adsorption of ambient moisture is a tendency of many medicinal compounds, especially watersoluble salt versions. Temperature, surface area, exposure, moisture uptake mechanism, and air humidity can all affect adsorption and equilibrium moisture content. Deliquescent compounds, as sodium chloride on a humid day, absorb enough water to dissolve entirely. Water is adsorbed by other hygroscopic materials due to hydrate formation or specific site absorption. Compatibility, flowability, and chemical stability are just a few of the crucial elements that can be greatly impacted by changes in the moisture content of the majority of hygroscopic materials.

To test for hygroscopicity, bulk drug samples are placed in open containers with a thin powder bed to guarantee maximum atmospheric exposure. These samples are then put in an environment generated with saturated aqueous salt solutions that has a regulated relative humidity. Different handling and storage intervals (0 to 24 hours and 0 to 12 weeks, respectively) should be used to monitor moisture uptake. The analytical methods for measuring the moisture level (such as gravimetry, TGA, Karl Fischer titration, or gas chromatography) depend on the amount of moisture adsorbed on the drug sample and the necessary precision [13].

C] Size of Particle

Bulk flow, formulation homogeneity, and surface area-controlled processes including chemical reactivity and dissolution are all directly impacted by the size, shape, and surface morphology of the drug particles. Using a light microscope with a calibrated grid, drug particles can usually be sufficiently described in terms of size and shape. Careful sampling and preparation of microscope slides are necessary to obtain a representative dispersion. When used with optical microscopy, stream counter devices like the coulter counter and HIAC counter often provide a useful means of characterizing the size distribution of compounds. Sieve techniques are mostly used for large samples of relatively big particles (100 microns).

Surface area can be measured more precisely using Brunauer, Emmett, and Teller (BET) nitrogen adsorption, which entails adsorbing a layer of nitrogen molecules to the sample surface at -1960C. When surface adsorption approaches equilibrium, the sample is heated to room temperature. After the nitrogen gas is desorbed, the ideal gas law is used to measure its volume and convert it to the number of adsorbed molecules.

D] Density of Bulk

A chemical's bulk density is greatly influenced by how it is formed, milled, or crystallized. When a density problem is identified, it is often easy to resolve by formulation or milling. Bulk density is usually important when assessing the size of a

high-dose capsule product or the homogeneity of a low-dose formulation with notable differences in drug and excipient densities.

Bulk density seems to be determined by pouring a putative bulk medication into a graduated cylinder with a large funnel, then measuring the weight and volume. A graduated cylinder with a specified mass of medication or formulation is placed on a mechanical tapper device, which is run for a predetermined number of taps (about 1000) until the powder bed volume reaches a minimum in order to measure the tapped density. The tapped density can be calculated using this minimal volume and the drug weight in the cylinder. True density is also preferred in addition to tapped density. It can be calculated using either the gas displacement approach or the liquid displacement method.

E] Properties of powder flow

Pharmaceutical powders can be broadly classified as either free-flowing or cohesive (non-free-flowing). Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge, and adsorbed moisture that may arise from formulation or processing. Therefore, during development, a free-flowing drug candidate may become cohesive, necessitating a completely other formulation strategy. The flow characteristics of powder can be estimated using metrics like angle of repose, Hausner's ratio, Carr's index, and compressibility of any powdered sample. When powder is forced through a funnel-shaped container, a cone-shaped pile of material assumes the angle of repose, which is a constant three-dimensional angle measured in reference to the horizontal base.

An angle of repose of less than 400 indicates good flowability, whereas an angle of repose of more than 400 indicates cohesiveness. This method has certain disadvantages despite being really simple. The powder's segregation, consolidation, or aeration all affect how the cone is formed. Many people do not believe that the angle of repose is a good approach to measure powder flow because it is not an intrinsic property of the powder and is highly dependent on experimental conditions. However, because it is a simple method that gives the powder a tendency to flow and has a general flowability scale that is consistent with Carr's classification, it is still seen as beneficial [14].

2. Analysis of Solubility

One of the main goals of the pre-formulation effort is to develop a method for producing drug solutions. A drug needs to be slightly soluble in water in order to be therapeutically effective. Before a drug may enter the systemic circulation and have a therapeutic impact, it must be in solution. Relatively insoluble compounds often exhibit partial absorption. For a solute to dissolve, the forces of attraction between the solute and solvent molecules must be greater than the intermolecular forces of attraction of the substance. The solute-solute and solvent-solvent forces must be broken in order to produce the solute-solvent attraction. It focuses on possible drug-solvent interactions that may occur during the delivery of a therapeutic candidate.

For example, a simulated gastric media should be used to test the solubility of an oral medicine. Assessing a new drug's solubility is necessary to lay the groundwork for further formulation attempts that could affect the drug's effectiveness. Drugs with an aqueous solubility of less than 1% (10 mg/ml) will have problems with bioabsorption.

A] Ionization constant-pKa Ph Solubility profile

For a medication that can ionize in the pH range of 1 to 10, finding the dissociation constant is essential since pH variations may affect solubility

and, consequently, absorption. The Henderson Hasselbach equation can be used to estimate the ionized and unionized drug concentration at a given pH.

Regarding acidic substances: pH is equal to pKa + log [ionized drug] / [unionized drug].

For fundamental substances: pH is equal to pKa + log [unionized drug] / [ionized drug].

The acidic contents of the stomach contain the unionized form of a weakly acidic medication with a pKa value more than three, but the drug is mostly ionized in the neutral media of the intestine. The ionized version is more common in the stomach and intestine for basic medications such Papaverine and erythromycin (pKa 8 to 9). Numerous analytical techniques can be used to calculate a pKa value. Ionic strength, temperature, buffer, and cosolvent impact. Using visible or ultraviolet spectroscopy to detect spectral shifts is the recommended approach. For substances with pKa values between 3 and 10, a second technique called potentiometric titration provides the highest sensitivity [15].

B] Common ion effect: Ksp

The degree of ionization and, thus, the solubility of basic and acidic compounds depend on the pH of the medium. Saturation solubility is the total solubility of these compounds in their unionized and ionized forms at a particular pH. In a saturated solution of a salt that contains some undissolved solid, there is equilibrium between the surplus solid and the ions created when the salt in the solution dissociates. When a common ion is added, the electrolyte, which was before mildly soluble, becomes less soluble. Salting out (drug precipitation) results from the removal of solvent molecules from the electrolyte's surface due to the hydration of the common ion. By opening the water molecules, adding salt to larger anions (hydrotropes) like salicylates and benzoates can make drugs that are poorly soluble in water more soluble. Hydrochloride salts often exhibit decreased solubility in gastric juice due to the high concentration of chloride ions.

C] Thermal Impacts

A solute's solubility in a solvent depends on temperature, solute type, and solvent type. The amount of heat emitted or absorbed when a mole of solute dissolves in a sizable volume of solvent is known as the heat of solution. Because they absorb heat during disintegration, the majority of the chemicals are endothermic. An increase in temperature causes these compounds to become more soluble. When exothermic compounds dissolve, they release heat. These substances become less soluble at higher temperatures. Caution is advised since heat can destroy a drug or change the solution in other ways. For example, the sucrose solution became inverted sugar due to excessive heat. Whether a reaction is endothermic or exothermic for example, a mixture of acetone and chloroform heat is either released or absorbed. The heat produced by the solute-solvent interaction is far greater than the heat needed to separate the acetone and chloroform molecules as the liquid's temperature rises.

D] Solubilization

To find possible paths for solubilization in drug candidates that are either poorly soluble in water or inadequately soluble for anticipated solution dosage forms, preformulation research should include limited experiments. To improve solubility, a cosolvent is frequently added to the aqueous solution. Weakly soluble nonelectrolytes can often be made orders of magnitude more soluble by using suitable cosolvents like ethanol, propylene glycol, and glycerin. These cosolvents solubilize drug molecules by disrupting the

hydrophobic interactions of water at the nonpolar solute/water interfaces. The most popular and authorized cosolvents for making aqueous liquids for oral solutions are ethanol, sorbitol, glycerin, and PEG. Dimethylacetamide is frequently used in parenteral formulations. However, oral liquids have few uses due to their unpleasant taste and odor. Cosolvent effects are usually much lower in dissociated medicinal compounds. Many poorly soluble drugs can be dissolved by molecular complexes like caffeine or micellar solutions like 0.01M Tween 20. These specific formulations are typically not developed during the preformulation stage.

E] Partition Coefficient

The oil/water partition coefficient is a measure of a drug's lipophilicity and an indicator of its ability to pass across cell membranes in systems such as octanol/water and chloroform/water. The partition coefficient is the proportion of unionized drug distributed between the organic and aqueous phases at equilibrium. Coi l/Cwater = Po/w It has been shown that the pace and extent of drug absorption in drug delivery are influenced by the lipophilic/hydrophilic balance.

F] Dissolution

The pace at which a drug dissolves only matters during the rate-limiting stage of the absorption process. No problems with bioavailability or differentiation were expected when a drug's solubility reached 1 mg/ml at pH 7. By controlling the pH of the microenvironment below 1 mg/ml, salt generation could improve absorption and solubility regardless of the drug and dosage form's placement within the GI tract. The rate at which a pharmaceutical material dissolves when its surface area stays constant is described by the modified Noyes-Whitney equation. (Cs-C) = DA/hv (dc/dt), where h is the thickness of the diffusion layer at the solid-liquid interface, D is the diffusion coefficient, and A is the surface area of the drug exposed to the dissolving media. Drug concentration in solution at time t. t-Time Volume of medium Cs-Solute concentration in a saturated solution in the dissolving media C When dissolution is fully controlled by diffusion, the rate of diffusion is precisely proportional to the drug's saturation concentration in solution. The rate constant K1 in these conditions is found to be K1 = 0.62. V1/6 W1/2 D2/3, where V is the drug's kinematic viscosity and W is its angular velocity [16].

3. Analysis of stability

Preformulation stability tests are frequently the first quantitative assessment of a novel drug's chemical stability. When designing sensible dosage forms, temperature, pH, and dosage form diluents are significant variables that impact chemical stability. The desired product's sterilizing method will be greatly impacted by the drug's temperature stability. Drugs that become unstable at high temperatures cannot be sterilized by autoclaving; instead, another technique, like filtering, must be employed. The impact of pH on pharmaceutical stability is substantial since oral administration needs to be protected from the highly acidic environment of the stomach. When selecting a buffer for potential dose forms, the drug's stability feature will be crucial.

A] Analysis of Stability

Samples of the toxicological preparations should frequently be examined for stability issues and possible homogeneity issues. Feed contains water, vitamins, minerals, and enzymes that can significantly shorten a drug's shelf life. Solution and suspension toxicological preparations should be stored at various temperatures in flame-sealed ampoules after being assessed for manufacturing ease. To evaluate both chemical stability and

dispersibility, the suspension should be periodically shaken.

B] Formulation Stability and Solution Stability

In solution form, degradation happens far more quickly than in dry form. It is essential to ensure that the drug does not degrade while GI fluid is present. Research on pH-based stability can be designed with different GI circumstances and stimulators. A low solution stability may cause the formulator to choose a less soluble salt form, provided that the drug's bioavailability is unaltered.

C] Solid State Stability pH Rate Profile

Chemical instability is usually caused by hydrolysis, oxidation, photolysis, and pyrolysis. The drug's vulnerability to either of these attacks depends on its chemical makeup. Because of their electron-rich centers, esters, lactase, and to a lesser extent amides are vulnerable to solvolysis, instauration, or oxidation by free radicals or photocatalysis. physical properties of drugs. Amorphous materials are less stable than their crystalline counterparts. Denser materials are more resilient to environmental stress.

D] Compatibility studies

Selecting the appropriate excipients for a formulation is aided by knowledge of the interactions between medications and excipients. The preformulation screening of drug-excipient interactions presented only requires 5 mg of the drug in a 50% combination with the excipients, increasing the likelihood of concealing an interaction. Mixtures under nitrogen should be examined using a consistent heating rate on DSC to ascertain their ultimate oxidation and paralytic action. This will include any drug-induced temperature changes as well as the emergence or disappearance of one or more peaks in drug excipient mixture thermograms, which are believed to be indicators of interaction [17].

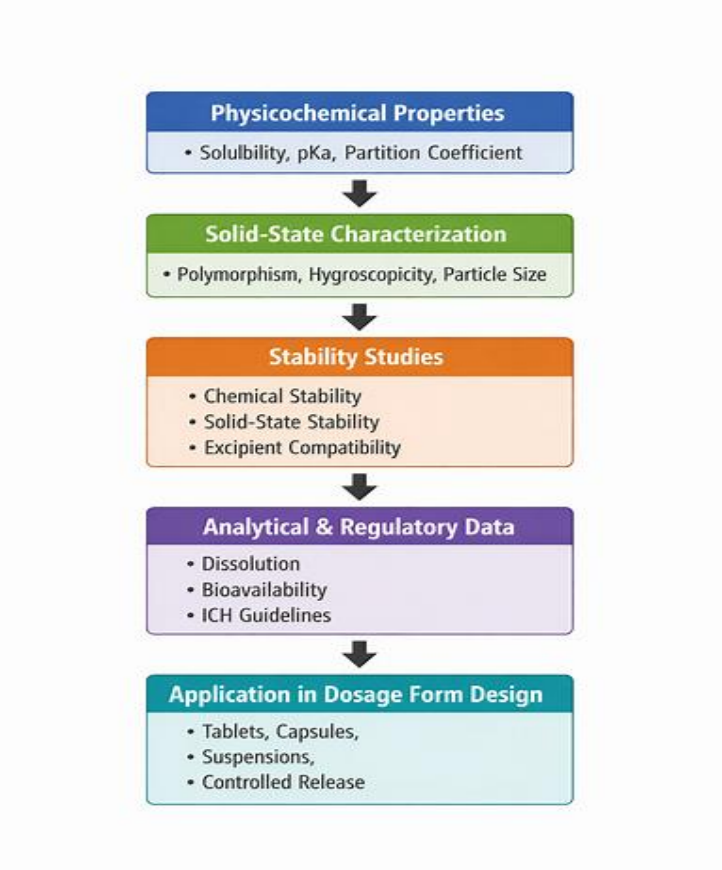
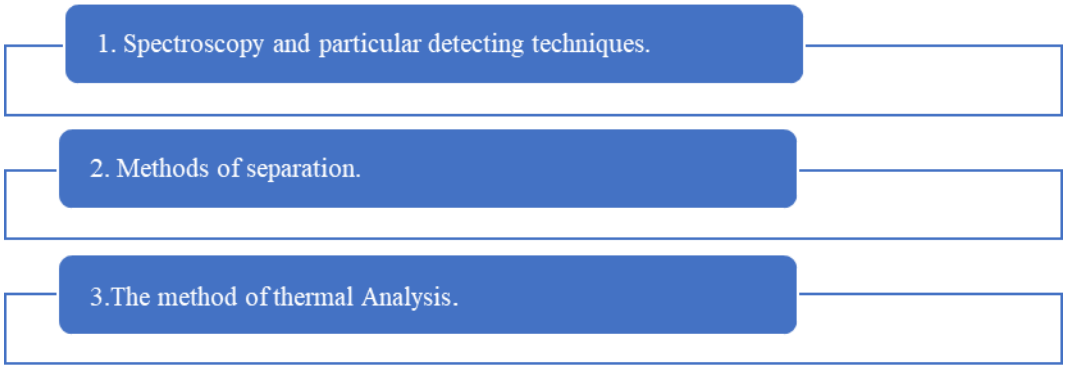


Figure 3: Analytical & Regulatory Data

METHODS OF ANALYSIS:

Three categories of analytical techniques are used for preformulation studies.



1. Spectroscopy and particular detecting techniques

Identification and structural clarity are necessary for newly found compounds, which drives the development of specific detection techniques utilizing mass spectrometry, NMR, and X-ray diffraction. Atomic absorption (AA), inductively coupled plasma spectroscopy (ICP), and X-ray fluorescence all rely on the identification of foreign metal contamination. The following is a discussion of the analytical methods frequently employed in preformulation studies.

A] UV Spectroscopy UV

Absorption is an essential tool for both qualitative and quantitative evaluation of a drug or isolated extract. In preformulation research, solubility, dissolving rate, and some stability (where degradation products have a different absorption maximum from the parent chemical) are determined using the UV method. UV is frequently used for HPLC detection. UV spectroscopy, a fairly accurate and simple technique, is employed as an estimate tool in the early phases of preformulation since most drugs contain aromatic rings and/or double bonds that absorb light in the ultraviolet spectrum. The drug's absorption coefficient can be computed using the formula.

Where, E = AF / X Absorbance (A) and dilution factor (F) X = weight of drug (mg) By measuring absorbance, one may now ascertain the drug's concentration in any solution. C = AF/E mg/m

B] Colorimetry and Visible Photometry

Visible spectroscopy and UV spectrometry are identical except for the wavelengths, which range from 400 to 750 µm. A colour product may be formed through a chemical reaction with a specific ingredient. The quantitative evaluation of the coloured chemical in drug assays is based on this concept. Another method for producing a colour complex that is subsequently removed is the dye-salt procedure. In an ion-pair reaction that creates a colour complex in response to the drug with a dye of opposite polarity, like bromethymnol blue, the complex is extracted into the organic layer and evaluated colorimetrically.

C] IR Spectroscopy

In pharmaceutical investigation, infrared spectroscopy is often used to identify medication molecules by fingerprint and provide evidence of their structure. Pharmaceutical solids can be physically characterized using infrared absorption spectroscopy, which is particularly effective when studied using the Fourier transform method (FTIR). IR can be used in preformulation to investigate solid crystal polymorphism. Polymorphs have distinct infrared properties and can be employed as a fingerprint identification technique. Furthermore, investigations of the solvation events connected to a solvate morphic system can benefit greatly from the use of solidstate vibrational spectra. The clinical response for some medications with nonconcentration dependent pharmacodynamics, like etc lactam antibiotics, is linked to the amount of time over a key therapeutic concentration rather than the peak concentration.

D] Raman Spectroscopy

Raman spectroscopy is another vibrational spectroscopy method that is perfect for characterizing polymorphism or solvate morphism in solids. This technology uses the inelastic scattering of the source energy after the sample is exposed to monochromatic laser radiation to acquire the vibrational spectrum of the analyte. Since most substances of medical interest have poor symmetry, the Raman spectrum will contain spectra characteristics at the same energies as those obtained using the FTIR technique. While symmetric vibrations and polar groups create the highest infrared absorption bands, symmetric vibrations and nonpolar groups frequently produce the strongest Raman scattering bands. These fluctuations can be useful in characterizing solid materials because they can sometimes be rather considerable.

E] NIR Spectroscopy

Overtones and combinations of fundamental molecular vibrational modes are responsible for all

of the absorption bands in the near-infrared (NIR) spectrum, which is usually believed to span 1000–2500 nm. Because environmental factors have a bigger effect on the energies of the overtone bands than on their fundamentals, small changes in the bonding can induce significant differences in frequency and amplitude in the NIR. The speed of analytical results without sample preparation or solvent use is an advantage of this technique. In the pharmaceutical industry, both qualitative and quantitative NIR applications are feasible. Materials including organic liquids and solvents, excipients, active pharmaceutical ingredients, and packaging materials can all be easily recognized at the reception area. Examples of quantitative determination utilizing NIR include content homogeneity, dissolution rate monitoring, dosage form testing, and moisture assessment during the drying process. Since NIR spectra are composed of overtone transitions of fundamental vibrational modes, they are not very useful for identification without the use of multicomponent analysis and access to spectral libraries of known vibrational modes.

F] X-Ray Diffraction

The X-ray diffractometry method provides atomic-level details about material structure. This method can be used to measure both crystalline and non-crystalline materials. The analysis is nondestructive and can be used to liquid, solid, and powdered samples. Powder diffraction is used to create fingerprints. Polymorphism can be detected using diffraction patterns with d-spacing that contain larger, overlapping peaks. The quantitative ratios of two polymorphs and their percentage of crystallinity can also be computed. In addition to identification techniques, X-ray powder diffraction technology is used for phase transition research, polymorphism and solvate morphism evaluation, and degree of crystallinity evaluation. Variable temperature XRD is a very helpful addition to standard PXRD.

G] NMR Spectroscopy

Solid-state nuclear magnetic resonance spectroscopy can be considered the most effective molecular level characterization technique for a pharmaceutical solid after X-ray crystallography since it offers information about the unique chemical surroundings of each atom in the molecule being studied. Electromagnetic radiation in the radiofrequency range of a longer wavelength spectrum is absorbed in NMR. The nuclei shift from the preferred, lowest-energy orientation to the undesirable, high-energy orientation at a particular frequency. The NMR spectrum of a material is thus a plot of radiation frequency against intensity. Broadline NMR is primarily used to quantify internuclear distances and other crystal characteristics that are crucial for studying polymorphism, hydrates, and solvates. It is feasible to quantify polymorphs quantitatively in addition to qualitatively examining polymorphs and solvates [18].

2. Methods of Separation

An extensive variety of analytical techniques, ranging from relatively simple to highly complicated, can be used to assess the chemical compatibility of a medicinal molecule with suggested excipients. The most widely used methods for collecting chemical composition data during the preformulation stage of development are based on various separation science techniques, such as thin-layer chromatography (TLC) or high-pressure liquid chromatography (HPLC), with the occasional use of gas chromatography (GC). The latter two methods are often used in conjunction with mass spectrometry (MS) when degradant species identification is required. Separation techniques including

capillary electrophoresis (CE) and counter current extraction (CCE) are frequently employed in preformulation research.

A] Thin-Layer Chromatography

TLC, a separation method with great sensitivity and multiple detection, has lost popularity as more sophisticated instrumental techniques have emerged. Over time, TLC's capabilities and technology have gradually improved, and preformulation characterization studies can still benefit from its application. The conventional method of detection entails spraying a sample with a detecting agent, which reacts chemically with the substance to be detected to produce a visible spot. Detection is accomplished by visual observation under either short-wavelength or long-wavelength UV light. TLC can be used as a separation method to remove impurities from dosage forms in a state suitable for further research. The disadvantages of TLC include reproducibility, uneven detection, individual differences, recordkeeping, and minimization of electronic data. High-performance TLC (HPTLC) has evolved as a unique new TLC approach to address these issues.

B] High-Pressure Liquid Chromatography

The HPLC approach is special because it combines the analytical separation stage with online analysis tools that identify every analyte as it elutes from the chromatographic system. The UV detector in conjunction with HPLC equipment is the most important analytical tool for preformulation, QC/QA, and in-process control in pharmaceutical analysis. HPLC is an essential and reliable analytical method for preformulation research because of its high-resolution capacity, accuracy, and consistency. Its primary responsibilities include identifying and quantifying degradation products to determine the stability of dosage forms and locating and detecting impurities in pharmaceutical ingredients. In a preformulation testing program, it was demonstrated that HPLC analysis was beneficial for a number of compounds, including fosinopril sodium, ceronapril, pravastatin sodium, sorivudine, and if etroban sodium. According to reports, drug-excipient compatibility samples were also analyzed using a reversed-phase method for measuring the quantity of nicotine in immediate- and extended-release formulations.

C] GC/MS, LC/MS

When paired with MS, this method probably provides the best set of instruments for identifying and detecting products of drug–excipient interactions. The early HPLC approaches are usually developed during the preformulation stage of research. Analytes must usually be vaporized, converted into charged species, and then allowed to fragment. The ion fragments must then be sorted and identified according to their mass-to-charge (m/e) ratio. The molecular ion's m/e value confirms the compound's formula weight even if the structures of the various fragments are consistent with the compound's structure. Every element utilized in the creation of an HPLC-MS method needs to be volatile and capable of moving the analytes into the vapor phase.

D] Electrophoresis with Capillaries

Capillary electrophoresis (CE) has been widely used in physicochemical profiling and pharmaceutical analysis. In pharmaceutical physicochemical profiling, such as the octanol-water partition coefficient (logPow) and the acid dissociation constant (pKa), capillary electrophoresis (CE) is a simple, flexible, automated, and powerful separation technique. CE calculates the pKa of acids and bases by measuring the electrophoretic mobility of charged species associated with acid-base equilibria as a function

of pH. Numerous direct and indirect methods have been applied to log Pow measuring. For direct log Pow readings, the shake-flask technique was once considered the standard assay [19].

3. The method of thermal Analysis

0810Thermometric and calorimetric methods have demonstrated a wide range of applications in preformulation and formulation development. Thermal analysis and calorimetric methods enable quick characterisation with low drug substance needs. Through polymorph characterization, salt form screening, and physical-chemical screening of early discovery leads, these techniques are crucial for determining the thermodynamic relationships between various crystal forms.

Thermal analytical techniques' function in preformulation research

A) They are special in the field of polymer analysis and useful methods for solid state analysis.
B) They are widely used in studies of polymorphism, impurity detection, and determining the moisture content of any medicinal component or excipient.

- Identification of impurities
- figuring out the amount of moisture in any medicine or excipient.
- Polymorphism research
- Hydrate and solvate characterization
- Crystallinity level.
- Examining the phase diagram
- Compatibility study of drug excipients
- Complexation research

1. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) is a method that is frequently used in the pharmaceutical industry because the spectrum of phase transitions that DSC can monitor usually provides near-complete physical characterization of a novel active principle early during preformulation.

Three contemporary variants of DSC technology have gained popularity as the technology continues to advance. These are:

- Fast-scan DSC,
- high-sensitivity DSC,
- temperature-modulated DSC

While high-sensitivity DSC (HS-DSC) was created for the study of diluted solutions of macromolecules (typically biologicals), temperature-modulated DSC (TM-DSC) is very helpful in the pharmaceutical industry for identifying and measuring glass transitions. Increasing the magnitude of the recorded signal and shortening the experimental duration are the primary advantages of fast-scan DSC (FS-DSC). DSC techniques give a number of parameters, including heat of fusion and crystallization, purity, polymorphism, pseudo polymorphism, glass transition, drug and excipient interaction/compatibility, and thermal stability. Pharmaceutical preformulation research and the subsequent development of a stable and effective dosage form require it. DSC performance is influenced by a number of experimental factors. Among the most important factors to consider are the type of crucible, the atmosphere, the heating rate, and the sample size.

Hot Stage Microscopy

Under a microscope, changes in a sample's thermal properties can be observed when it is heated on a hot stage using a temperature programming device. At the time of the incident, the temperature can be recorded and the melting point can be seen.

Thermal Gravimetric Analysis (TGA)

TGA can be used to quantify the moisture content linked to weight loss in isothermal or non-

isothermal stability tests. In the preformulation investigation, TGA is the appropriate method for distinguishing polymorph from hydrate or recognizing monohydrate among other hydrates, which may not be possible with DSC alone [20].

DEVELOPMENT OF DRUGS:

The pre-clinical stage is preceded by human clinical trials in phases I, II, and III. Phase I clinical studies employ "first time in human" or "first time in man" formulations. These can be simple liquid or solid formulations, like "chemical in bottle" and "chemical in capsule." On occasion, the recommended commercial formulation can also be used to initiate phase ICTs. The sophistication of the formulation increases as the clinical trial stage progresses. Late phase 2 or phase 3 clinical trials should be initiated using the recommended commercial formulation. The drug development process includes research on "lead molecules" or "candidate molecules" discovered during the drug discovery phase. The main element of these investigations is clinical examination. Human subjects are used in phase I, II, and III clinical trials (CTs). Phase IV trials involve keeping an eye on the new drug once it is put on the market [21].

Phases of CTs

Phase I

In order to determine the range of doses that human volunteers can take for both single and multiple doses, these trials entail preliminary safety testing on a novel chemical entity (NCE). These are often performed on healthy participants, while occasionally they are performed on very sick individuals (for example, in the case of cancer). They offer details on the molecule's pharmacokinetics and safety.

Phase II

Phase II studies are carried out to show effectiveness and offer more information on the safety of the NCE. They are further divided into phases IIA and IIB, where phase IIA is meant to assess dosage requirements and phase IIB is meant to look at efficacy at the suggested dosages.

Phase III

Phases IIIA and IIIB compose this stage of CT. Phase IIIA consists of trials conducted after the medication's efficacy has been determined, but prior to the submission of a New Drug Application (NDA) or other dossier to the government. The goal of these multicentric, randomized trials is to provide definitive evidence of the NCE's superiority over the current "gold standard" of care. After the NDA is filed, Phase IIIB trials start and last until marketing authorization is obtained. These trials may be used to complete or enhance earlier studies, or they may concentrate on novel trial types (such as marketing or quality of life).

Phase IV

After a medication is put on the market, studies or trials are carried out to provide further information regarding its safety profile or efficacy [22].

CONCLUSION

Preformulation studies serve as the scientific foundation for successful dosage form development. They provide essential data on physicochemical, stability, and compatibility parameters that guide rational formulation design. Understanding major areas such as solubility, polymorphism, and excipient interaction ensures that the drug candidate achieves optimal bioavailability, stability, and patient compliance.
This systematic approach minimizes formulation failures, supports regulatory documentation, and accelerates the transition from laboratory research to clinical application. Hence, preformulation

research remains a crucial step in transforming a potential molecule into a safe, effective, and marketable pharmaceutical product.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this research work. All experimental procedures, data interpretations, and conclusions have been carried out independently without any financial, commercial, or personal influence from external organizations or individuals.

ACKNOWLEDGMENT

We would like to sincerely thank our esteemed mentor, Mrs. Archna Pawar Mam, for her invaluable advice, unwavering support, and encouragement during the production of this review article. Her energy and wise advice were really helpful to us in finishing this project.

We are also thankful to Mr. Aasif Mulani Sir for his kind support and guidance during the preparation of this review paper.

We extend our heartfelt thanks to Nootan College of Pharmacy for providing the necessary facilities and academic environment to carry out this review work successfully.

Finally, we are grateful to all those who directly or indirectly supported us in completing this review paper.

REFERENCES:

1. Allen LV, Popovich NG, Ansel HC. Pharmaceutical Dosage Forms and Drug Delivery Systems. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
2. Aulton ME, Taylor K. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. 5th ed. London: Churchill Livingstone; 2018.
3. Banker GS, Rhodes CT. Modern Pharmaceutics. 4th ed. New York: Marcel Dekker; 2002.
4. ICH Harmonised Tripartite Guideline. Stability Testing of New Drug Substances and Products Q1A(R2). International Conference on Harmonisation; 2003.
5. Jain N, Patel R. Role of preformulation studies in rational drug development. Int J Pharm Sci Rev Res. 2020;64(2):45-50.
6. Florence AT, Attwood D. Physicochemical Principles of Pharmacy. 6th ed. London: Pharmaceutical Press; 2016.
7. Martin A. Physical Pharmacy and Pharmaceutical Sciences. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
8. Singh R, Kaur P. Research goals and academic writing strategies in pharmaceutical sciences. J Pharm Educ Res. 2022;13(3):101-7.
9. Sharma P, Gupta R. Role of mentorship and institutional support in pharmaceutical research. J Pharm Educ Res. 2021;12(4):87-92.
10. WHO. Guidelines for Stability Testing of Pharmaceutical Products. Geneva: World Health Organization; 2009.
11. Brittain HG. Polymorphism in pharmaceutical solids. Drugs Pharm Sci. 1999; 95:183-210.
12. Byrn SR, Pfeiffer RR, Stowell JG. Solid-State Chemistry of Drugs. 2nd ed. West Lafayette: SSCI Inc; 1999.
13. Carstensen JT. Pharmaceutical Principles of Solid Dosage Forms. New York: Marcel Dekker; 1993.
14. Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72(2):163-8.
15. Higuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum. 1965; 4:117-212.

16. Noyes AA, Whitney WR. The rate of solution of solid substances in their own solutions. J Am Chem Soc. 1897;19(12):930-4.
17. Yalkowsky SH, Valvani SC. Solubility and partitioning I: solubility of nonelectrolytes in water. J Pharm Sci. 1980;69(8):912-22.
18. Rawlins EA. Bentley's Textbook of Pharmaceutics. 8th ed. London: Baillière Tindall; 1982.
19. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia: Lea & Febiger; 1986.
20. Remington JP. Remington: The Science and Practice of Pharmacy. 22nd ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
21. Sweetman SC, editor. Martindale: The Complete Drug Reference. 38th ed. London: Pharmaceutical Press; 2014.

HOW TO CITE: Sandhya Malekar, Akshata Birajdar, Pruthviraj Mali, Archana Pawar, Asif Mulani, Recent Advances in Preformulation Studies and Pharmaceutical Development, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 4432-4448, https://doi.org/10.5281/zenodo.20267800