
1 Dosage Form Design

An important milestone in the drug development process is the discovery of an active compound, which is a long and multifaceted process. The evolution of new chemical entity has vastly increased over the last few decades mainly because of the commencement of high throughput methods for drug synthesis and screening. Drug development primarily involves investigations on 'lead molecules' identified in drug discovery stage. A lead compound has to voyage through a series of investigations and experimentations to provide a researcher early efficacy and safety evaluation.

Ideally drugs must be, properly absorbed into the systemic circulation, distributed to the proper site of action, metabolized efficiently and effectively, excreted well from the body and should be not toxic. Preformulation studies help researchers scrutinize lead compounds early in the discovery process. The lead molecule is used to generate specific chemical compounds with the optimal physiochemical, pharmaceutical, pharmacokinetics, pharmacodynamic, pharmacological and safety characteristics. The potential for these features can be predicted from reasonably interim preclinical and clinical studies and for the proper and speedy drug development, it is obligatory to select a compound with favourable pharmaceutical and pharmacological properties.

A new compound after its identification has to undergo a complete procedure of drug development before it can be transformed into its proper dosage form. It is important to characterize physicochemical, pharmacodynamic properties and pharmacological screening of the new drug substance for the development of safe and sound dosage forms. The objectives of formulation development are to ensure accurate dose and dosing regimen to present the drug substance in a convenient form for the patient and to increase the stability of the drug to prolong its shelf-life.

Drugs are hardly ever administered alone; they are always and preferably given in the form of formulated preparations due to different physical, chemical and biological constraints. To provide some basic pharmaceutical functions, drugs or chemical substances are administered as a component of formulation in combination with one or more

additives. Transforming a drug into a proper dosage form not only provides various advantages like ease of handling, ease of administration, better stability but may also lead to better therapeutic efficacy and bioavailability.

A dosage form is defined as a physical form of a drug such as a solid, liquid, or gas by which it is delivered in its proper form to particular sites of action within the body. Common dosage forms include solutions, tablets, capsules, semisolids, injections, and aerosols. The proper designing and formulation of any dosage form requires consideration of the physical, chemical, and biologic characteristics of the drug moiety and additives to be used in formulating the product.

Dosage form is necessary because there are certain conditions where only particular route of administration is feasible or preferable. In case of dysphasia, nausea and vomiting, oral administration is not suitable and one has to opt for other routes such as parenteral, topical or inhalation. Similarly, in case of joint pain, local application or topical route is preferable.

Pharmaceutics can be defined as an area of study concerned with the formulation, fabrication, stability, and efficacy of pharmaceutical dosage forms. There must be compatibility between drug and pharmaceutical additives to make a stable, efficacious, attractive, easy to administer, safe and sound pharmaceutical product. The product should be manufactured in strict quality control which contributes to its stability. The product should be properly packaged and stored under appropriate conditions that contribute to maximum shelf life.

1.1 Characteristics of Ideal Dosage Form

Dosage forms are pharmaceutical products that involve combination of active drug and non-drug substances, along with other non recoverable materials. Drug needs to be in the most convenient and proper form, so that it reaches to the desired site of action, which is greatly influenced by the types of dosage form of the drug. There are various types of dosage forms available which are used in accord with a particular reason; as on the basis of characteristics and advantage.

Many factors specify the characteristics of an ideal dosage form. Ideal Dosage Form should be:

- Easy and safe to administer
- Easy to handle

- Easy to reproduce and manufacture
- High patient compliance
- Efficacious
- Physically and chemically stable
- Biocompatible
- Economical to the patient
- Maintain its therapeutic activity throughout the shelf life

1.2 The Need for Dosage Forms

Drug substances hardly are ever taken without adding additives, due to difficulty in taking precise amount of dose and the desired therapeutic effect may not be obtained. The drug and excipients are suitably compounded to convert them into various suitable dosage forms such as solution, tablets, capsules, suspensions, emulsions, ointments, paste etc. The selection and processing of excipients are as equally important as the selection of drugs alone as it may alter the therapeutic properties of drug (Figure 1.1). By controlling the organoleptic properties using suitable additives such as colours, flavors etc. patient acceptability can be enhanced Dosage form provides desired therapeutic level of a drug.

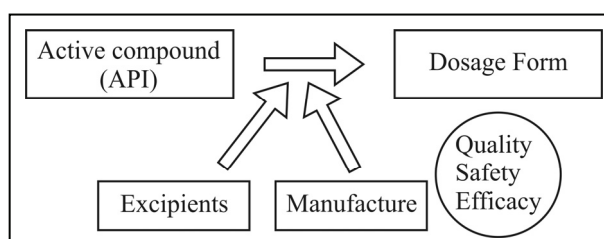


FIGURE 1.1 Flow chart of need for dosage form.

For a potent and low dose drug it could be difficult for the patients to take appropriate and exact dose of a drug from the bulk material. Most drug substances available for use are administered in milligram and micrograms, which are too small to weigh.

It is impossible for a patient to obtain exact amount from a bulk supply (100 mg) of Diclofenac sodium. How could one weigh Levothyroxine with dose 0.1 mg. When the dose of a drug is small, it will lead to patient inconvenience.

TABLE 1.1

Dose of some drugs

Drug	Usual dose (mg)	Category
Ethinyl estradiol	0.05	Estrogen
Levothyroxin	0.10	Antiulcerative
Digoxin	0.25	Cardiotonic
Nitroglycerine	0.40	Antianginal
Alprazolam	0.50	Antianxiety
Clonazepam	1.00	Anticonvulsant
Aripiprazole	2	Antipsychotic
Estropiate	1.25	Estrogen
Risperidone	2.00	Antipsychotic
Prazosine HCL	2.00	Antihypertensive
Lisinopril	5	Antihypertensive
Chlorpheniramine maleate	4	Antihistaminic
Naltraxone	4.5	Multiple sclerosis
Enalapril Maleate	5	Antihypertensive
Omeprazol	10	Antiulcerative
Nifedapine	10	Vasodilator

When the dose of the drug is less as is with so many drugs (Table 1.1), a suitable dosage form such as tablets or capsules should be prepared by adding bulking agents (diluents) to make dosage form sufficient enough to handle properly. The overall objective of dosage form design is to increase the stability of the drug substance to extend its shelf life, ensure accurate dosing and to deliver the drug in a suitable form.

1.3 Primary Reasons for Designing a Dosage Form

A. Protection

1. To protect the drug from the external environmental conditions such as, atmospheric oxygen, temperature and humidity (coated tablets, capsules, ampoules)
2. To prevent degradation of acid labile drug from gastric acid in the stomach (Enteric-coated)

B. Improve Therapeutic Activity

1. To provide optimal drug action to the appropriate site (ointments, creams, transdermal patches)
2. Placement of drugs directly in the body's orifices (rectal, vaginal suppositories)
3. To provide optimal drug action in the bloodstream or body tissues (injections, inhalants, inhalation aerosols)
4. To provide rate controlled drug action (prolonged release delivery)
5. To improve bioavailability of drug with narrow absorption window (gastroretentive delivery)

C. Patient Compliance

1. Accuracy of dose by providing unit dose (tablets, capsules)
2. Reduction in frequency of dosing (sustained and prolonged release delivery)
3. Masking the bitter and unpleasant taste or odour of the drug. (Film coated tablets, Capsules, suspension, emulsion)
4. Placement of drugs within body tissues and cavities (otic, rectal, vaginal, buccal, sublingual)
5. Ease of handling and administration (chewable tablets)

1.4 Types of Dosage Form

Depending on the physical form, and route of administration, dosage forms can be classified as shown in Table 1.2.

A. On the basis of Physical Form**1. Solid dosage form**

E.g. conventional and modified release tablets, powders, capsules, films, lozenges, chewing gum, pellets.

2. Liquid dosage form

E.g. solution, syrup, elixir, spirit, aromatic water, tincture, injections, mouth washes gargles, suspension, emulsion.

3. Semisolid dosage form

Semisolid dosage form used for the application to the skin and mucous membrane (otic, nasal, vaginal, or rectal). *E.g.* ointment, cream, gel, liniment, lotions, and pastes.

4. Gaseous dosage form

Combination of an active ingredient with propellant which upon actuation emits a fine dispersion of liquid and/or solid materials in a gaseous medium *E.g.* aerosol, inhaler, nebulizer.

B. On the basis of Route of Administration**1. Oral-through oral route**

- Powder
- Tablet-buccal, sub lingual, or orally disintegrating, modified release.
- Capsule-Hard gelatin and soft gels
- Liquids–Monophasic and Biphasic

2. Topical-applied over the skin surface and mucosa

- Cream, gel, liniment or balm, lotion, or ointment, etc.
- Ear drops (otic)
- Eye drops (ophthalmic)
- Skin patch (transdermal)
- Vaginal rings

3. Parenteral-applied through the skin

- Intradermal (ID) Injection in the dermal region
- Intramuscular (IM) injection directly into a muscle
- Intraosseous (IO) injection directly into the marrow of a bone
- Intravenous (IV) is the infusion or injection of liquid drug directly into a vein
- Subcutaneous (SC) is the administration as a bolus into the subcutaneous layer
- Intrathecal (IT) Injection into the spinal column

4. Inhalational

- Instilled through the nasal and pulmonary route
E.g. aerosol, inhale, nebulizer

5. Instilled in the body cavities

Suppository, douche, pessary etc.,

- Rectal
- Vaginal

TABLE 1.2

Dosage forms with their merits and demerits

Types of dosage form	Merits	Demerits
Solid dosage forms:	1. Dose accuracy 2. Stability of the drug	1. Not suitable for unconscious patient
Tablets, Capsules, Lozenges, Chewing gum, Pellets, Films	2. Portability 3. Uniformity of dose 4. Reproducibility 5. High Mechanical strength 6. Tamper resistance 6. Masking of taste, odour 7. Easy to pack, handling and transportation	2. Patient non compliance due to difficulty in swallowing (Dysphasia) 2. Formulation complications 3. Not preferable for acid labile and stomach irritant drugs.
Liquid dosage forms		
Monophasic:	1. Easy to swallow 2. Easy to manufacture	1. Non uniformity of dose. 2. Prone to microbial attack 3. Bulky
Solutions, Elixir, Syrups,	3. Fast absorption 4. Improves bioavailability	4. More chances of loss by the breakage during shipping and transportation
Biphasic:	5. Less processing steps 6. Less excipients required as compared to tablets	5. Unsuitable for unpleasant taste and obnoxious odour drugs 6. Less stability
Suspensions, Emulsions		
Semisolid dosage forms:	1. Easy to use. 2. More stable than liquid dosage form. 3. Avoidance of first pass metabolism 4. Local action of drug on affected area 5. Patient convenience (easy to apply and remove)	1. Difficult to handle. 2. Chances of contamination (Application with finger) 3. More prone to environment effect. 4. May cause staining and irritation.
Cream, Gel, Liniment , Lotion, or Ointment, etc		
Gaseous dosage form	1. Easy to handle and convenient 2. Withdrawal of dose without Contamination 3. Environmental protection of unstable drug 4. Provides medication to local area 5. Dose adjustment possible (metered valves) 6. Tamper proof	1. Expensive 2. May create environmental Hazards 3. Dosing not reproducible 4. Non Reliable performance 5. Limited safety.

1.5 General Considerations in Dosage Form Design

- Preformulation studies
- Drug and Drug Product Stability

For rational design of the dosage forms, preformulation is an important development step used to characterize the properties of drug substance and also to understand the challenges that a particular compound may possess during the formulation. It helps to optimize both the preclinical and clinical development with fast and high quality delivery of drug product in the proper dosage forms.

1.5.1 Preformulation Concept

After drug discovery, with a knowledge based on physical, chemical and biopharmaceutical properties of the drug molecule, the foremost aim of pharmaceutical scientist is to formulate drug in the suitable form which improves patient compliance and that is apt for easy administration. All the activities carried out at and before formulation stage of dosage form, are collectively called as pre-formulation studies. It helps to understand the concept of formulation development on a scientific basis. It is a requisite to characterize physical and chemical properties of drug before the formulation and development into a dosage form.

Preformulation testing includes all studies performed on a newly identified drug substance in order to produce a stable and therapeutically effective drug dosage form. Thus, initial learning phase related to drug is known as pre-formulation. This information provides an outline for the drugs combination with additives in the manufacturing of a robust dosage form.

The consideration of the physical, chemical, and biological characteristics of drug substance and excipients to be used in formulating the dosage form is utmost necessary for the appropriate design and formulation of the dosage form. Preformulation also involves the application of pharmacokinetic and biopharmaceutical principles to the physicochemical properties of drug substance with the aim of designing most favourable drug delivery (safe, effective, and stable) system. Preformulation is the border line between development of new drug substances and formulation development. It helps to endow road map for full formulation and development.

Before beginning the proper pre-formulation studies, it is important to glance into the following factors:

- Innovative molecule or abbreviated
- Therapeutic category of drug compound
- Amount of drug substance available
- Physicochemical properties of the drug
- Physicochemical properties of excipient and possible interaction with drug
- Therapeutic dose/potency of a compound
- The category of dosage form to be prepared
- Stability parameters

1.5.2 Goal of Preformulation

A comprehensive understanding of the properties of the newly synthesized drug substance helps to minimize problems related to the later stages of formulation and development; reduces the overall cost of formulation and development, and curtail the time required for complete development of drug product.

The goals of preformulation studies are:

1. Selection of correct form of the drug substance (solid, liquid, gas) based on a type of dosage form development
2. Evaluation of physical and chemical properties of drug substance
3. To understand biopharmaceutical properties of drug
4. To reduce drug development time and cost
5. To produce safe, effective and reproducible drug delivery system

Three factors drive the preformulation studies:

1. Regulatory requirements,
2. Commercial requirements and
3. Technological development

1.5.3 Significance of Preformulation Study

It is a process of designing the drug delivery thorough determination of physical, and chemical properties of newly synthesized drug molecule and it provide useful information for subsequent formulation of a

physicochemically stable and biopharmaceutically suitable dosage form. Preformulation study helps to:

- Establish the new drug molecule's identity
- Characterize physicochemical properties of new drug molecule.
- Determine drug and excipients compatibility
- Correlate pharmacokinetics and biopharmaceutical properties.
- Establish kinetic rate profile of new drug
- Optimize preclinical and clinical process
- Provide necessary data for development of analytical methods
- Produce safe, innovative, stable cost effective dosage form.

Data from preformulation studies minimizes problems in various phases of drug development and provides critical foundation for the successful formulation effort and thus reducing the overall cost of development of product

Preformulation factors include physical properties such as particle size, crystalline structure, melting point, solubility, partition coefficient, dissolution, membrane permeability, dissociation constants, and drug stability. For successful development of any formulation various factors need to be considered such as the type of drug and excipients, compatibility, storage condition selection of containers, packaging, stability and patient compliance such as, considerations of organoleptic properties i.e., taste, appearance, odour and palatability.

These preformulation investigations provide a rationale for the design of proper formulation and support the need for the drugs modification (salts formation, prodrug, and chemical modification) for the effective and reproducible product development with maximum bioavailability. Alterations in drug substance are carried out for improvements of certain pharmaceutical properties as shown in Table 1.3.

TABLE 1.3

Improvement of pharmaceutical properties

Pharmaceutical properties	Examples
Solubility enhancement	Doxycycline, Erythromycin
Stability	Cephalexin, Theophylline
Prolonged action	Heptominol, Alkylbiguanide
Reduce toxicity	Bephenium, Kanamycin
Improve organoleptic properties	Vincamine, Propoxyphene
Activity enhancement	Tetracycline, Propoxyphene
Absorption	Aspirin, Ampicillin

Salt form modification is restricted to ionisable molecules. Alternately, for molecular drug prodrugs may be formed. Prodrugs are synthetic derivatives of drug molecules which liberate parent molecules *in vivo* after some modification. Erythromycin is a bitter taste drug and is hydrolyzed in gastric acid. This problem can be solved by preparing a prodrug of parent molecules, Erythromycin estolate.

1.5.4 Preformulation Types

Preformulation can be broadly classified into two classes as depicted in Table 1.4.

Fundamental Properties: Properties which are dependent on the chemical structure and surface morphology of the drug molecule which include:

- (a) **Solubility:** Solubility parameters in different solvents, pH solubility profile, dissociation constant (pK_a) of drug, salt formation, partition or distribution coefficient ($\log P$ or $\log D$), and dissolution kinetics
- (b) **Permeability**
- (c) **Solid state properties:** solid form, polymorphism, solvated forms and amorphous form
- (d) **Stability:** Solid state and solution state stability, inherent stability, pH stability profile and photo stability

Derived Properties: These properties are derived from the fundamental properties which include:

- (a) Characterization of particle properties like morphology, particle size and shape
- (b) Bulk density, tap density
- (c) Flow properties
- (d) Compaction behaviour: Hausner ratio and Carr's Index
- (e) Drug-excipient compatibility

TABLE 1.4

Preformulation drug characterization properties

Fundamental properties	Derived properties
Samples assay by UV spectroscopy	Particle size and size distribution-Microscopy
Solubility - Aqueous, pKa, Salt, Solvents, Partition coefficient, Dissolution	Bulk density
Melting point	Flow properties
Assay development	Compression properties
Stability in solution and solid state	Drug- excipient compatibility

Bulk characterization

- (a) Physical description: Particle size and surface characterization
- (b) Crystal properties and polymorphism
- (c) Hygroscopicity
- (d) Purity: Melting point depression
- (e) Flowability

Solubility analysis

- (a) Solubility
- (b) Ionization constant (pK_a)
- (c) Partition coefficient
- (d) Dissolution
- (e) Common ion effect

Stability analysis

- (a) Solid state
- (b) Solution state
- (c) Compatibility

1.5.4.1 Bulk Characterization

During the process development, bulk properties of the drug substance such as particle size, crystallinity, powder flow, compaction case, melting point and other physical characteristics influence the final dosage form during the preformulation stage.

- (a) **Physical Description: Particle Size and Surface Characterization:** Bulk properties of the formulation differ from pure drug. But these properties do not change for solid form of drug. Each new drug candidate has to be tested for particle size and shape during preformulation study as with the smaller particle size it is impractical to make possible uniform and homogenous formulation. Various physicochemical and bio-pharmaceutical properties of drug substances are affected by their particle size distribution and shapes.

The particle size and size distribution characteristics of the drug have a large impact on its rate of delivery in the body. As a part of the drug validation process the regulatory agencies have a stringent requirement for determining the chemical and physical characteristics of drug particles.

Surface characteristics of a drug play a fundamental role in determining both bulk powder and suspension properties. The most important physical property of particulate samples is particle size and shape as they have a direct influence on material properties such as, dissolution rate. (Tablets), stability (Suspension), efficacy of delivery (Aerosols), appearance, packing, density and porosity (powder), texture feel (topical), flowability, handling (granules), and viscosity (semisolids).

The particle size and distribution of drug substance and excipients have significant and potential effects on the quality of the final dosage form, like product colour, appearance, mixing, flowability, solubility, dissolution, bioavailability, stability, content uniformity, compressibility, drying, packaging and quality control. Particle size and distribution analysis of a sample can be performed using a variety of techniques, both qualitative and quantitative.

There are many different methods available for particle size analysis such as:

- Sieving
- Sedimentation
- Optical microscopy
- Electron microscopy
- Coulter counter
- Laser diffractometers.

Microscopy and sedimentation are the simplest technique of determining size distribution and shapes, but shortcoming include being

slow and tedious for quantitative determination. Sieving is less practical technique due to lack of bulk material at preformulation stage. Coulter counter and Laser diffractometers techniques are becoming more popular due to advantages such as, rapid counting, flexibility, reliability and used for the wide range of sizes.

Surface morphology may be determined by scanning electron microscopy (SEM) technique, atomic force microscopy (AFM) and Scanning tunneling microscopy (STM) which precisely gives qualitatively determination of shape and surface area of particles. SEM uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimen. It is technique where only few milligram quantity of material is used to determine particle size, shape and texture, but having disadvantage that it unable to characterizing finer particles and agglomerates. AFM has several advantages over the SEM. Unlike the electron microscope which provides a two-dimensional image of a sample, the AFM provides a three-dimensional surface profile. In a very short time this technique is helpful to collect significant data on the size and morphology of the particles.

Laser diffraction spectroscopy, is a technique that utilizes diffraction patterns of a laser beam passed through any object to measure geometrical dimensions of the particle. The techniques are based on the diffraction theory, which states that the intensity of light scattered by a particle is directly proportional to the particle size. The various techniques used to estimate particle size with their ability of determining the size range is depicted in the Table 1.5.

TABLE 1.5

Particle size techniques and size range

Method	Size range (μ)
Sieving (woven wire)	20–125,000
optical Microscopy	0.5–150
electron Microscopy	0.001–5
Sedimentation	0.1–50
Coulter counter	1–200
Laser diffractometers	0.001–1

- ***Surface Area Determination***

Surface area is most commonly determined by gas adsorption method based on Brunauer, Emmett and Teller (BET) theory of nitrogen adsorption. Most substances adsorb a mono molecular layer of gas under certain conditions of partial pressure of gas and temperature. Knowing the monolayer capacity of adsorbent and the area of absorbable molecule, the surface area can be calculated.

- (b) **Crystal Properties and Polymorphism:** Polymorphism is the property of a solid material to exist in two or more different molecular arrangements or crystalline structures of the same chemical compound. A polymorph is a solid material with two or more different molecular arrangements giving distinct crystal species. Solid drug materials generally occur as amorphous and crystalline. Stability and pharmacological activity of drug substance greatly depends on its amorphous or crystalline nature. Amorphous drugs have randomly arranged atoms or molecules. They have higher thermodynamic energy, solubility and dissolution rate than corresponding crystalline form. But, during the various stages of processing and storage, they tend to change to more stable form. Crystals are characterized by repetitious arrangements of the constituent atoms in a regular three dimensional structure. Crystalline forms of drugs may be more preferable than the corresponding amorphous form because of greater stability. For example, sodium salt of crystalline forms of Penicillin G is more stable and has better therapeutic activity than corresponding amorphous forms.

Crystal habit and the internal structure of a drug is found to affect various properties such as, flowability, solubility, dissolution and stability. Habit is the description of the outer appearance of a crystal whereas the internal structure is the molecular arrangement within the solid. A single internal structure for a compound may have several different habits, depending on the environment of crystal growth.

Many drug substances which exist in more than one crystalline form with different space lattice arrangements are known as polymorphs and generally have different morphology, solubility, dissolution, tensile strength, density and melting points.

Polymorphism may be of two types

Enantiotropic: One polymorph reversibly changes into another form by a change in temperature and pressure, *e.g.*, Sulphur.

Monotropic: One polymorphic form is unstable at all temperatures and pressures *e.g.*, glyceryl stearates.

A drug substance may exist in two or more polymorphic forms but, only one form is found to be thermodynamically stable at a given temperature and pressure. The other forms would convert to the stable form with the progress of time. The stable polymorph exhibits the highest melting point, the lowest solubility, and the maximum chemical stability.

Chloramphenicol exists in three polymorphic forms A, B and C, in which B form is found to be most stable.

Parameters to be considered during polymorphism study are: number and type of polymorphs, solubility parameters, degree of stability, stability of metastable form, temperature stability range, effect of processing conditions like drying, milling, micronization etc.,

Crystalline Nature and Polymorphism can be Measured by

Various Methods used to study crystalline nature and polymorphism, such as, microscopy, Fourier Transform Infrared Spectrometer (FT-IR), Differential scanning calorimeter (DSC), X-ray powder diffraction (XRD), thermal analysis, and dilatometry. Investigation of polymorphism and crystal habit of a drug substance during preformulation is essential as it relates greatly to the pharmaceutical processing.

Infrared Spectrophotometry

Infrared spectroscopy deals with the infrared region (longer wavelength and lower frequency than visible light) of the electro magnetic spectrum. Infrared Spectroscopy is the analysis of infrared light interacting with a molecule and can be analyzed by measuring absorption, emission and reflection. When IR radiation is passed through a sample, some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). Absorption occurs when the frequency of the IR is the same as the vibrational frequency of a bond. The resulting spectrum represents the molecular absorption and transmission, creating a molecular finger print of the sample. This can be achieved by scanning the wavelength range using a monochromator. Alternatively, the whole wavelength range is measured at once using a Fourier transform instrument and then a transmittance or absorbance spectrum is generated. Analysis of the position, shape and intensity of peaks in this spectrum reveals details about the molecular structure of the sample and can be used to identify and study crystallinity of drugs. Fourier transform infrared spectrometers (FTIR) have found to be of more superior speed and sensitivity than dispersive instruments.

Differential Scanning Calorimetry (DSC) and Differential Thermal Analysis (DTA)

DSC and DTA measures the temperature difference between the sample and a reference as a function of temperature or time when heating at a constant rate. DSC is similar to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference i.e., it measures the enthalpy of transition. Depending on

the type of change within the sample, the thermal event may be endothermic or exothermic.

Hot Stage Microscopy (HSM)

Drug crystals show various changes during heating that can be examined under a microscope. Properties which are analyzed under a microscope include melting point, range of melting, crystal nucleation, crystal growth and crystal transformations. HSM allows the observation of physical appearance and characterization of small quantities of drug substance. This technique is simple and economical as it comprises of a heating stage with a sample holder and gaseous atmosphere control coupled with a suitable polarized-light microscope and a system that allows the capturing and measurements of observations and temperatures.

X-Ray Powder Diffraction (XRD)

X-ray powder diffraction (XRD) is one of the most potential tool and a non-destructive technique for characterizing the qualitative and quantitative analysis of different solid state forms. When X-ray light reflects on any crystal, it leads the formation of many diffraction patterns which reflect the physicochemical characteristics of the crystal structures. Powder X Ray Diffraction (PXRD) a widely used tool for both the analogous to light passing through a prism, as crystals are rotated through an X-ray beam, the beam is diffracted at characteristic angles. PXRD has numerous advantages like non-destructive nature, high sensitivity, reliability, easy sample preparation, convenient, low maintenance cost and easy data interpretation PXRD is helpful in identification and characterization of crystal morphology and polymorphism.

- (c) **Hygroscopicity:** Like many other substances, water soluble salt form of drugs has a tendency to absorb atmospheric moisture. Such types of materials can be classified as:

Hygroscopic material is which has a tendency to absorb moisture and get in equilibrium with water in the atmosphere.

Deliquescent substance is which partially or wholly liquefies after absorbing moisture from atmosphere.

Efflorescent substance is which has a tendency to loose water and becomes anhydrous.

Importance of hygroscopicity in preformulation

High susceptibility for moisture absorption leads to various processing related problems such as poor flow, weight variation, cracking, picking,

sticking, handling problem, particle agglomeration and stability related problems such as, chemical breakdown, cake formation and colour change on storage.

Hygroscopicity can be measured by

1. ***Dynamic vapour sorption method:*** It is a gravimetric technique that measures the amount of a solvent which is absorbed by powder.
2. ***Isothermal microcalorimetry:*** This method is used for the determination of the critical relative humidity.

(d) ***Purity: Melting Point Depression:*** The melting point of a solid is the temperature at which the material changes from a solid to a liquid state i.e. solid in equilibrium with liquid state under an external pressure of one atmosphere. This physical property plays a vital role in preformulation phase to identify and characterize a drug substance.

Melting point can be measured by

The melting point of a drug can be measured using three techniques such as, capillary melting, hot stage microscopy and differential scanning calorimetric or thermal analysis.

Capillary melting: Drug substance is placed in a thin walled capillary tube closed at one end and heated slowly and evenly. The temperature at which the sample is observed to melt is taken as the melting point. Capillary melting gives information about the melting range.

Hot Stage Microcopy: Also known as Thermal microscopy where melting process is observed with the help of a microscope equipped with a heated and wrapped sample stage. It enables to study and characterize material physically as a function of temperature and time.

Differential Scanning Calorimetric and Differential Thermal Analysis

Differential scanning calorimetry (DSC) is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment.

Differential thermal analysis (DTA) measures the temperature difference between the sample and a reference as a function of

temperature or time when heating at a constant rate. In this technique it is the heat flow to the sample and reference that remains the same rather than the temperature.

Powder Flow Properties: Powder flow determination is crucial for the pharmaceutical manufacturing process. Powders are classified as free flowing or cohesive. Flow properties of the powder affected by a small variation on particle size, shape, density electro static charge and moisture level which ultimately affect the processing parameters. A powder flow investigation helps to assess an improvement in various stages of the formulation developments.

There are various methods available to measure the powder flow, which, include measurement of angle of repose, bulk density, tapped density, Carr's compressibility index and Hausner ratio.

- **Angle of Repose**

It is most important tool for estimation of flow property of powder. Determination is done by "fixed height funnel method" The angle of repose is the maximum angle which is formed between the horizontal base of the surface and the pile of the powder.

The angle of repose (θ) was calculated as follows:

$$\tan \theta = \frac{h}{r}$$

where, h = height of the pile

r = radius of base of pile

- **Carr's Compressibility Index and Hausner Ratio**

Carr's compressibility index (CI) and Hausner ratio (HR) are determine by calculating bulk and tapped densities to provide a measure of the flow properties and compressibility of powders.

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 1.6 depicts the relationship between angle of repose, Carr's index and Hausner's ratio on the flow property of the power.

TABLE 1.6

Flowability scale

Flow	Angle of repose	Carr's index (%)	Hausner ratio
Excellent	25-30	5-10	1.0-1.11
Good	31-35	11-15	1.12-1.18
Fair to passable	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	>56	>32	> 1.46

Recently powder rheometers are also used to measure powder flow. Powder flow properties can be determined by measurements of bulk density and angle of repose.

1.5.4.2 Solubility Analysis

Solubility can be defined as the molarity of the substance in a solution that is in chemical equilibrium with an excess of the undissolved substance. The solubility is an important physicochemical property as it affects the dissolution parameters, rate of drug release, bioavailability of the drug and ultimately therapeutic efficiency. An important goal of the preformulation is to develop a method for making drug in its solution form. The solubility of the molecules in various solvents is determined as a first step. Solubility is usually determined in variety of commonly used solvents and some oils, if they are lipophilic. Solvents commonly used for solubility determination are water, buffers at various pH, methanol, isopropyl alcohol, ethyl alcohol, benzyl alcohol, castor oil, peanut oil, sesame oil. For therapeutic efficacy a drug must possess aqueous solubility in physiological pH range of 1 to 8 at 37 °C. Poor solubility of drug substance results in bioavailability problems.

- (a) **Intrinsic Solubility:** It is the equilibrium solubility of the free acid or free base form of an ionisable compound at a pH where it is fully unionized. The increase in solubility of weakly basic/acidic drug in respective solution is due to intrinsic solubility. An increase in solubility in acidic aqueous solution compared to that in pure water, suggests weak base. An increase in solubility in alkaline solutions suggests weakly acid drug. The solubility of weakly acidic and basic drug as a function of pH can be predicted with the help of equation.

$$S = S_0 \{1 + (K_1 / [H^+])\} \quad \text{for weak acids}$$

$$S = S_0 \{1 + ([H^+] / K_2)\} \quad \text{for weak bases}$$

where, S = Solubility at given pH

S_0 = Solubility of the unionized form

K_1 = Acid Dissociation constant

K_2 = Dissociation constant of conjugated acid

Methods to determine solubility

1. Equilibrium solubility method.
2. Turbidometric solubility method.
3. Nephelometric solubility method.
4. Ultrafiltration LC/MS solubility method.
5. Direct solubility method.

- (b) **Ionization Constant (pK_a):** When we administer either a weakly basic or acidic drug, it will undergo ionization in GI fluids. Determination of the dissociation constant for a drug capable of ionization within a pH range of 1 to 10 is important since solubility and consequently absorption, can be altered by orders of magnitude with changing pH. The relative conc. of unionized & ionized form of weakly acidic or basic drug in a solution at a given pH can be calculated using the Henderson-Hassel batch equation:-

$$pH = pK_a + \log [\text{unionized form}] / [\text{ionized form}] \quad \text{for weak bases}$$

$$pH = pK_a + \log [\text{ionized form}] / [\text{unionized form}] \quad \text{for weak acids}$$

The unionized forms are more lipid soluble & more rapidly absorbed from GIT.

Methods to determine pK_a

1. Potentiometric method.
2. Conductivity method.
3. Dissolution rate method.
4. Liquid-Liquid partition method.
5. Spectrophotometric method.

- (c) **Partition Coefficient:** Partition Coefficient (oil/water) ($P_{o/w}$) is a measure of a drug's lipophilicity and is an indication of its ability to cross cell membranes. It is defined as the ratio of a unionized

drug distributed between the organic and aqueous phases at equilibrium.

$$P_{o/w} = (C_{oil} / C_{water}) \text{ equilibrium}$$

C_{oil} – Concentration of oil

C_{water} – Concentration of water

The gastrointestinal membranes are primarily lipoidal in character hence the lipid solubility of a drug is an important factor in the assessment for its absorption. Partition coefficient provides a means of characterizing the lipophilic and hydrophilic nature of the drug which affects the rate and extent of drug absorption. Since biological membranes are lipoidal in nature. The rate of drug transfer for passively absorbed drugs is directly related to the lipophilicity of the molecule. The partition coefficient is commonly determined using an oil phase of octanol or chloroform in water.

Methods to determine partition coefficient

1. Shake Flask Method.
2. Chromatographic Method (TLC, HPLC).
3. Counter Current & Filter Probe method.

Applications of partition coefficient

- Measure of lipophilic/ hydrophilic character of molecules.
- Recovery of antibiotics from fermentation broth.
- Extraction of drug from biological fluid for therapeutic monitoring.
- Absorption of drug from dosage forms. (Ointments, Suppositories and Transdermal patches).
- Study of distribution of flavoring oil between oil & water in emulsion.

(d) ***Dissolution study:*** In many instances dissolution rate or the time, it takes for the drug to dissolve in the fluid at the absorption site is the rate limiting step in the absorption process (drugs administered orally in solid forms such as tablets, capsules, or suspensions, and for those administered intramuscularly). Chemical form, crystal habit, particle size, surface area, wetting and solubility are the properties that widely influence the dissolution of the drug. Dissolution rate of drug can effect onset and intensity of action and control the overall bioavailability of drug form.

Dissolution rate of the drug substance as represented by modified Noyes-Whitney equation is given as follows (where surface area remains constant during disintegration).

$$\frac{dC}{dt} = \frac{DA}{hV}(C_s - C)$$

where, D = diffusion coefficient in the dissolution medium

h = thickness

A = surface area

V = volume

C_s = concentration of the drug in saturated solution

C = concentration at particular time t

Method to determine dissolution

- 1. Rotating disk method:** This method allows for the determination of dissolution from constant surface area, obtained by compressing powder into a disc of known area with a die-punch apparatus.
 - 2. Particulate dissolution:** This method determines the dissolution of solids at different surface area. A weighed amount of powder sample from a particular sieve fraction is introduced in the dissolution medium. A constant speed propeller usually provides agitation. It is used to study the influence on dissolution of particle size, surface area & mixing with excipients.
- (e) **Common Ion Effect:** A common ion significantly reduces, the solubility of a slightly soluble electrolyte. The “salting out” results from the removal of water molecules as solvent due to the competing hydration of other ions. So weakly basic drug which are given as HCl salts have decreased solubility in acidic solution. Eg. Chlortetracycline, Papaverine, Bromhexine, Triamterene, etc. The reverse process “salting in” arises with larger anions. (E.g. Benzoate, Salicylate) which can open the water structure. These hydrotropes increase the solubility of poorly water soluble compounds.

Methods to determine common ion effect

To identify a common ion interaction the IDR (Intrinsic dissolution rate) of HCl salt should be compared between

1. Water & water containing 1.2% W/V NaCl.
2. 0.05 M HCl & 0.9% NaCl in 0.05 M HCl.

Both saline media contains 0.2 M Cl^- which is typically encountered in fluids *in vivo*.

1.5.4.3 Stability Studies

Stability is defined as the extent to which a drug product maintains same properties and attribute within specified limits and throughout its shelf life which it possess at the time of manufacturing. Every drug substance possesses inherent stability, a critical factor in preformulation studies and plays a pivotal role in the development of the drug product. Various processing stages such as milling, drying, compression, storage condition, and gastrointestinal condition, influence the stability of a drug substance.

The first qualitative assessment in preformulation stability studies is chemical stability of a new drug, which includes both solid and solution state stability carried out under various condition for the administration, handling, compounding, storage and stability in presence of additives. Factors which influence chemical stability in development of dosage form design include temperature, pH and dosage form. A typical preformulation practice involves evaluating physical, chemical and compatibility stability. Stability studies help to select processing conditions, environmental condition and packaging system. Instability of drug may lead to undesired change in physical appearance, solubility, dissolution and ultimately bioavailability. Chemical degradation of drug may lead to a substantial loss of potency or formation of degraded product which may be unsafe or toxic.

- (a) **Solid State Stability:** Solid state degradation studies are more difficult to interpret as they do not follow Arrhenius kinetics outside a narrow range. Solid **instability** basically results from hydrolysis, oxidation, photolysis and pyrolysis depending on the chemical structure of drug substances. Esters, lactases and amides are prone to solvolysis. Amorphous materials are less stable than their crystalline forms. Solid state stability generally comprises effect of temperature, humidity conditions, light and oxygen. Degradation products may result in adverse events or be unsafe. Instability may cause-Undesired change in performance i.e., change in dissolution/bio-availability, substantial changes in physical appearance of the dosage form causing product failures.

- (b) ***Solution Phase Stability:*** Solution state stability is a critical part of the drug development process. The rate of degradation is much rapid in solution form when compared to the dry solids. Major source of the solvent for the degradation are, the residual moisture content from wet granulation, excipients (starch, lactose) inherent moisture, moisture migrates from the capsule shell and drug/ingredient which has a low melting point. A solvate or hydrate loses its lattice solvent due to time and temperature variation. Stability studies of solution phase provides essential information for the development of efficacious product, helps in dosage form selection, in designing of dosage form and analytical method development.

Factors affecting drug stability

pH: pH stability studies both in solution state and solid state, are performed to understand the behavior of drug substance with vehicles and in gastrointestinal environment. The acidity or the alkalinity of a solution influence the decomposition of most of the drug. Aspirin buffered solution, decomposes maximum above 10 pH and was found to be stable at pH 2.4. pH can also influence the rate of oxidation. pH decomposition profile of a drug is important in pre-formulation study to formulate the solution at a pH which is physiologically effective and stable.

Elevated temperature studies: High temperature accelerates various reactions such as, oxidation, reduction and hydrolysis which lead to drug degradation. The elevated temperatures commonly used are 40, 50, and 60°C with ambient humidity. The samples stored at highest temperature are observed weekly for physical and chemical changes and compared to an appropriate control. If a substantial change is seen, samples stored at lower temperature are examined. If no changes are seen after 30 days at 60 degrees centigrade, the stability prognosis is excellent. All the drug products are stored at suitable temperatures to avoid thermal acceleration of decomposition.

Stability under high humidity conditions: Water catalyses chemical reactions such as oxidation, hydrolysis and reduction reaction. Water promotes microbial growth. Solid drug samples can be exposed to different relative humidity conditions by keeping them in laboratory desiccators containing saturated solutions of various salts. The closed desiccators inturn are kept in oven to provide constant temperature. The pre-formulation data of this nature are useful in determining if the

material should be protected and stored in controlled low humidity environment or if non aqueous solvent be used during formulation. Packing materials are chosen (usually glass and plastic) to prevent exposure of drug products to high humid condition.

The most common routes for the degradation of drugs are solvolysis, hydrolysis, photolysis, oxidation and racemization.

Photolytic stability: Light especially ultraviolet light enhances photolysis and humidity enhances hydrolytic decomposition. Photolysis affects drug stability through its energy or thermal effect which lead to oxidation. Many drugs fade or change their colour on exposure to light. Though the extent of degradations is small and limited to the exposed surface area, it presents aesthetic problem. Exposure of drug to 400 and 900 foot-candles of illumination for 4 and 2 week periods respectively is adequate to provide some idea on photosensitivity. Resulting data may be useful in determining if an amber coloured container is required or if colour masking dye should be used in the formulation. All the drug products are stored at suitable temperatures to avoid thermal acceleration of decomposition. Light sensitive materials are stored in amber coloured bottles.

Stability upon oxidation: Drug's sensitivity to oxidation can be examined by exposing it to atmosphere of high oxygen tension. Usually a 40% oxygen atmosphere allows for rapid evaluation. Samples are kept in desiccators equipped with three-way stop cocks, which are alternatively evacuated and flooded with desired atmosphere. The process is repeated 3 or 4 times to ensure 100% desired atmosphere. Results may be useful in predicting if an antioxidant is required in the formulation or if the final product should be packaged under inert atmospheric conditions. Proper packing keeping the oxygen content of the solution less and leaving very little head space in the bottle above the drug products are methods to fight against oxidation.

- (c) **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 5 mg 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 of

one or more peaks in thermograms of drug excipient mixtures are considered as indication of interaction.

1.6 Methods for Characterizing Pharmaceutical Solids

Thermal methods

- Differential Scanning Calorimetry (DSC)
- Thermogravimetric Analysis (TGA)
- Hot stage microscopy

Solubility methods

- Solubility
- Dissolution rate

Diffraction methods

- Single-crystal X-ray diffraction
- Powder X-ray diffraction
- Neutron diffraction

Spectroscopic methods

- Infrared spectroscopy
- Raman spectroscopy
- Solid-state NMR spectroscopy

UV Spectroscopy: The first requirement of any preformulation study is the development of a simple analytical method for quantitative estimation. 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:

$$E = \frac{AF}{X}$$

where, A = Absorbance
F = dilution factor
X = weight of drug (mg)

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

$$C = AF / E \text{ mg / ml}$$