e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

Review article

PHARMACEUTICAL PREFORMULATION FOR PRODUCT DEVELOPMENT & ANALYTICAL TECHNIQUES USE IN NEW DOSAGE FORM

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ABSTRACT

Fundamentals to preformulation studies are analytical techniques. Evaluation of the quality of materials, precursors of products or final product is not possible without them. Measuring pharmacological and biological response in the clinical and preclinical stages are also not possible without them. Analytical techniques should be selected based on several categories such as specificity, accuracy, precision, sensitivity, and speed of a test must be verified for selection of the method. Several analytical techniques like Spectroscopic, Chromatographic, Thermal methods and some specific detection methods like Capillary electrophoresis are very convenient method for generating preformulation data. The intrinsic chemical data and physical properties of every drug are distinctively considered before development of pharmaceutical formulation. This property of drug act as the basic structure that is responsible for the binding of drug with other pharmaceutical ingredients. Several research scientist carries out these preformulation studies and they are again reviewed later. When a preformulation study is executed on a newly synthesized compounds or extracted compound, several crucial information such as the degradation process, any adverse conditions relevant to the drug, bioavailability, pharmacokinetics and formulation of similar compound and toxicity can be obtained. Preformulation studies strengthen the scientific foundation of the steerage, give restrictive relief and conserve resources within the drug development and analysis method, improve public safety standards, enhance product quality within the fabrication of indefinite quantity type. Objective of preformulation study is to develop the exquisite, stable, effective and safe indefinite quantity kind by establishing kinetic rate profile, compatibility with the opposite ingredients and establish physicochemical parameter of new drug substances. Polymorphic substances who have both amorphous and crystal forms shows totally different chemical, physical and therapeutic description of the drug molecule. The main purpose of this review article focuses on the various preformulation factors which distinctly impacts the development of new dosage form like drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability. The present article is framed with the target to produce an in-depth insight the appliance of Analytical Techniques in Preformulation Study.

Key Words:- Preformulation Study, Thermal Methods, Dosage Forms, Quality Control, Solubility analysis, Compressibility.

Access this article online

Home page: http://ijptjournal.com/

DOI: http://dx.doi.org/10.21276/ijpt.2017.8.1.3

Quick Response code

Received:	Revised:	Accepted:
25.11.16	12.12.16	15.01.17

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INTRODUCTION

Preformulation is a developmental stage during which the pharmacokinetic and pharmacodynamic properties of the drug is characterized and established. A complete data of the relevant therapeutic and physicochemical properties (&) of the drug allows determination of its proper formulation and delivery technique (Sunisha *et al., 2015*). Every drug's intrinsic chemical and physical properties are evaluated before development of a suitable pharmaceutical formulation. This property ensures the infrastructure for drug's combination with pharmaceutical ingredients in the formulation of dosage form. Objective of preformulation study is to enhance the appropriate (stable, effective, and safe) dosage form by establishing kinetic rate profile, compatibility with the excipients & establish physicochemical parameter of new drug substance. Among these properties, drug solubility, partition coefficient, dissolution rate, polymorphic forms and stability plays important role in preformulation study. Polymorphic substances that have both crystal and amorphous form shows variant physicochemical properties and therapeutic description of the drug molecule. Before starting the preformulation, several different summary of similar compounds is studied to acknowledge and understand (i) the degradation process, (ii) any adverse conditions relevant to the drug, (iii) bioavailability, (iv) pharmacokinetics and formulation of similar compound and (v) toxicity. Preformulation influences (a) selection of the drug candidate itself, (b) selection of formulation components, (c) API & drug product manufacturing processes, (d) determination of the most appropriate container closure system, (e) development of analytical methods, (f) assignment of API retest periods (g) the synthetic route of the API, (h) toxicological strategy(Gopinath *et al.,* 2011).

Preformulation initiates when a newly synthesized drug shows enough pharmacologic response in animal models to conduct evaluation in man. These studies should emphasize on those physicochemical properties of the newly obtained compound that could affect drug performance and development of an effective dosage form. A detailed understanding of these properties may therefore provide a rational formulation design, or support the need for molecular modification(Yalkowiski *et al*., 1981).

PREFORMULATION DURING DRUG DISCOVERY (Prasanna *et al.,* 2015)

Apart from helping formulation development, preformulation studies also help in lead identification during drug discovery phase. A new chemical entity should possess optimal biopharmaceutical properties to become a drug molecule. Mere possession of potency and selectivity does not ensure 'drug ability'. Preformulation studies help in assessing the 'drug ability' of a molecule. Preformulation can thus be considered as critical decision-making tool during both – drug discovery and development phase. A comprehensive understanding of physicochemical properties and its effect on biological performance, allows selection of potential lead molecules and in identification of drug delivery challenges.

NEED OF DOSAGE FORMS: (Ansel *et al.,* 2005; Aulton *et al.,* 1996)

Formulation development is required at various stages during drug development. As we have discussed earlier, drugs are rarely administered alone. Incorporation of the drug into a formulation provides various advantages like ease of handling, ease of administration, better stability or better bioavailability. Different stages of clinical trials as described above require different formulations. Preclinical stage is performed in animals and requires simple liquid formulations that can be easily administered to animals. A comprehensive preformulation study helps in understanding the physico-chemical properties of the drug molecule. It provides the foundation for development of a robust dosage form that can sustain the rigors of processing and shelf life. Efforts spent on preformulation provide cost savings in the long run, by reducing challenges during formulation development**.**

a) To provide mechanism for the safe & convenient delivery of accurate dose.
b) To protect from environment i.e. destructive effect of oxygen or humidity.
c) To protect from the destructive effect of gastric acid after oral administration Ex. Enteric coated tablet.
d) To conceal the bitter, salty, nauseous odor of drug substance. Ex. Capsule, Coated tablet.
e) To provide liquid preparation which are unstable or insoluble in vehicle. Ex. Suspension
f) To provide clear dosage forms of substance. Ex. Syrups , Solutions
g) To provide rate controlled drug action. Ex. Sustained Release & Controlled release Tablets
h) To provide optimal drug action from topical administration. Ex. Ointments, Creams, Patches.

OBJECTS: (Ansel *et al.,* 2005; Aulton *et al.,* 1996)

a) To develop the elegant dosage forms (stable, effective & safe)
b) It is important to have an understanding of the physical description of a drug substance before dosage form development.

c) It is 1st step in rational development of a dosage form of a drug subt before dosage form development.
d) It generates useful information to the formulator to design an optimum drug delivery system

GOALS:
a) To establish the physico-chemical parameters of new drug substance.
b) To establish the physical characteristics
c) To establish the kinetic rate profile.
d) To establish the compatibility with the common excipient.
e) To choose the correct form of a drug substance**.**

PREFORMULATIONSTUDIES

Preformulation is the study of the chemical and physical properties of the drug components prior to the compound ing process of the formulation. The purpose of the study is to understand then at unread characteristics of each component and to optimize conditions of the dosage for manufacture .Before formulation development, preformulation data must be generated to aid the development process and the physicochemical properties must be defined.

A. Stages of PreformulationStudies: (Ahuja *et al*., 2001)

Timely preformulation data availability is critical because it is an essential prerequisite of development. Physical properties, such as melting point, ultraviolet spectrum, and thin-layer chromatography (TLC) from preformulation are essential for the preliminary specification. The preformulation is performed in several stages with different development cycles, which are discussed in the following.

1. Physicochemical Properties and Analytical Testing for Drugs:

The data consist of physicochemical properties of the chemical substance and analytical properties useful in the development of analytical methods, the evaluation of material quality, and testing for the acceptance of the formulation developed. The portion of this report consisting of analytical data may be known as an "analytical profile".

2. Data Supporting the Development of Dosage Forms:

Before formulation development stability, incompatibility, and solid-state characteristics of a drug must be studied to support product development and improvement. The selection of the appropriate methods for dosage form evaluation may also be considered as part of the preformulation studies. The evaluation of the dosage form is based on testing: pharmaceutical testing (friability, hardness, disintegration, and dissolution, etc.), bioburden testing (microbiology, etc.), and bioavailability studies.

3. Support for Quality Control and Finished Product Manufacturing:

Analytical methods of the interim developed product, and issues regarding difficulty of QA/QC may be included in Part 3 of the preformulation report. It must be published before the marketed product is finalized in "Biobatch," a scale-up production of 10% of a manufacturing lot.

PREFORMULATIONPARAMETERS:
A. PHYSICAL CHARACTERISTICS.
1) Organoleptic properties

2) Bulk characteristics
a) Solid state characteristics b) Flow properties c) densities d) compressibility e) crystalline
f) polymorphism g) hygroscopicity

3) Solubility analysis
a) Ionization constant (Pka) b) Partition co-efficient c) Solubilization d) Thermal effect e) Common ion effect(Ksp) f) Dissolution

4) Stability analysis

B. ANALYTICAL TECHNIQUES
For Preformulation Studies Analytical techniques divided into three types of Methods
A. Spectroscopic and specific detection Methods.
B. Separation Methods.
C. Thermal Analytical Methods

ORGANOLEPTIC PROPERTIES: (Prasanna *et al.*, 2015)

A typical preformulation program should begin with the description of the drug substance. The color, odour and taste of the new drug must be recorded using descriptive terminology. The color, odour and taste of the new drug must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties in order to avoid confusion among scientists using different terms to describe the same property. A list of some descriptive terms to describe the most commonly encountered colors, tastes and odours of pharmaceutical powders is provided in table. The color of all the early batches of the new drug must be recorded using the descriptive terminology. A situation in which use of, or exposure to, a violate product is not likely to cause adverse health Consequences (Hasan *et al*., 2016). A record

of color of the early batches is very useful in establishing appropriate specifications for later production. When the color attributes are undesirable or variable, incorporation of a dye in the body or coating of the final product could be recommended.

BULKCHARACTERISTICS: (Prasanna *et al.*, 2015)

a) Solid state characteristics:

Powders are masses of solid particles or granules surrounded by air (or other fluid)and it is the solid plus fluid combination that significantly affects the bulk properties of the powder. Salt or ester formation: Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents (Rashid *et al.*, 20 16).It is perhaps the most complicating characteristic because the amount of fluid can be highly variable.Powders are probably the least predictable of all materials in relation to flow ability because of the large number of factors that can change their rheological properties. Physical characteristics of the particles, such as size, shape, angularity, size variability and hardness will all affect flow properties. External factors such as humidity, conveying environment, vibration and perhaps most importantly aeration will compound the problem.

Particle size and size distribution:

Various chemical and physical properties of drug substances are affected by their particle size distribution and shapes. The effect is not only on the physical properties of solid drugs but also in some instances on their biopharmaceutical behaviour.For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drug. It is now generally recognized that poorly soluble drugs showing a dissolution rate- limiting step in the absorption process will be more readily bioavailable when administered in a finely sub divided state than as a coarse material.Size also plays a role in the homogeneity of the final tablet. When large differences in size exist between the active components and excipients, mutual sieving (de-mixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps.

b) Powder Flow Properties

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. If a drug is identified at the preformulation stage to be "poorly flowable," the problem can be solved by selecting appropriate excipients. In some cases, drug powders may have to be precompressed or granulated to improve their flow properties. Some of these methods are angle of repose, flow through an orifice, compressibility index, shear cell, etc. Changes in particle size and shape are generally very apparent; an increase in crystal size or a more uniform shape will lead to a smaller angle of repose and smaller carr'sindex .

Angle of Repose:

The maximum angle which is formed between the surface of pile of powder and 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

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

c) Densities:

The ratio of mass to volume is known as density

Types of density:

(a) Bulk density: It is obtained by measuring the volume of known mass of powder that passed through the screen.

(b)Tapped density: It is obtained by mechanically tapping the measuring cylinder containing powder.

(c)True density: It actual density of the solid material.

(d)Granule density: may affect compressibility, tablet porosity, disintegration, dissolution

d) Compressibility:

"Compressibility" of a powder can be defined as the ability to decrease in volume under pressure and "compactability as the ability of the powdered material to be compressed into a tablet of specified tensile strength. It can be used to predict the flow properties based on density measurement.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{pored density} * 100}{\text{Tapped density}}$$

e) Crystallinity (Leon *et al*., 2009, Jenes *et al*., 2000)**:**

Generally most of drugs exist in solid state. Very few are in liquid state like valproic acid and even less in gaseous form like some general anesthetics. A crystal structure is a unique arrangement of atoms in a crystal. Physical properties affected by the solid-state properties can influence both the choice of the delivery system and the activity of the drug, as determined by the rate of

delivery. Chemical stability, as affected by the physical properties, can be significant. A crystalline particle is characterized by definite external and internal structures. Crystal habit describes the external shape of a crystal, whereas polymorphic state refers to the definite arrangement of molecules inside the crystal lattice. Crystallization is invariably employed as the final step for the purification of a solid. The use of different solvents and processing conditions may alter the habit of recrystallized particles, besides modifying the polymorphic state of the solid.

f) Polymorphism:

Many drug substances can exist in more than one crystalline form with different space lattice arrangements. This property is known as polymorphism. The different crystal forms are called polymorphs. When polymorphism occurs, the molecules arrange themselves in two or more different ways in the crystal; either they may be packed differently in the crystal lattice or there may be differences in the orientation or conformation of the molecules at the lattice sites.

Methods to identify polymer

1) Optical crystallography
2) Hot0stagemicroscopy
3) X-Ray Diffraction method
4) NMR technique
5) FTIR technique.
6) Microcalorimetry
7) Thermal methods

g) Hygroscopisity

Many compounds and salts are sensitive to the presence of water vapor or moisture. When compounds interact with moisture, they retain the water by bulk or surface adsorption, capillary condensation, chemical reaction and, in extreme cases, a solution (deliquescence). Deliquescence is where a solid dissolves and saturates a thin film of water on its surface. It has been shown that when moisture is absorbed to the extent that deliquescence takes place at a certain critical relative humidity, the liquid film surrounding the solid is saturated. This process is dictated by vapor diffusion and heat transport rates.

Moisture is also an important factor that can affect the stability of candidate drugs and their formulations. Sorption of water molecules onto a candidate drug (or excipient) can often induce hydrolysis. In this situation, by sobbing onto the drug-excipient mixture, the water molecules may ionize either or both of them and induce a reaction. For example, we have found that a primary amine, when mixed with lactose was apparently stable even when stored at 90°C for 12 weeks. However, when the experiment was carried out in the presence of moisture, extensive degradation by way of the well-known Milliard reaction took place. Other properties such as crystal structure, powder-flow, compaction, lubricity, dissolution rate and polymer film permeability may also be affected by moisture adsorption.

3. Solubility Analysis:

An important Physical-chemical property of a drug substance is solubility, especially aqueous solubility. A drug must possess some aqueous solubility for therapeutic efficacy in the physiological $_{P}$H range of 1 to 8. For a drug to enter into systemic circulation, to exert therapeutic effect, it must be first in solution form. If solubility of drug substance is less than desirable, than consideration must be given to increase its solubility. Poor solubility (< 10mg/ml) may exist incomplete or erratic absorption over PH rang 1-7 at 37°C. However, knowledge of two fundamental properties is mandatory for a new compound.

i) Intrinsic solubility (Co)
ii) Dissociation constant (Pka).

i) Intrinsic Solubility (Co)

The intrinsic solubility should be measured at two temp: 4 to 5°C to ensure good physical stability and to extend short term storage and chemical stability until more definite data is available. 37°C to support biopharmaceutical evaluation. The solubility of weakly acidic and weakly basic drug as function of $_{P}$H can be predicted with help of equation. (Table 3).

a) Ionization Constant (PKA) (Guy *et al*., 1987, Aulton *et al*., 1996, Kandavili *et al*., 20002)**:**

Many drugs are either weakly acidic or basic compounds and, in solution, depending on the pH value, exist as ionized or un-ionized species. The problem is how to deliver drugs right where we need it (Hasan MM *et al*., 2016). The un- ionized species are more lipid-soluble and hence more readily absorbed. The gastrointestinal absorption of weakly acidic or basic drugs is thus related to the fraction of the drug in solution that is un- ionized. The conditions that suppress ionization favor absorption. The factors that are important in the absorption of weakly acidic and basic compounds are the pH at the site of absorption, the ionization constant, and the lipid solubility of the un- ionized species. These factors together constitute the widely accepted pH partition theory. The relative concentrations of un-ionized and ionized forms of a weakly acidic or basic

drug in a solution at a given pH can be readily calculated using the Henderson-Hasselbalch equations.

$$pH = pKa + \log \frac{[\text{Un- ionized form}]}{[\text{ionized form}]} \quad \text{for bases}$$

$$pH = pKa + \log \frac{[\text{Ionized form}]}{[\text{un ionized form}]} \quad \text{for acids}$$

Weakly acidic compounds (pKa< 4.3) were absorbed relatively rapidly. Those with pKa values ranging between 2.0 and 4.3 were absorbed more slowly; and strong acids (pKa> 2.4) were hardly absorbed. For bases, those with pKa values smaller than 8.5 were absorbed relatively rapidly; those with a pK a between 9 and 12 were absorbed more slowly; and completely ionized quaternary ammonium compounds were not absorbed. In pharmacokinetic area, the extent of ionization is imp. Effect of its extent and absorption, distribution, elimination. The extent of Pka, in many cases, highly dependent on PH of the medium containing the drug.

Determination of Pka:

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

b) Partition Coefficient:

This ratio is known as the partition coefficient or distribution coefficient and is essentially independent of concentration of dilute solutions of a given solute species. Log P = 0 means that the compound is equally soluble in water and in the partitioning solvent. The lipophilicity of an organic compound is usually described in terms of a partition coefficient; log P, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

Po/w = (C oil/water) equilibrium

$$\text{Log P} = \frac{\text{(un ionized compound)org}}{\text{(un ionized compound)aq}}$$

This ratio is known as the partition coefficient or distribution coefficient and is essentially independent of concentration of dilute solutions of a given solute species. Log P = 0 means that the compound is equally soluble in water and in the partitioning solvent. If the compound has a log P =5, then the compound is 100,000 times more soluble in the partitioning solvent. A log P = –2 means that the compound is 100 times more soluble in water, i.e., it is quite hydrophilic. Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug. Although it appears that the partition coefficient may be the best predictor of absorption rate, the effect of dissolution rate. Must not be neglected. Lipids occurring in living membranes are complex and difficult to obtaining pure form. An indication of the relative lipid solubility, however, can be obtained by determining how a drug substance distributes itself between water and an immiscible organic solvent. When a solute is added to two immiscible liquids that are in contact with each other, it will distribute itself between the two phases in a fixed ratio. This ratio is known as the partition coefficient, or distribution coefficient, and is essentially independent of concentration of dilute solutions of a given solute species. Various organic solvents such as chloroform, ether, amyl acetate, is opropylmyristate, carbon tetrachloride, and n - Octanol can be used in the determination of the partition coefficient, with the latter gaining increasing acceptance.

Methods offending Partition coefficient:

1) Shake-flask method
2) Chromatographic method.
3) Countercurrent and filter probe method.
4) Tomlinson's filter probe method.
5) Micro electrometric titration method
6) Automated instrument is now available.

Applications of Partition coefficient:

1) Recovery of antibiotics from fermentation broth. Extraction of drug from biological fluid for therapeutic monitoring.
2) Absorption of drug from dosage forms. (Ointments, Suppositories, Transdermal patches).
3) Study of distribution of flavoring oil between oil & water in emulsion.

c) Solubilization:

For drug candidates, with either poor water solubility or insufficient solubility for projected solution dosage form, preformulation study should include limited experiments to identify possible mechanism for solubilization.

Methods for Increasing Solubility:

a) Change in pH
b) Co-Solvency

c) Dielectric Constant
d) Solubilization by Surfactant
e) Complexation
f) Hydrotropy
g) Chemical Modification of drug

d) Thermal Effect:

We determine the effect of temp. on the solubility of drug candidate. This can be determined by measuring heat of solution i.e. HS

$$\ln S = -\frac{\Delta H_S}{R}\left(\frac{1}{T}\right) + C$$

Where,

dC / dt = dissolution rate

pKa, and solubility on absorption

Where, S = molar solubility at temp. T (° K) R = gas constant.

Heat of solution represents the heat released or absorbed when mole of solute is dissolved in large quantity of solvent. It is determined from solubility value for saturated solution equilibrated at controlled temperature over the range of interested. Typically the temperature range should include 5°C, 25°C, 37°C and 50°C.If heat of solution is positive (endothermic process) thus, increasing solution temp. Increased the drug solubility. For non-electrolyte and un-ionized form of weak acid and weak bases dissolved in water, heat of solution range from 4 to 8 Kcal/mol.

e) Common Ion Effect:

A common interaction with solvent, which often overlooked, is the common ion effect. The addition of common ion often reduces the solubility of slightly soluble electrolyte. This salting out results from the removal of the water molecule as the solvent due to competing hydration of other ions. So, weakly basic drug which are given as HCL salts have decreased solubility in acidic (HCL) solution. Eg. Chlortetracycline, methacyclin, papaverine, cyproheptadine, bromhexine, Triamterene.

To identify a common ion interaction, the intrinsic dissolution rate of hydrochloride salt should be compared between, Water and water containing 1.2%W/V NACL 0.05M HCL and 0.9%W/V NACL in 0.05M After this, if solubility is not decreased than we can give drug in chloride salt, otherwise it should be eliminated.

f) Dissolution:

In many instances, dissolution rate in the fluids at the absorption site, is the rate limiting steps in the absorption process. This is true for the drug administered orally in the solid dosage forms such as tablet, capsule, and suspension as well as drug administered I.M. in form of pellets or suspension. Dissolution is of 2 types.

a) Intrinsic dissolution b) Particulate dissolution

a) Intrinsic Dissolution

The dissolution rate of a solid in its own solution is adequately described by the Noyes-Nernst equation:

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{hv}$$

A = surface area of the dissolving solid
D = diffusion coefficient
C= solute concentration in the bulk medium
h= diffusion layer thickness
V = volume of the dissolution medium
Cs = solute concentration in the diffusion layer During the early phase of dissolution, Cs » C and is essentially equal to saturation solubility S. Surface area A and volume V can be held constant. Under these conditions and at constant temperature and agitation, Equation reduces to

$$dC/dt = KS$$

Where

K=AD/hV= constant.

Dissolution rate as expressed in Equation is termed the intrinsic dissolution rate and is characteristic of each solid compound in a given solvent under fixed hydrodynamic conditions. The intrinsic dissolution rate in a fixed volume of solvent is generally expressed as mg dissolved x(min-1 cm- Z). Knowledge of this value helps the preformulation scientist in predicting if absorption would be dissolution rate-limited.

Particulate dissolution:

It will determine dissolution of drug at different surface area. It is used to study the influence on dissolution of particle size, surface area and mixing with excipient. So, if particle size has no influence on dissolution than other method like addition of surfactant will be considered.

STABILITY ANALYSIS:

Preformulation stability

Studies are usually the first quantitative assessment of chemical stability of a new drug. Factor effecting chemical stability critical in rational dosage form design include temperature, pH and dosage form diluents. Physicochemical properties of the inserts were evaluated like uniformity of thickness, drug content, weight, swelling index and surface pH (Hasan *et al*., 2016). The type of process selection requires thorough knowledge of physicochemical properties of the drug, excipients, required flow and release properties, etc (Jannat *et*

al., 2016).The method of sterilization of potential product will be largely dependent on the temperature stability of the drug. Drugs having decreased stability at elevated temperatures cannot be sterilized by autoclaving but must be sterilized by another means, e.g., filtration. The effect of pH on drug stability is important in the development of both oral administration must be protected from the highly acidic environment of the stomach. Buffer selection for potential dosage forms will be largely based on the stability characteristic of the drug. Accelerated stability study is shown in (Table 5).

Stability in Toxicology Formulation:

It is often advisable to evaluate samples of the toxicology preparations for stability and potential homogeneity problems. Water, vitamins, minerals, enzymes are present in feed, which can severely be reduce the shelf life of drug. Solution and suspension toxicology preparations should be checked for ease of manufacture and then stored in flame-sealed ampoules at various temperatures. In addition to chemical stability, the suspension should be subjected to an occasional shaking to check dispersibility.

Solid state stability:

Chemical instability normally results from either of the following reaction hydrolysis, oxidation, photolysis and pyrolysis, Chemical structure of the drug is the determination of drug to either of these attacks. Esters and lactase and to lesser extent, amides are to prone to solvolysis, instauration or electron rich centre in the structure make the molecule vulnerable for free radical mediated orphoto-catalyzed oxidation. Physical properties of drugs. Amorphous materials are less stable than their crystalline forms. Denser materials are more stable to ambient stress.

Compatibility studies:

The knowledge of drug excipients interaction is useful for the formulation to select appropriate excipients. The described preformulation screening of drug excipients interaction requires only 5mg of drug in a 50% mixture with the excipients to maximize the likelihood of obscuring an interaction. Mixtures should be examined under nitrogen to ultimate oxidation and paralytic effect at a standard heating rate on DSC, over a temperature range, which will encompass any thermal changes due to both the drug and appearance or disappearance one or more peaks in thermo grams of drug excipient mixtures are considered of indication of interaction.

Solution stability:

As compared with the dry form, the degradation is much rapid in solution form. It is important ascertain that the drug doesn't degrade when exposed to GI fluid. The pH based stability study, using different stimulator GI condition can be designed. A poor solution stability of drug may urge the formulator to choose a less soluble salt form, provided the bioavailability is not compromised.

ANALYTICAL TECHNIQUES

For Preformulation Studies Analytical techniques divided into three types of Methods

A. Spectroscopic and specific detection Methods.
B. Separation Methods.
C. Thermal Analytical Methods.

A. **Spectroscopic and specific detection Methods**

The need for identification and structure elucidation for newly discovered compounds drives the progress of specific detection techniques with NMR and X-ray diffraction and MS. The detection of foreign metal contaminants is essential with inductively coupled plasma spectroscopy (ICP), atomic absorption (AA), and X-ray fluorescence. The analytical techniques commonly used in the preformulation study are discussed in the following.

UV Spectroscopy

UV absorption is an essential tool for qualitative and quantitative determination of a single component drug or isolated extract. In a preformulation study, solubility, dissolution rate, and some stability studies (when degradation products have a different absorption maximum from the parent compound) are performed with the UV technique. UV is extensively used for HPLC detection. Most of drugs have aromatic rings and/or double bonds as part of their structure and absorb light in UV range, UV spectroscopy being a fairly accurate and simple method is a performed estimation technique at early preformulation stages. The absorption Co-efficient of the drug can be determined by the formula:-

$E = AF / X$

Where,

A = Asborbance

F= dilution factor

X = weight of drug (mg)

It is now possible to determine concentration of drug in any solution by measuring absorbance.

$C = AF / E$ mg/ ml

Visible Photometry and Colorimetry

Visible spectrometry is identical to UV spectrometry, with the exception of the wavelengths, which are 400–750 μm in visible spectrometry. A color product may be formed with a specific agent as a result of chemical reaction. Quantitative determination of the colored compound is based on this principle for drug assay. Another method of forming a color compound (subsequently separated by extraction) is the dye–salt method. In an ion-pair reaction forming a color complex in reaction to the drug with a dye of opposite polarity such as bromthymol blue, the complex is extracted into the organic layer and determined colorimetrically.

IR Spectroscopy: (Harry *et al*., 2008)

IR spectroscopy is used extensively in pharmaceutical analysis for fingerprint identification of a drug molecule and the proof of its structure. Infrared absorption spectroscopy, especially when measured by means of the Fourier transform method (FTIR), is a powerful technique for the physical characterization of pharmaceutical solids. In preformulation, IR may be applied to the study of polymorphism of solid crystals. Polymorphs pose different IR characteristics, and they may be used as a tool for fingerprint identification. In addition, solid-state vibrational spectra can be very useful in studies of the solvation phenomena associated with a solvate morphic system . For certain drugs that have non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration (Hasan *et al.*, 2016).

Acquisition of solid-state FTIR spectra suitable for use in the characterization of different crystal forms can be performed using Nujol mull, diffuse reflectance, or (most preferably) attenuated total reflectance (ATR) techniques. Any use of pelleting techniques is to be strictly avoided, since too many complications and spurious effects can arise with compaction of the KBr pellet, and these can limit the utility of the spectroscopic method. The main drawback to the mull technique is that regions in the IR spectrum overlapping with carbon–hydrogen vibrational modes will be obliterated owing to absorbance from the oil.

Raman Spectroscopy: (Grasselli *et al*., 1981,Lewis *et al*., 2001)

Another technique of vibrational spectroscopy that is ideally suited for the characterization of polymorphism or solvate morphism in solids is Raman spectroscopy. In this methodology, the sample is irradiated with monochromatic laser radiation, and the inelastic scattering of the source energy is used to obtain a vibrational spectrum of the analyte. Since most compounds of pharmaceutical interest are of low symmetry, the Raman spectrum will contain spectra features at the same energies as those obtained using the FTIR method . In general, symmetric vibrations and nonpolar groups yield the most intense Raman scattering bands, while ant symmetric vibrations and polar groups yield the most intense infrared absorption bands. These differences can, at times, be quite profound and can therefore be successfully exploited in the characterization of solid materials.

Raman spectroscopy is a nondestructive tool and requires little or no sample preparation. A sample may be analyzed in solid or powder form or in an aqueous solution and placed in glass containers such as an NMR tube, GC vial, test tube, light- path cell, or glass bottle. Aside from structure elucidation and functional group analysis, FT- Raman may be used for quantitative determination of polymorphs in a preformulation study.

NIR Spectroscopy: (Stark *et al*., 1986)

The absorption bands found in the near-infrared (NIR) region of the spectrum (typically considered to cover 1000–2500 nm) are all due to overtones and combinations of fundamental molecular vibrational modes. The energies of the overtone bands are more affected by environmental details than are the energies of their fundamentals, so slight perturbations in the bonding can yield drastic frequency and amplitude changes in the NIR. The advantage of this technique is the rapidity of analytical determinations without sample preparation and the use of solvent. The application of NIR in the pharmaceutical industry can be qualitative or quantitative. Materials such as active drug substances, organic liquids and solvents, excipients, and packaging materials can be tested rapidly for identity in the receiving area . The use of NIR for quantitative determination includes moisture determination for the drying process, assay of dosage form, and content uniformity, as well as dissolut ion rate monitoring. Since NIR spectra consist of overtone transitions of fundamental vibrational modes, they are not terribly useful for identity purposes without the use of multicomponent analysis and access to spectral libraries of known .

X-Ray Diffraction: (Harry *et al*., 1986, Klug *et al*, 1974)

The X-ray diffractometry technique obtains information on substance structure at the atomic

level. This technique allows measurement of both crystalline and no crystalline materials. The analysis is nondestructive in nature and handles samples in the form of powders, solids, and liquids. Powder diffraction is used for fingerprint purposes. Polymorphism may be identified by diffraction patterns with d-spacing that has broader and overlapping peaks. Quantitative ratios of two polymorphs and their percentage of crystallinity may also be determined. Besides the identification methods, other applications of X-ray powder diffraction methodology include the evaluation of polymorphism and solvate morphism, the study of phase transitions, and evaluation of degrees of crystallinity. A very useful complement to ordinary PXRD is variable temperature XRD. In this method, the sample is contained on a stage that can be heated to any desired temperature. The method is extremely useful for the study of thermally induced phenomena and can be a vital complement to thermal methods of analysis . XRPD has become exceedingly important to pharmaceutics because it represents the primary method whereby one can obtain fundamental structural information on the structure of a crystalline substance. The technique is ideally suited for the study of large numbers of polycrystalline samples and has found widespread use in the evaluation of crystal structures, comparison of polymorphism and solvate structures, evaluation of degrees of crystallinity, and the study of phase transitions. When the phase identity, or degree of crystallinity, of a drug substance is important to its performance in a drug product, PXRD can serve as a vital stability- indicating method. For example, amorphous clarithromycin was prepared by grinding and spray-drying processes, and PXRD was used to follow changes in crystallinity upon exposure to elevated temperature and relative humidity.

NMR Spectroscopy: (Fyfe *et al*., 1983)

` After X-ray crystallography, solid-state nuclear magnetic resonance spectroscopy can be considered as being the most powerful molecular level characterization technique for a pharmaceutical solid, since this spectroscopic method yields information regarding the individual chemical environments of each atom in the compound under study. NMR involves the absorption of electromagnetic radiation in the radiofrequency of a longer wavelength spectrum. The nuclei shift from the preferred orientation with lowest energy to a less preferred, high- energy orientation at a particular frequency. Thus a plot of frequency versus intensity of radiation results in the NMR spectrum of a material. The major application of broadline NMR is in the measurement of the internuclear distances and other crystal parameters important in the study of polymorphism as well as hydrates and solvates . In addition to qua litative investigation of polymorphs and solvates, the quantitative measurement of polymorphs is also possible. In NMR analysis with liquids, the sample is commonly dissolved in denudated solvents (such as chloroform-d, benzene-d, or D_2O) and fills a sample tube. The liquid technique is widely used for structure elucidation to provide detailed information on the presence or absence of certain magnetic nuclei in different functional groups, along with structural and geometric relationships among the magnetic nuclei but powder samples are suitable for generating a spectrum to illustrate the crystal structure by the solid NMR technique.

Metal Analysis: (Edward *et al*., 2001)

The methods of metal analysis of pharmaceuticals include X-ray fluorescence spectroscopy, AA spectroscopy, and ICP. High-sensitivity methods and techniques for metal analysis are essential for quality control. The classical method of detecting metal contamination is the heavy metal testing described in the USP.

a) X-Ray Fluorescence

When a beam of high-intensity X-rays strikes a sample, the elements in the sample are excited and emit their own characteristic X-rays. Powder samples, solutions, or liquids can be placed in a sample cup wrapped with Mylar film that is transparent to X-rays. This method is nondestructive and can be an automatic operation.

b) Atomic Absorption

In AA, the sample in solution is atomized in a flame, producing atomic vapor with elements from the solution. A monochromatic light source with a hollow cathode tube containing the element of interest emits light at the same wavelength as the element of interest passing through the atomic vapor sample in the flame. The amount of radiation absorbed is proportional to the concentration of the elements in the solution.

c**) ICP-AES/ICP-MS**

In ICP-AES the sample introduced in the form of aerosol by the nebulizer is instantaneously decomposed in the plasma (plasma temperature 6,000–10,000 K) to form analyte atoms that are simultaneously ionized. The ions produced are extracted from the plasma into the atomic emission spectrometer For ICP with a mass spectrometer (ICP-MS), ions are transferred to a high vacuum in an MS. and the analyte ions are then focused by a series of ion lenses into a mass

analyzer. The analyzer separates the ions based on their mass/charge ratio. Finally, the ions are measured with an electron multiplier and collected by a counter for each mass number. In the mass spectrum, each elemental isotope appears at a different mass, with peak intensity directly proportional to the initial concentration in the sample solution isotope

B. Separation Sciences

The range of analytical methodology suitable for the evaluation of chemical compatibility between a drug substance and proposed excipients is extremely large, and methods can range from the relatively simple to the extremely complex. The most frequently used methods for obtaining chemical composition information in the preformulation stage of development are based on various types of separation science, 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 coupled with mass spectrometry (MS) when the identity of degradant species is required. Separation techniques such as counter current extraction (CCE), and capillary electrophoresis (CE) are extensively employed in preformulationstudies .

1. Thin-Layer Chromatography:(Fried *et al*., 2001)

TLC is a separation technique characterized by high sensitivity and multiple detection, but its use has gone somewhat out of vogue owing to the development of newer instrumental methods. Nevertheless, TLC still can play an important role in preformulation characterization studies and has undergone a steady evolution in technology and capability over the years . The general detection technique is to spray a sample with a detecting agent, which reacts chemically with the ingredient to be detected, so that a visible spot develops. Detection by visual observation under short- or long-wave UV light is employed. TLC can be used as a separation method to obtain impurities from dosage forms in a state suitable for further analysis . The disadvantages of TLC include reproducibility, detection inconsistency, person- to-person variations, documentation, and electronic data reduction . The modern practice of TLC is now distinguished as high-performance TLC (HPTLC) to eliminate these disadvantages of TLC.

2. High-Pressure Liquid Chromatography: (Scott *et al*., 2005)

HPLC methodology is unique in that the analytical separation step is coupled with on-line analysis instrumentation that senses all analytes as they elute out of the chromatographic system. The UV detector coupling with HPLC equipment is the most important analytical instrument for preformulation, QC/QA, and in-process control in pharmaceutical analysis . HPLC is a basic and reliable analytical tool for preformulation study because of the high-resolution capacity, accuracy, and reproducibility of the equipment. Its primary function includes search for and detection of impurities in drug substances, as well as stability evaluation of dosage forms in terms of detection and quantization of degradation products . The utility of HPLC analysis in a program of preformulation testing was demonstrated for a number of compounds, including fosinopril sodium, ceronapril, pravastatin sodium, sorivudine, and if etroban sodium. A reversed- phase method for the determination of nicotine in immediate- and extended-release formulations has been reported that also was used in the analysis of drug–excipient compatibility samples.

3. LC/MS: (Burinsky *et al*., 2003)

The first HPLC methods are usually developed during the preformulation stage of development; the combination of this technology with MS probably represents the ideal combination of technologies for the detection and identification of drug–excipient interaction products. In usual practice, one must vaporize the analytes, convert these into charged species, allow the ions to undergo fragmentation, and finally separate and detect the ion fragments on the basis of their mass-to-charge (m/e) ratio. The m/e value of the molecular ion confirms the formula weight of the compound, while the structures of the various fragments are consistent with the structure of the compound. The key element in developing an HPLC-MS method is that all components must be volatile and capable of carrying the analytes into the vapor phase.

4. Capillary Electrophoresis: (Zhongjiang *et al*., 2005)

Capillary electrophoresis (CE) has been widely used in physicochemical profiling and pharmaceutical analysis. Capillary electrophoresis (CE) is a simple, versatile, automated, and powerful separation technique and widely applied in physicochemical profiling for pharmaceuticals such as acid dissociation constant (p*K*a), octanol- water partition coefficient (logPow). The p*K*a determination of acids and bases by CE is based on measuring the electrophoretic mobility of charged species associated with the acid-base

equilibria as a function of pH. A number of direct and indirect methods have been applied for log *P*ow measurement. Conventional shake-flask method was historically considered to be the standard assay for direct measurements of log *P*ow.

Micellarelectro kinetic chromate graphy(MEKC)

MEKC is an analytical technique with combined features of conventional chromatography and capillary electrophoresis, which enables the separation of neutral and charged analytes. An anionic surfactant, sodium dodecyl sulfate, is commonly used as a micellar agent. In addition, cyclodextrin, a chiral selector, is added to the system, which contains three phases: aqueous, micelle, and cyclodextrin. Detection is accomplished with UV light, a diode array, laser-induced fluorescence, or a mass spectrometer.

C. Thermal Analytical Methods

Thermal analysis and calorimetric methods have demonstrated a wide array of applications in the preformulation, and formulation development. Thermal analysis and calorimetric techniques permit rapid characterization with small drug substance requirements. These techniques are critical in physical–chemical screening of early discovery leads, during salt form screening, and in the characterization of polymorphs to determine the thermodynamic relationships between the various crystal forms.

ROLE OF THERMAL ANALYTICAL METHODS IN PREFORMULATION STUDY: (Denette *et al*., 2008)

1)They are unique methods in the field of polymer analysis & of high value for a solid state analysis.
2) They finds wide application in
A) Detection of impurity
B) Determination of moisture content in any drug substance or any excipient
C) Study of polymorphism
D) Characterization of hydrates & solvates
E) Degree of Crystallinity
F) Study of phase diagram
G) Drug excipient compatibility study
H) Study of complexation

1. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) is a widely used technique within the pharmaceutical industry because the range of phase transitions it can measure usually allows near complete physical characterization of a new active principal early during preformulation.

DSC technology is constantly evolving and improving and three recent derivatives have become popular. These are:
• Temperature-modulated DSC
• High-sensitivity DSC
• Fast-scan DSC
Temperature-modulated DSC (TM-DSC) is particularly useful pharmaceutically for isolating and quantifying glass transitions while high- sensitivity DSC, (HS-DSC) was developed for studying dilute solutions of macromolecules (usually biologicals). The main benefits of fast- scan DSC (FS-DSC) are simply to increase the size of the measured signal and to reduce the experimental time-frame. DSC techniques provide information regarding the melting point (temperature)/range, heat of fusion and crystallization, purity, polymorphism, pseudopolymorphism, glass transition, drug and excipient interaction/compatibility, thermal stability, etc. which is essential for preformulation studies of pharmaceuticals and the subsequent development of a stable and effective dosage form. The performance of DSC is dependent on a number of experimental factors. Some of the important factors to be considered are the sample size, the heating rate, the atmosphere, and crucible type.

2. Hot Stage Microscopy

Changes in thermal properties are observed through a microscope during the heating of a sample placed on a hot stage with a temperature-programming device. Melting point can be observed and the temperature at the time of the occurrence can be noted.

3. Thermal Gravimetric Analysis (TGA)

TGA may be used to determine moisture content related to weight loss in isothermal or no isothermal stability studies. In the preformulation study, TGA is the appropriate technique for differentiation of polymorph from hydrate or identification of monohydrate from among other hydrates which may not be possible by DSC alone.

DRUG DEVELOPMENT

1. Selection of a Drug Substance for Dosage Form Development
   a) Structure Modifications b. Purity
   b) Chirality
   c) Salt Forms Selection
   d) Prodrugs
   e) Metabolites
2. Intellectual Property Protection and Patent Filing.
3. Selection of Analytical Technique and

Development.
4. Preparation and Submission of IND.
5. Clinical Trial Studies.
6. Development and Manufacturing of Dosage Forms.

Establishment of a QA/QC System.Pre-clinical phase is proceeded by human clinical trials, consisting of phase I, II and III. Formulations used for phase I clinical trial are called as 'first time in human' or 'first time in man' formulations. These can be simple solid or liquid formulations and includes formulations like 'chemical in capsule' and 'chemical in bottle'. Sometimes Phase ICTs can also be initiated using the proposed commercial formulation. The sophistication of the formulation increases as the stage of clinical trial progresses. It is desirable to initiate late phase 2 or phase 3 clinical trials with the proposed commercial formulation.Drug development involves investigations on 'lead molecules or candidate molecules identified in drug discovery stage. These investigations mainly involve clinical evaluation. Clinical trials (CTs) are conducted in human subjects and involve phase I, II and III. Phase IV trials involve post-marketing surveillance of the new drug.

Phases of CTs

Phase I

These trials involve initial safety trials on a new chemical entity (NCE), to establish the dose range tolerated by human volunteers for single andfor multiple doses. These are usually carried out on healthy subjects and sometimes on severely ill patients (e.g., in the field of cancer). They provide information on safety and pharmacokinetics of the molecule. Pharmaceutical product development is a crucial task which is directly dependent on its therapeutic objectives (Hasan *et al*., 2016).

Phase II

Phase II trials are carried out to establish evidence of efficacy and generate more information on safety of the NCE. They are further classified as phase IIA and IIB. Phase IIA is specifically designed to assess dosing requirements and phase IIB is specifically designed to study efficacy in the prescribed doses. Once an inactive ingredient has been approved for a product through a particular route of administra-tion, it can be used in any new drug (Hasan *et al*., 2017).

Phase III

This phase of CT is also categorized into IIIA and IIIB. Phase IIIA includes trials conducted after efficacy of the medicine is demonstrated, but prior to regulatory submission of a New Drug Application (NDA) or other dossier. These trials are randomized, multi-centric and focus on generating definitive evidence of efficacy of the NCE against the current 'gold standard' treatment.Phase IIIB includes trials that continue after submission of the NDA and continue till marketing approval is obtained This is current technology; a lot of it is determined by the price point (Hasan *et al*., 2016). These trials may supplement earlier trials, complete earlier trials, or may be directed toward new types of trials (e.g., quality of life, marketing).

Phase IV

Studies or trials conducted after a medicine is marketed to provide additional details about the medicine's efficacy or safety profile.

Table 1. Shows Preformulation Drug Characterization in a Structured Program

S.No	Test	Method/Function Characterization
	Fundamental	
1	Spectroscopy	UV Simple assay
2	Solubility	Phase solubility/purity
	a)Aqueous	Intrinsic & pH effect
	b)pKa	Solubility control, salt formation
	c)Salt	Solubility, hygroscopicity & stability
	d)Solvents	Vehicles& Extraction
	e)$K_{O/W}$	Lipo phillicity, structure activity
	f)Dissolution	Bio pharmacy
3	Melting point	DSC-polymorphism, hydrate & solvent
4	Assay development	UV,HPLC,TLC
5	Stability	
	In Solution	Thermal, hydrolysis,Ph

	In solid state	Oxidation, proteolysis metalion
	Derived	
6	Microscopy	Particle size and morphology
7	Bulk density	Tablet and capsule formation
8	Flow properties	Tablet and capsule formation
9	Compression properties	Acid/excipient choice
		Preliminary screen byDSC,Conformation by

Table 2. Relationship between Flow, Angle of Repose, Carr's Index Free Powder Flow

Flow	Angleof Repose	Carr'sIndex
Excellent	<25	5-15
Good	25-30	12-16
Fair to passable	30-40	18-21
Poor	>40	23-35
Very poor	-	33-38
Extremely poor	-	>40

Table 3. Different Classes of Hygroscopic Substances

Hygroscopicity Classification		
Class 1	Non- Hygroscopic	Essentially no moisture increases occur at relative humilities below 90%.
Class 2	Slightly hygroscopic	Essentially no moisture in occurat relative humidity below80%
Class 3	Moderately hygroscopic	Moisture Content does not increase more than 5%after storagefor1week at relative humidity below60%
Class 4	Very hygroscopic	Moisture content increase may occur at relative humidity as low as 40 to50%

Table 4. Intrinsic Solubility (CO)

S = So	{1 + (K1/ [H+])}	For weak acid.
S = So	{1+ ([H+]/ K2)}	For weak base.

Where, S = solubility at given PH.
So = intrinsic solubility of neutral form.
K1 = dissociation constant for the weak acid.
K2 = dissociation constant for weak base.

Table 5. Approximate Solubility's of Pharmacopeial and National Formulary Substances

Descriptive Terms	Part of Solvents Requiredfor1Part of Solute
Very Soluble	Less than1
Freely soluble	From 1to10
Sparingly Soluble	From 32to100
Slightly Soluble	From 100 to1000
Very slightly	From 1000 to over

Table 6. Accelerated Stability Studies

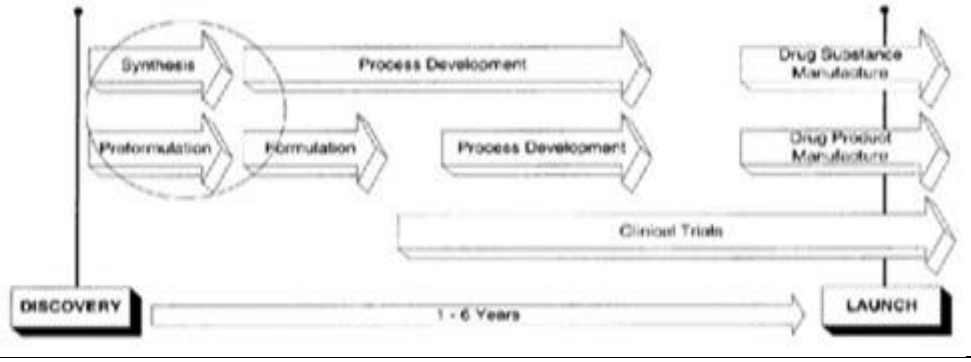
Stress	Conditions
Solid	
Heat(0^0C)	4, 20, 30 ,40, 40/70% RH,50 and 75

Moisture uptake	30,45,60,75,and 90% RH at RT[a,b]
Physical stress	Ball milling
Aqueous Solution	
pH	1 to 9 and11at RT and 37^{0}C. Refluxin1M HCl&1M NaOH
Light[c]	UV(254 and 366 nm)
Oxidation[c]	Sparling with oxygen with at RT; UV may accelerate breakdown
a)RT is ambient room temperature can vary between50and250^{0}C	

Table 7. Analytical Preformulation

S.No	Attribute	Test
1.	Identity	Nuclear Magnetic Resonance(NMR)Infrared spectroscopy(IR)Ultraviolet spectroscopy(UV) Differential scanning calorimetry(DSC) Optical rotation
2.	Purity	Moisture(water and solvent) Inorganic elements Heavy metals Organic impurities and DSC
3.	Assays	Titration ,UV,HPLC
4.	Quality	Appearance, odor Solution color pH of the slurry(Saturated solution) melting point

Figure 1. The Drug Development Process



CONCLUSION

Preformulation controls selection of the drug candidate itself, selection of formulation ingredients, API & drug product manufacturing processes, determination of the most proper container closure system, improvement of analytical methods, assignment of API retest periods the synthetic route of the API, toxicological strategy. Preformulation studies help to fortify the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, enhance public safety standards, improves product quality, promotes the implementation of new technologies, aids policy development and regulatory decision making. Preformulation studies provides pathways for development of formulation in choice of drug form, excipients, composition, physical structure, helps in regulation of pharmacokinetic and biopharmaceutical properties, guide for process development of drug substance support for PAT (Process Analytical Technology) (critical process parameters),produce necessary and useful data for development of analytical methods. This review article gives specific information which perfectly prove that a pharmaceutical preparation cannot be formulated without preformulation studies.

ACKNOWLEDGEMENT: The authors wish to thank Prof. Dr. Abu Yousuf Md Abdullah, Chairman, Northern University Bangladesh Trust, for providing their support to our research work.

CONFLICT OF INTEREST: The authors declare that they have no conflict of interest.

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Cite this article:
Md. Mehdi Hasan, Sabbir Al Habib, Mumu Mishouri Islam, Md. Mohshin Islam, Md. Salimul Karim, Kallol Banik, Harun Ar Rashid. Pharmaceutical preformulation for product development & analytical techniques use in new dosage form. *International Journal of Pharmacy & Therapeutics*, 8(1), 2017, 16-32.
DOI: **http://dx.doi.org/10.21276/ijpt.2017.8.1.3**