REVIEW ARTICLE

General Considerations of Design and Development of Dosage Forms: Pre-formulation Review

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Abstract

Goal of formulation development is to convert active drug moiety into suitable dosage forms. This can be achieved by investigating of physicochemical properties of a drug substance alone and along with excipients before the formulation. The main objective of pre-formulation testing is to collect the information useful to develop stable, bioavailable dosage forms with safety consideration. Pre-formulation investigations are designed to collect all necessary data, especially physicochemical, physico-mechanical, and biopharmaceutical properties of drug substances, excipients, and packaging materials. This review provides information about pre-formulation parameters such as physical, chemical, solubility, stability, storage, and precaution to be taken for ensure the quality of product.

Key words: Flow properties, Fourier transform infrared spectroscopy, preformulation, solubility, stability

INTRODUCTION

Drug is any chemical entities intended to its therapeutic purpose but it cannot be taken in its pure form, so it is formulated into suitable dosage forms for their safe and compatible administration into the body.

GOAL OF DRUG/DOSAGE FORMS[1]

Following qualities of features are required in drug and dosages form design:

1. Drug would produce specifically desired (therapeutic) effect
2. Be administered by most desired route at minimal dose and dosing frequency
3. Drugs have short onset and optimum duration of activity, without any side effect
4. Would be completely eliminated from the body efficiently without any residual effect
5. Pharmaceutically dosage forms should be elegant, physically, and chemically stable at various conditions of use and storage.

Biopharmaceutical aspects, therapeutic consideration, drug factors (pre-formulation) aspects to be considered for achieving the above goal.[1]

Biopharmaceutical aspects of dosage form design

A route of administration varies with pharmacokinetic parameters of drug, such as, absorption, distribution, metabolism, and elimination (ADME). Drug is administered into body by various routes such as oral, topical, parentral, respiratory (inhalation), rectal, nasal, ear, and eye. According to drug candidate pharmacokinetic profile (ADME) and type of illness (disease condition), route of administration is preferred.

Therapeutic consideration

Nature of clinical indication, disease/illness for that drug is intended is an important factor for selection of dosages form and route of administration. In case of emergency sublingual, an injection is given. In infants: Liquid drops, children's: Liquid dosage forms (e.g., syrup), in geriatric and patients

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suffering from swallowing difficulties chewing tablets is preferred.

Drug factors: Preformulation

Each type of dosages forms requires careful study of the physical and chemical properties of drug substances to achieve stable, efficious product.

PREFORMULATION

For the achieving goals of drug and dosage forms, pre-formulation testing is a first step in the development of dosage forms before the formulation. Preformulation is defined as an investigation of physical and chemical properties of a drug substance alone and along with excipients before the formulation. The main objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms before formulation development. Pre-formulation investigations are designed to deliver all necessary data, especially physicochemical, physico-mechanical, and biopharmaceutical properties of drug substances, excipients, and packaging materials.[2]

PRE-FORMULATION PARAMETERS

Physicochemical characterization

1. Organoleptic properties
2. Bulk characteristics
   a. Assay development
   b. Melting point
   c. Solid state characteristics: Particle size, surface area
   d. Flow properties
   e. Densities
   f. Compressibility
   g. Crystalline and amorphous
   h. Polymorphism
   i. Hygroscopicity.
3. Solubility analysis
   a. Ionization constant (pKa)
   b. Partition coefficient
   c. Dissolution
   d. Solubilization
   e. Thermal effect
   f. Common ion effect (Ksp).
4. Stability analysis
   a. Solid-state stability
   b. Solution-state stability
   c. Drug-excipients compatibility.

Organoleptic properties

This includes appearance, color, odor, and taste of the new drug substances must be recorded using descriptive terminology. It is important to establish a standard terminology to describe these properties to avoid confusion among scientists using different terms to describe the same property.

Bulk characteristics

Assay development

The strength of a drug substance may be its concentration (quantity of the drug per unit measure), its potency, or both. The potency of a drug is a measurable amount of therapeutic active constituents of drug per unit weight or volume of the drug preparation. No relevant physicochemical property can be measured without an assay. Assay development is a first step of preformulation.

Percent purity (assay) of drug is determined using different techniques. In this method, development for particular drug substance is necessary, and this can be developed by ultraviolet (UV) spectrophotometer or for better accuracy high-performance liquid chromatography (HPLC).

Assay development determines the approximate values if these are acceptable to make a "go/no go" decision in respect of a particular drug candidate. The assays that may be used to quantify them and as function of molecular structure.[2] Absorption maxima (λ_{max}) also used to determine purity of drug substance using UV-spectrophotometer.[3]

Melting point

The melting point of a pure solid substance is defined as the temperature at which solid and liquid exist in equilibrium. A melting point or range of a drug can be used as an indicator of purity of drug substances (characterized by very sharp melting peak in differential scanning calorimetry [DSC]). A change in a peak or peaks at different temperature may indicate an adulterated or impure drug. Melting point of a drug substance can be measured using three techniques, (1) capillary melting, (2) hot stage microscopy, and (3) DSC.[2]

Solid state characteristics

Powders are masses of solid particles or granules surrounded by air (or other fluid). Means it is the solid plus fluid combination, which significantly affects the bulk properties of the powder. Physical characteristics of the particles, such as size, shape, angularity, size variability, and hardness will all affect flow properties. External factors affect during handling such as humidity, conveying environment, vibration, and perhaps most importantly aeration will change the properties of solid.

Particle size and size distribution

Particle size distribution and shapes are affected on various chemical and physical properties of drug substances. These changes in properties may affect on their biopharmaceutical behavior. For example, the bioavailability of griseofulvin and phenacetin is directly related to the particle size distributions of these drugs. Size also plays a role in the homogeneity of the final tablet. When ununiform size exists between the active components and excipients, mutual sieving (demixing) effects can occur making thorough mixing difficult or if attained difficult to maintain during the subsequent processing steps.

Washington (1992) has reported the concepts and techniques of particle size analysis.[4] There are many different techniques available for particle size analysis. The techniques most readily available include sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter, and laser diffractometry. Table 1 lists particle size measurement methods commonly used and the corresponding approximate useful size range.[5]

The particle size distribution of a micronized powder determined by scanning electron microscopy and laser light scattering. The Malvern mastersizer is an example of an instrument that measures particle size by laser diffraction. The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced.

Surface areas

The surface areas of drug particles are important because they alter the rate of dissolution (as predicted by the Noyes-Whitney equation).[6,7] Surface area can also be quoted if the particle size is difficult to measure.[8] Surface areas are usually determined by gas adsorption technique (nitrogen or krypton) and Brunauer, Emmet and Teller (method) describes this phenomenon. Singh, 1992 have been reviewed in detail gas adsorption methods for surface area determination.[9]

Table 1: Particle size techniques and size range[5]

Method	Size range (μm)
Sieving (woven wire)	20-125,000
Sieving (electroformed)	5-120
Sieving (perforated plate)	1000-125,000
Microscopy (optical)	0.5-150
Microscopy (electron)	0.001-5
Sedimentation (gravity)	1-50
Sedimentation (centrifugal)	0.01-5
Electrical zone sensing (e.g., Coulter)	1-200
Laser light scattering (Fraunhofer)	1-1000
Laser light scattering (quasi-elastic)	0.001-1

Powder flow properties

For efficient tableting, flow properties of powders are critical. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and uniform weight of the compressed tablets. If a drug is identified at the pre-formulation stage to be "poorly flow" the problem can be solved by selecting appropriate excipients. In some cases, improve flow properties of drug powders by precompression or granulation. Some of these methods used to measure flow properties 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's index.[10,11]

Angle of repose

Maximum angle which is formed between the surface of powder pile and horizontal surface called as angle of repose. For most pharmaceutical powders, the angle of repose values range from 25° to 45°. The angle ≤30° indicate free-flowing material while ≥40° indicate poor flowing material. Angle of repose can be determined using fixed funnel method, fixed cone method, rotating cylinder method, and tilting box method.[12]

$$\tan \theta = (h/r)$$

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

Densities

It may be affect on the floe properties of material and tableting operation. 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 untapped powder that passed through the screen
b. Tapped density: It is obtained by measuring the volume of known mass of powder after tapping the measuring cylinder
c. True density: It actual density of the solid material
d. Granule density: May affect compressibility, tablet porosity, disintegration, dissolution, and settling of particles in diffusible mixtures or suspension.[13,14]

Compressibility

"Compressibility" of a powder can be defined as the ability to reduction in volume under pressure and compatibility as the ability of the powdered material to be compressed into a tablet of specified tensile strength (plastic deformation). It can be used to predict the flow properties of solids based on density measurement.[12]

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

Crystalline

The external shape of a crystal is termed the habit whereas the internal structure is the molecular arrangement within a solid [Figure 1]. Crystal morphology or habit is important since it can influence many properties of the compound. For example, powder flow properties, compaction, and stability have all been found to be dependent on crystal morphology. A single internal structure for compound has several different habits, depending on environment for growing crystal. 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. Crystallanity is determined by X-ray diffraction technology, estimate the degree of crystallanity was based upon the measurement of the total scattering [Figure 2].[12]

Amorphous forms

Amorphous forms mean non-crystalline nature of materials, i.e. they possess no long range order. Their structure can be prepared by rapid precipitation, lyophilization, or rapid cooling (supercooling) of liquid melts and milling and compaction of crystals.[12]

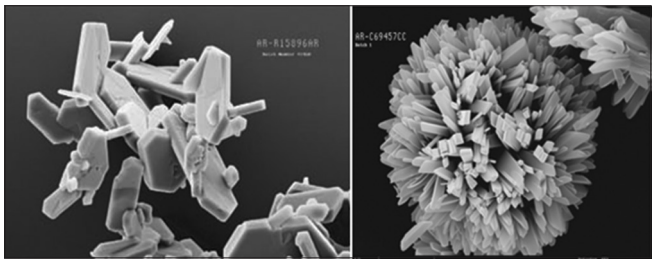

Figure 1: Scanning electron microscope micrographs of some crystal morphologies

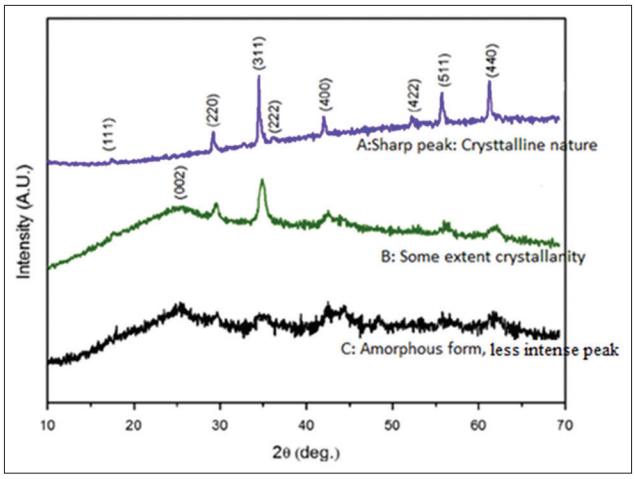

Figure 2: Powder X-ray diffraction spectra of solids

One consequence of a disordered structure is that they are the most energetic form, thermodynamically unstable; therefore, the tendency of amorphous forms is to revert in a more stable form, this is particularly true when the formulation is in an aqueous suspension.[15] Another consequence for some compounds with a low degree of crystalline can be a decrease in chemical stability. Because of these problems with physical and chemical stability, attempts to crystallize the amorphous phase should always be undertaken; however, it should be borne in mind that amorphous phases, if chemically and physically stable, can have some advantages over the crystalline phase. For example, a stabilized amorphous form of novobiocin was found to be 10 times more soluble and therapeutically active compared to the crystalline form.[16]

Polymorphism

Many drug substances can exist in more than one crystalline form with different internal 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.[12,17]

In general, polymorphs of a given compound have different physicochemical properties, such as melting point, solubility and density, so that the occurrence of polymorphism has important formulation, biopharmaceutical, and chemical process implications. In addition to polymorphs, solvates (inclusion of the solvent of crystallization), hydrates (inclusion of water of crystallization), and amorphous forms (where no long-range order exists) may also exist[18] (e.g., polymorphism shown by estrone). Solvates has also termed as pseudopolymorphs.[19,20]

Hygroscopicity

Many pharmaceutical compounds and salts are sensitive to water vapor or moisture. When compounds come in contact 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 drugs candidate and their formulations. Sorption

of water molecules onto a candidate drug (or excipient) can often induce hydrolysis.[21] In this situation, by sorbing onto the drug-excipient mixture, the water molecules may ionize either or both of them and induce a reaction.

Solubility analysis

The solubility of solid is defined as the concentration at which solution phase is equilibrium with a given solid phase at stated temperature and pressure. The solubility of a candidate drug may be the critical factor determining its usefulness, since aqueous solubility dictates the amount of compound that will dissolve; therefore, the amount available for absorption. If a compound has a low aqueous solubility, it may be subject to dissolution rate-limited absorption within the gastrointestinal residence time. Solubility expression given in Table 2.

Recently, the importance of solubility, in biopharmaceutical terms, has been highlighted by its use in the Biopharmaceutical Classification System. In this system, compounds are defined in terms of combinations of their solubility and permeability [Figure 3].[22,23]

- Class I: High solubility, high permeability
- Class II: Low solubility, high permeability
- Class III: High solubility, low permeability
- Class IV: Low solubility, low permeability.

Table 2: Solubility classification

Descriptive term	Parts of solvent (in ml) required for 1 part (per gram) of solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

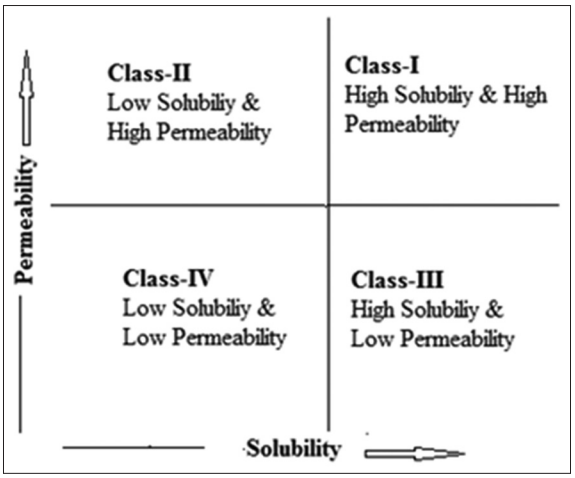

Figure 3: Biopharmaceutical Classification System

High solubility is defined as the highest dose strength that is soluble in 250 ml or less of aqueous media across the physiological pH range. Poorly soluble drugs can be defined as those with an aqueous solubility of <100 g/mL. If a drug is poorly soluble, then it will only slowly dissolve, perhaps leading to incomplete absorption.[22,24]

The importance of solubility (and permeability) in drug discovery and development has been discussed by Lipinski *et al.* 1997.[25] The "rule of 5" states that poor absorption or permeation more likely when there are more than 5 H-bond donors (expressed as the sum of OHs and NHs); the MWT is over 500; the Log P is over 5 (or M LogP is over 4.15); there are more than 10 H-bond acceptors (expressed as the sum of Ns and Os); James *et al.*, 1986 has provided some general rules regarding solubility.[26]

i. Electrolytes dissolve in conducting solvents
ii. Solutes containing hydrogen capable of forming hydrogen bonds dissolve in solvents
iii. Capable of accepting hydrogen bonds and vice versa
iv. Solutes having significant dipole moments dissolve in solvents having significant dipole moments
v. Solutes with low or zero dipole moments dissolve in solvents with low or zero dipole moments.

pKa determinations

The majority drug candidates are weak acids or bases; therefore, one of the most pertinent determinations carried out before development is the pKa or ionization constant. pH of the medium imparts the solubility of acidic and basic compounds. Strong acids, e.g., HCl, are ionized at all pH values, whereas the ionization of weak acids is dependent on pH. It is useful to know the extent to which the molecule is ionized at a certain pH, since properties such as solubility; stability, drug absorption, and activity are affected by this parameter.[12,27]

For basic compounds:

$$pH = pKa + \log \frac{(\text{Concentration of ionized species})}{(\text{Concentration of unionized species})} \quad (1)$$

For acidic compounds:

$$pH = pKa + \log \frac{(\text{Concentration of unionized species})}{(\text{Concentration of ionized species})} \quad (2)$$

Thus at pKa = pH, 50% dissociation (or ionization) and 50% unionization.

The partition and distribution coefficients

The relationship between chemical structure, lipophilicity, and an indication of its ability to cross biological cell membrane is oil/water coefficient. These include solubility, absorption potential, membrane permeability, plasma protein binding, volume of distribution, and renal and hepatic clearance. The lipophilicity of an organic compound is usually described in terms of a partition

coefficient log P or K o/w, which can be defined as the ratio of the concentration of the unionized compound, at equilibrium, between organic and aqueous phases:

$$\log P = \frac{[\text{Unionized compound}]org}{[\text{Unionized compound}]aq}$$

It is worth noting that this is a logarithmic scale; therefore, a 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. In other words, if log *P* value is more than 1 then compound is lipophilic while log *P* value is <1 then hydrophilic.[12,28,29]

Dissolution

The dissolution rate, rather than saturation solubility, is most often primary determinant in the absorption process of a sparingly soluble drug. Experimental determinations of the dissolution rate are therefore of great importance. The main area for dissolution rate studies is evaluation of different solid forms of a drug (e.g. salts, solvates, polymorphs, amorphous, stereoisomers) or effects of particle size.[12] The dissolution rate can either be determined for a constant surface are as follows:

a. Intrinsic dissolution: The dissolution rate of a solid in its own solution is adequately described by the Noyes-Nernst equation. The intrinsic dissolution rate in a fixed volume of solvent is generally expressed as mg dissolved × (min^{-1} cm^{-2}). Knowledge of this value helps the pre-formulation scientist in predicting if absorption would be dissolution rate limited
b. 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. Hence, if particle size has no influence on dissolution than other methods such as addition of surfactant will be considered.

Solubilization

Solubility is defined as the drug goes into solution. Solubility of drug substance affect on the bioavailability of drug. Poor water solubility or insufficient solubility for projected solution dosage form, pre-formulation study should include limited experiments to identify possible mechanism of solubilization for improves solubility. The methods used to increase solubility are change in pH, cosolvency, dielectric constant, solubilization by surfactant, complexation, hydrotropy, and chemical modification of drug, etc.[26]

Thermal effect

Since dissolution is usually an endothermic process, increasing solubility of solids with a rise in temperature is the general rule. Therefore, most graphs of solubility plotted against temperature show a continuous rise, but there are exceptions, e.g., the solubility of sodium chloride is almost invariant, while that for calcium hydroxide falls slightly from a solubility of 0.185 g/mL at 0°C to 0.077 g/mL at 100°C.[30,31]

Common ion effect (Ksp)

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. Salting out is results from the removal of the water molecule as the solvent due to competing hydration of other ions. Hence, weakly basic drug which are given as HCl salts have decreased solubility in acidic (HCl) solution.[12]

Physicochemical stability of drug substances

Pre-formulation stability studies are usually the first quantitative assessment of chemical stability of a new drug. These studies include solution and solid state stability in the presence of other recipients. Factor effecting chemical stability critical in rational dosage form design include temperature, pH, and dosage form diluents. 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.[12,32]

Physical stability (initial solid-state stability)

Physical stability of active pharmaceutical ingredients (APIs) includes: Change in physical appearance, color, odor, identity, specific gravity, and optical rotation of API.

Depending on the conditions of temperature and the humidity to which the solid is exposed, the acceleration phase may follow zero, first, or higher orders. In terms of the chemical stability of compounds with respect to moisture uptake, the following descriptions have been used to describe classes of surface moisture.[32]

Limited water

Water is used up during the degradation reaction, and there is not enough present to degrade the compound completely. Adequate water: Sufficient water is present to decompose the compound completely. Excess water: This is an amount of water equal to or greater than amount of moisture necessary to dissolve the drug. As such, this may decomposes drug with time.

Loss of volatile constituents

Iodine, camphor, menthol, ethyl alcohol, anesthetic, and chloroform have tendency to evaporate from product. Nitroglycerine tablets may lose their potency owing to vitalization of medicament. Color changes: Color fading is a fairly common type of instability.

Loss of water

Loss of water leads to decrease in weight and raise the dose of drug and increase potency. For example, borax, caffeine, and quinine sulfate have a natural tendency to lose water.

Absorption of water

Leads to increase the weight and dilute and decrease the potency of drug. Amorphous transformation: Amorphous substances have high energy and readily converted to crystalline state at elevated temperature through melting. Moisture also enhances the rate of amorphous transformation. Crystal growth, polymorphic transformation: By absorption of moisture change in crystal habit of crystal and change from metastable form to most stable polymorphic form. This leads to decreases solubility of drug substances.[33,34]

Preventive measures

The product is protected from light and air. Reducing substances are avoided as additives (e.g., dextrose). Select excipients at low moisture/water content for drug product.[33]

Chemical stability (liquid-state stability)

Chemical stability study includes many ways that cause instability of drug through the chemical reaction resulting in a reduction of potency.[35]

Hydrolysis

Hydrolysis means breakdown of drug molecules in presence water and or sometimes acid. Degradation by hydrolysis is affected by a number of factors of which solution pH, buffer salts, and ionic strength are the most important. In addition, the presence of cosolvents, complexing agents, and surfactant can also affect this type of degradation. As noted, solution pH is one of the major determinants of the stability of a compound.

Drug with esters and amide group react with one molecule of water and undergoes hydrolysis. Ester group hydrolyses faster than amide group.

Drugs are either weak acid or bases. Therefore, the may be available as ionic form or neutral form. Hydrolysis reaction between ionic form proceeds faster than neutral molecules.

- Examples; Esters: Aspirin, procaine, atropine
- Amide: Chloramphenicol, ampicillin, barbituric acid.[34-36]

Preventive measures against hydrolysis

Hydrolysis reactions are due to presence of moisture, catalytic species H^+, and $(OH)^-$ it can be prevented by following way,

a. Buffer: Use of buffer for stabilization of product
b. Complexation: Complexing agent form complex with drug and prevent hydrolysis and shelf life of drug is prolonged
c. Suppression of solubility: Less solubility decreases concentration of drug in solution phase and reduce rate of hydrolysis
d. Removal of water: Presence of water is responsible for hydrolysis, so it is better to avoid by storage of drug in dry form and using water immiscible vehicle.

Oxidation

The second most common way a compound can decompose in solution is through oxidation. Reduction/oxidation reactions involve either the transfer of oxygen or hydrogen atoms reaction can be initiated by the action of heat, light, or trace metal ions that produce organic free radicals. These radicals propagate the oxidation reaction, which proceeds until inhibitors destroy the radicals or until side reactions eventually break the chain.

Oxidation involves removal of electrons from molecules. To test whether a compound is sensitive to oxygen, simply bubble air through the solution, or add hydrogen peroxide, and assess the amount of degradation that takes place.

Reaction between compound and molecular oxygen is called autoxidation. In fats and oils autoxidation of unsaturated fatty acid is done.

Example: Arachis oil, clove oil, cinnamon oil, Vitamin A, riboflavin, ascorbic acid, morphine.

Preventive measures against oxidation

Oxidation reaction is due to the presence of moisture, oxygen, trace metals, H^+, and $(OH)^-$ ions. Use of antioxidant: Tocopherol, chelating agents: Use when the presence of traces of heavy metals, use of buffer, prevents light exposure, oxygen free environment, and low-temperature storage.[34,35]

Racemization

Although hydrolysis and oxidation constitute the main mechanisms by which drugs can decompose; racemization is another way in which the compound can change in solution. In this optically active compound loses its optical activity without changing its chemical composition and converted into its inactive form that is racemic mixture. For example, levo-adrenaline is 15-20 times more active than dextro adrenaline. Solution of levo-adrenaline form racemic mixture of equal parts of levo and dextro-adrenaline with half of its pharmacological action over the pure levo compound.

The kinetics of racemization may be studied in a manner similar to hydrolytic reactions. Racemization reactions, in general, undergo degradation in accordance with first-order kinetic principles.[34-36]

Photolysis

Many drug molecules enhance the rate of chemical reaction under the influence of light energy, such as heat. Drug which undergoes light-induced chemical degradation is called photolablie or photosensitive drugs.

Mechanism of photodecomposition

Electronic configuration of drug overlaps with the spectrum of sunlight or any artificial light where energy is absorbed by the electron resulting in excitation. As they are unstable, they release the acquired energy and return to the ground state by decomposing the drug. The phenomenon where molecules or excipients which absorb energy but do not participate themselves directly in the reaction but transfer the energy to others which cause cellular damage by inducing radical formation is known as photosensitization.

Example: Riboflavin, tetracycline, chlorpromazine. Color development or color fading is also example of photodegredation.[34-36]

Preventive measures

Prevent light exposure, low-temperature storage.

Polymerization

It is a continuous reaction between molecules. More than one monomer reacts to form a polymer. E.g., darkening of glucose solution is attributed to polymerization.

Drug-excipient compatibility studies

During development of stable and effective dosage form it is not only depends on quality of API but also the careful selection of excipients and selection of a good quality of excipient is also vital role in designing of good quality of dosage forms. During this stage, selection of excipients is based upon their compatibility with drug substance. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may already be in existence for known drugs. For new drugs or new excipients, the pre-formulation scientist must to generate the needed information. This study predicts the potential incompatibility and provides justification for selection of excipients in formulation as required in regulatory filings. The ratio of drug to excipient used in these tests is very much subject to the discretion of the pre-formulation scientist.[35,37]

Following techniques are used for determination of drug-excipient compatibility. Figure 4 shows Fourier transform infrared spectroscopy used to investigate structural changes and lack of a crystal structure.[38,39] DSC investigates melting

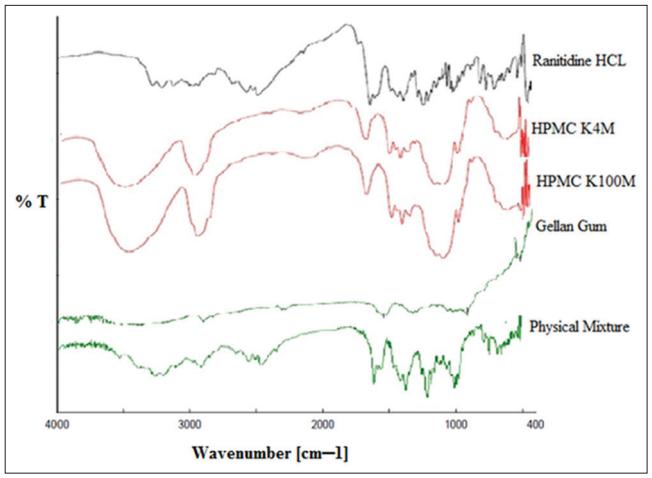

Figure 4: Fourier transform infrared compatibility study of drug and excipients

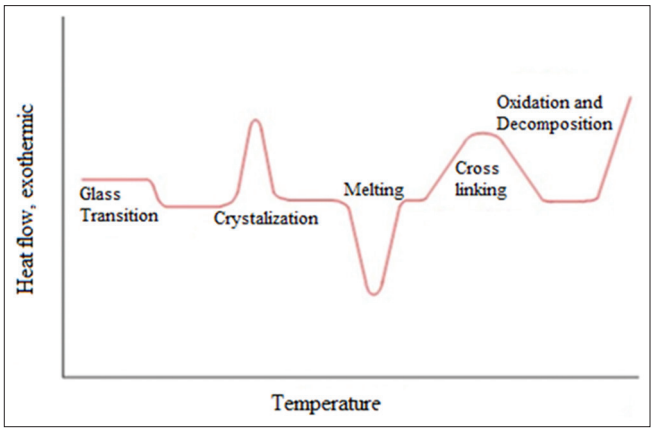

Figure 5: Typical differential scanning calorimetry thermogram of drug substance

point and decomposition shown in Figure 5, differential thermal analysis, thin-layer chromatography, and HPLC.[40-43]

STABILITY TESTING[44]

Stability testing provides evidence on how the quality of drug substance or dosage form varies with the influence of environmental conditions such as temperature, humidity, and light. This information is useful for the recommendation of storage conditions and shelf life. According to ICH guidelines, stability testing carried out in different conditions of temperature and humidity for different period shown in Table 3.

Testing frequency (intervals) for long-term testing will normally be every 3 months, over the 1st year, every 6 months over the 2nd year and then annually.

For the stability study design minimum, three batches should be studied and evaluated for their physicochemical and microbiological characteristics.

Table 3: Stability testing

Type of study	Conditions	Minimum time period at submission
Long-term testing	25±2°C/60±5% RH	12 months
Accelerated testing	40±2°C/75±5% RH	6 months

RH: Relative humidity

CONCLUSION

Development of stable and effective dosage form does not only depend on quality of API but also the careful selection of a good quality of excipients play a vital role in designing of quality dosage forms. Formulation scientists must generate the needed information for safe and effective dosage forms. This study predicts the potential incompatibility and provides justification for selection of excipients in formulation as required in regulatory filings. The ratio of drug to excipient used in these tests is very much subject to the discretion of the pre-formulation scientist. This article provides thoroughfare for pre-formulation testing and important information for formulation design and molecular modification and stability testing before final formulation development.

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