Review Article

An Overview on Preformulation for Pharmaceutical Product Development and Drug Excipient Incompatibility Studies

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ABSTRACT

Activities done prior to formulation development are called as preformulation studies. It provides the scientific basis for formulation developmentPreformulation studies can be broadly classified into two classes – (i) fundamental properties and (ii) derived properties. Fundamental preformulation properties are specific to the drug molecule and are dependent on the chemical structure of the drug molecule. In contrast, derived preformulation pre-formulation properties are carried out to learn about the issues related to development of a particular dosage form like solid oral, liquid oral or parenteral.Fundamental preformulation properties include – Solubility, dissociation constant (pKa), salt formation, partition or distribution coefficient, pH solubility profile and dissolution kinetics, permeability, solid state properties like polymorphism, stability profile etc. Derived preformulation properties are specific to the intended dosage form to be developed. The last activity performed in pre-formulation studies is the compatibility studies, wherein the physical and chemical stability of the drug molecule is studied in presence of excipients. Obviously, the choice of excipients is dictated by the type of dosage form to be developed. Preformulation studies strengthen the scientific foundation of the guidance, provide regulatory relief and conserve resources in the drug development and evaluation process, improve public safety standards, enhance product qualityin the fabrication of dosage form.

Keywords: Fundamental properties, derived properties, physicochemical properties, compatibility studies.

INTRODUCTION

Preformulation studies were evolved in 1950 & early 1960.Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. Preformulation investigations are designed to deliver all necessary data especially physicochemical, physico- mechanical and bio pharmaceutical properties of drug substances, excipients and packaging materials[1,2].

Which may influence

- Formulation design
- Method of manufacture of API and drug product
- Pharmacokinetic/biopharmaceutical properties of the resulting product.
- Packaging of the product (stability).

Preformulation during Drug Discovery

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.

Objectives

- To develop the elegant dosage forms (stable, effective & safe}
- It is important to have an understanding of the physical description of a drug substance before dosage form development.
- It is 1st step in rational development of a dosage form of a drug subt before dosage form development.

GOALS OF PREFORMULATION

To establish the necessary physicochemical parameters of a new drug substance. To determine its kinetic rate profile. To establish its physical characteristics and, To establish its computability with common excipients. To choose the correct form of a drug substance. Generate a thorough understanding of the material_s stability under the conditions that will lead to developme t of an optimal drug delivery system.

PREFORMULATION PARAMETERS

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
   a) Solution-state stability
   b) Solid-state stability
   c) Drug-excipients compatibility

B. CHEMICAL CHARACTERISTICS

1) Hydrolysis
2) Oxidation
3) Photolysis

1) ORGANOLEPTIC PROPERTIES

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, odor 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 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.

Terminology to describe organoleptic properties of pharmaceutical powders

Colour	odour	Taste
Off-white	Acidic	Bland
Pungent	Bitter	intense sweet
Cream yellow	Fruity	tasteless
Sulfurous	Aromatic	-
Tan	Odouerless	-

2. BULK CHARACTERISTICS

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. 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.

Table 2: Common Techniques for Measuring Fine Particles of Various Sizes

Technique Particle size	Technique Particle size
Microscopic	**1-100**
Sieve	**>5**
Sedimentation	**>1**
Elutriation	**1-50**
Centrifugal	**<50**
Permeability	**>1**
light scattering	**0.5-50**

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's index[3,4].

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.

$$\text{Tan } \theta = h / r$$

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.

Carr's index= Tapped density

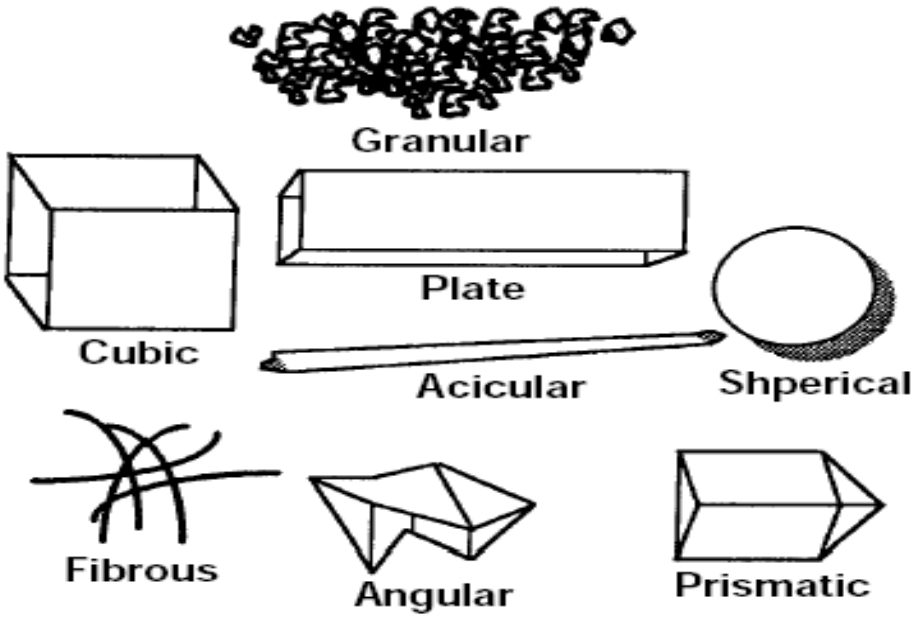
$$\text{Carr's index} = \frac{\text{Tapped density} - \text{pored density} * 100}{\text{Tapped density}}$$

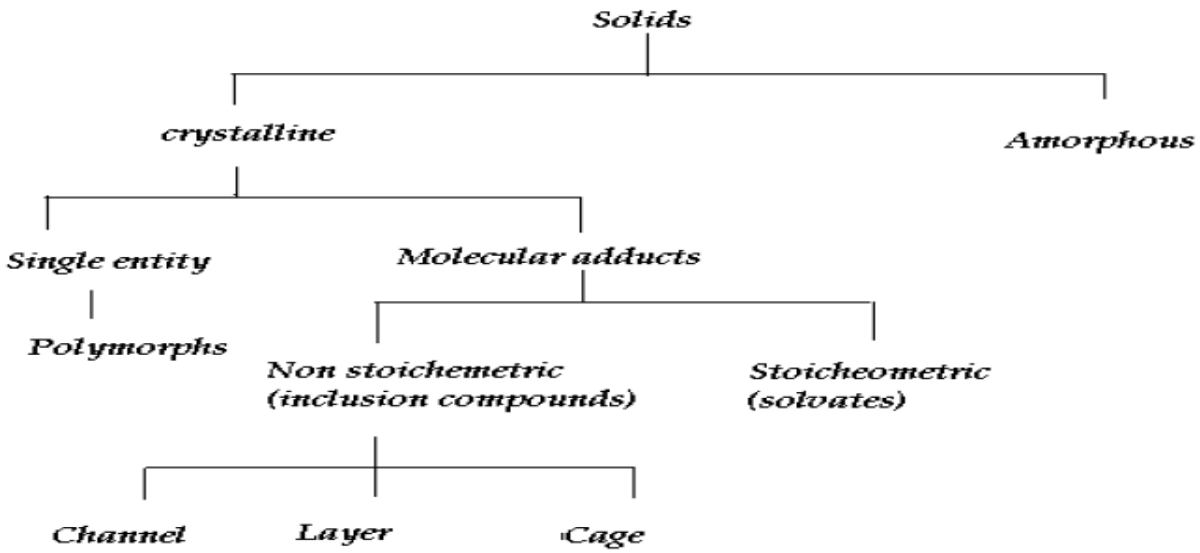
Relationship between flow, angle of repose, carr's index

flow	Angle of repose	Carrs index
Excellent	<25	5-15
Good	25-30	12-16
Fair to passable	30-40	18-21
Poor	>40	23-35
Very poor	-	33-38
Extremerly poor	-	>40

e) Crystallinity[5-8]

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.



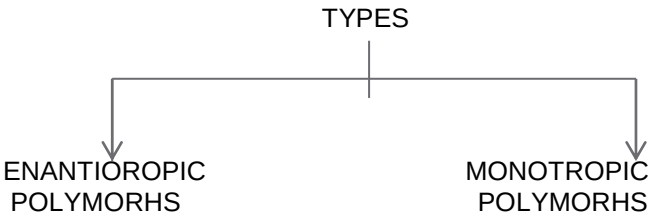


Analytical method used for characterization of crystal

1) Microscopy
2) Differential scanning calorimerty
3) Infared spectroscopy
4) Thermogravemetric analysis
5) X-ray Diffraction

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 polymorphism

- Optical crystallography
- Hot 0stage microscopy
- X- Ray Diffraction method
- NMR technique
- FTIR technique.
- Microcalorimetry
- Thermal methods
- Melting point determination

PROPERTIES OF POLYMORPHS

- Polymorphs show the same properties in liquid or gaseous state but they behave differently in solid state.
- Polymorphs differ from each other with respect to physical properties like
- Melting and sublimation temperature
- Vapour pressure
- Solubility and dissolution rate
- Stability
- Optical and electrical properties
- Crystal habit
- Hygroscopicity
- Heat capacity
- Solid – state reactions
- Conductivity
- Compression characteristics

g) Hygroscopisity

Many compounds and salts are sensitive to the presence of water vapour 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 vapour 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 sorbing 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 Mailliard 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.

Table 2: Different classes of hygroscopic substances

Hygroscopicity Classification		
Class 1	Non- Hygroscopic	Essentially no moisture increases occur at relative humidities below 90%.
Class 2	Slightly Hygroscopic	Essentially no moisture in occur at relative humidity below 80%
Class 3	Moderately Hygroscopic	Moisture Content does not increase more than 5% after storage for 1 week at relative humidity below 60%
Class 4	Very Hygroscopic	Moisture content increase may occur at relative humidity as low as 40 to 50%

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 stabilityuntil more definite data is available. **37° C** to support biopharmaceutical evaluation. The solubility of weakly acidic and weakly basic drug as function of PH can be predicted with help of equation

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.

a) Ionization Constant(PKA)[9-12]

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 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 sit e 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 [unionized form] / [ionized form] ---- for weak bases.**
- **pH = pKa + log [ionized form] / [unionized form] ---- for weak 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. affect 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

- Potentiometric Titration
- Spectrophotometric Determination
- Dissolution rate method
- Liquid-Liquid Partition method

b). Partition Coefficient

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

logP=(un ionized compound)org
(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 thebest predictor of absorption rate, the effect of dissolution rate, pKa, and solubility on absorption Must not be neglected. Lipids occurring in living membranes are complex and difficult to obtainin 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, isopropylmyristate, carbon tetrachloride, and n - Octanol can be used in the determination of

the partition coefficient, with the latter gaining increasing acceptance.

Methods of finding Partition coefficient

1) Shake-flask method
2) Chromatographic method.
3) Counter current and filter probe method.
4) Tomlinson's filter probe method.
5) Microelectrometrictitratation method
6) Automated instrument is now available.

Applications of Partition coefficient

Measure of Lipophilic 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, Transdermalpatches). Study of distribution of flavouring 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

- Change in pH
- Co-Solvency
- Dielectric Constant
- Solubilization by Surfactant
- Complexation
- Hydrotropy
- 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**

$$\ln S = \frac{-\Delta HS \ (1) + C}{RT}$$

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 describedby the Noyes-Nernst equation:

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

Where,
dC / dt = dissolution rate
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

$$K = AD/hV = \text{constant}$$

Dissolution rate as expressed in Equation is termed the intrinsic *dissolution rate* and is characteristic ofeach solid compound in a given solventunder 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.

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. So, if particle size has no influence on dissolution than other method like addition of surfactant will be considered.

4. STABILITY STUDIES

Incompatibility- general aspects

When we mix two or more API and / or excipient with each other & if they are antagonistic & affect adversely the safety, therapeutic efficacy, appearance or elegance then they are said to be incompatible.

(A). Solid State Stability Studies

Sample A	Sample B	Sample C
• Prepare a small mixture of drug and excipient. • Place above mix in vial. • Palce a rubber closure on vial and dip the stopper in molten carnuba wax to render it hermetically sealed.	Sample preparation method is same as sample A but 5% moisture is added in mixture.	Drug itself without any excipient is taken as a sample for solid state stability study.

Solid state reactions are much **slower** and more **difficult to interpret** than solution state reactions, due to a reduced no. of molecular contacts between drug and excipient molecules and to the occurrence of multiple phase reactions.

- All the samples of drug-Excipient blends are kept for 1-3 weeks at specified storage conditions.
- Then sample is physically observed for (1) caking (2) liquefaction (3) Discoloration (4) odor (5) gel formation.
- It is then assayed by TLC or HPLC or DSC.
- Whenever feasible, the degradation products are identified by MASS SPECTROSCOPY, NMR or other relevant analytical techniques.

(B) Solution State Stability Studies[13]

It is easier to detect liquid state reactions as compared to solid state reactions. For detection of unknown liquid incompatibilities, the program set up is same as solid dosage forms. Now according to —Stability guidelinesǁ by FDA states that: Following conditions be evaluated in studies on solutions or suspensions of bulk drug substances:

1) Acidic or alkaline pH.
2) Presence of added substances- chelating agents, stabilizers etc.
3) High Oxygen and Nitrogen atmospheres.
4) Effect of stress testing conditions……

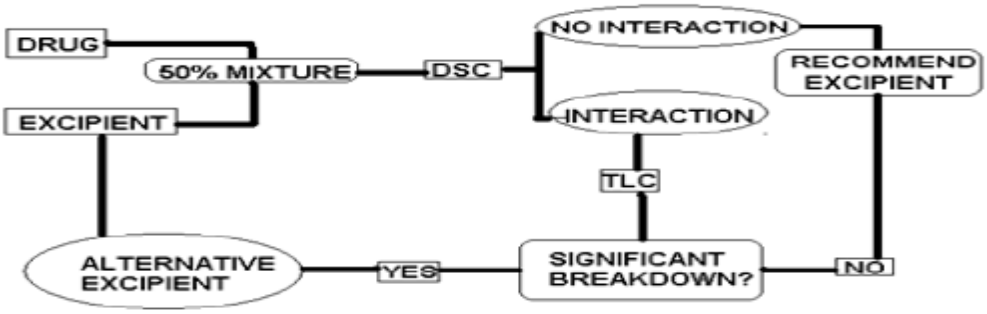
Methodology

- Place the drug in the solution of additives.
- Both flint and amber vials are used.
- Autoclave conditions are employed in many cases. This will provide information about Susceptibility to oxidation. Susceptibility to light exposure. Susceptibility to heavy metals.
- In case of oral liquids, compatibility with ethanol, glycerine, sucrose, preservatives and buffers are usually carried out.

(C) Drug-Excipient Compatibility Studies

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. 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 excipents, the preformulation scientist must generate the needed information. A typical tablet contains binders, disintegrants, lubricants, and fillers. Compatibility screening for a new drug must consider two or more excipients from each class. The ratio of drug to excipient used in these tests is very much subject to the discretion of the preformulation scientist.



IDENTIFY CHEMICALLY COMPATIBLE EXCIPIENT USING DSC WITH CONFIRMATORY TLC

Importance of Drug Excipient Compatibility Study

- Stability of the dosage form can be maximized. Any physical or chemical interaction between drug and excipient can affect bioavailability and stability of drug.
- It helps to avoid the surprise problems. By performing DECS we can know the possible reaction before formulating final dosage form. It bridges the drug discovery and drug development. Drug discovery can emerge only new chemical entity. It becomes drug prod uct after formulation and processing with excipients.
- By using DECS data we can select the suitable type of the excipient with the chemical entities emerging in drug discovery programs. DECS data is essential for IND (investigational new drug) submission. Now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

Analytical techniques used to detect Drug-Excipient Compatibility

1) Thermal methods of analysis
I. DSC- Differential Scanning Calorimetry
II. DTA- Differential Thermal Analysis
2) Accelerated Stability Study
3) FT-IR Spectroscopy
4) DRS-Diffuse Reflectance Spectroscopy
5) Chromatography
I. SIC-Self Interactive Chromatography
II. TLC-Thin Layer Chromatography
III. HPLC-High Pressure Liquid Chromatography
6) Miscellaneous
I. Radiolabelled Techniques
II.Vapour Pressure Osmometry
III. Fluorescence Spectroscopy

DSC (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 are measured as a temperature. Both the sample and reference are maintained at very nearly the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time.
- The reference sample should have a well defined heat capacity over the range of temperatures to be scaned.
- The basic principle underlying this technique is that, when the sample undergoes a physical transformation such as phase transition, more (or less) that will need to flow to it than the reference to maintain both at the same temperature.
- Whether more or less heat must flow to the sample depends on whether the process is exothermic or endothermic. For example as a solid sample melts to a liquid it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid.
- Likewise, as the sample undergoes exothermic processes (such as crystallization) less heat is required to raise the sample temperature by observing the difference in heat flow

between the sample and reference, differential scanning calorimeters are able to measure the amount of energy absorbed or released during such transitions. DSC is widely used in industrial settings as a quality control instrument due to its applicability in evaluating sample purity and for studying polymer curing.

- An alternative technique, which shares much in common with DSC, is differential thermal analysis (DTA).
- In this technique it is the heat flow to the sample and reference that remains the same rather than the temperature. When the sample and reference are heated identically phase changes and other thermal processes cause a difference in temperature between the sample and refferance. Both DSC and DTA provide similar information.
- DSC is the more widely used of the two techniques.
- DSC is widely used to investigate and predict any physico-chemical interaction between drug and excipients involving thermal changes..
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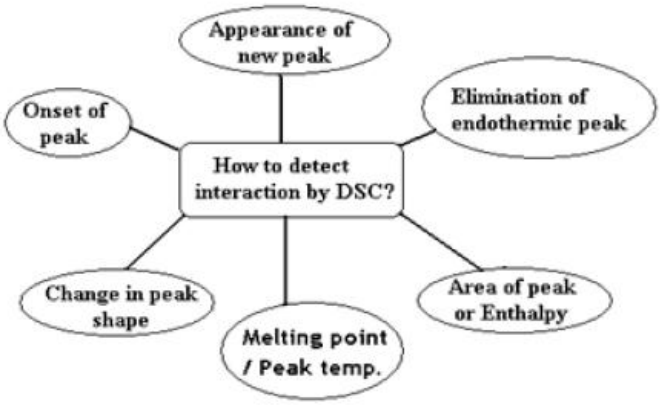
- Thermal Analysis is useful in the investigation of solid-state interactions. It is also useful in the detection of eutectics. Thermograms are generated for pure components and their 1:3, 1:1, 3:1 physical mixtures with other components. In the absence of any interaction, the thermograms of mixtures show patterns corresponding to those of the individual components. In the event that interaction occurs, this is indicated in the thermogram of a mixture by the appearance of one or more new peaks or the disappearance of one or more peaks corresponding to those of the components.

METHOD

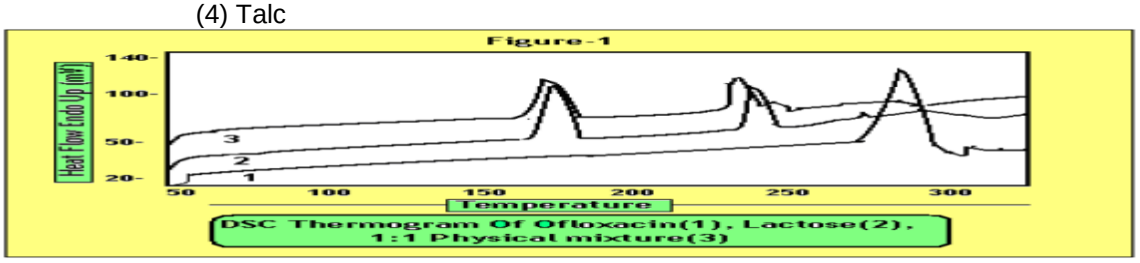
- The preformulation screening of drug-excipient interaction requires 5 mg of drug, in 50% mixture (1 : 1) with excipient, to maximize the likehood of observing an interaction.
- Mixture should be examined under N2 to eliminate oxidative and pyrrolytic effects at heating rate(2, 5 or 100c / min) on DSC apparatus.



However, some changes in peak shape, peak ht. & width are expected b'coz of possible differences in mixture geometry.

Drug: Ofloxacin

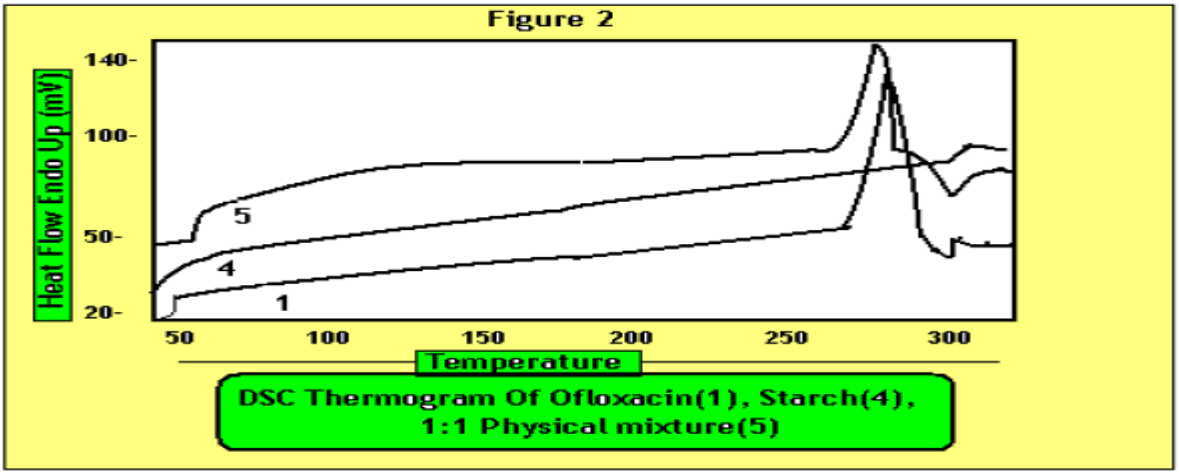
- **Excipients:** (1) Lactose
  (2) Starch
  (3) PVP
  (4) Talc



Trace 1 of figure 1-4 shows peak at 278.33 0C. (melting endothermic peak of Ofloxacin).

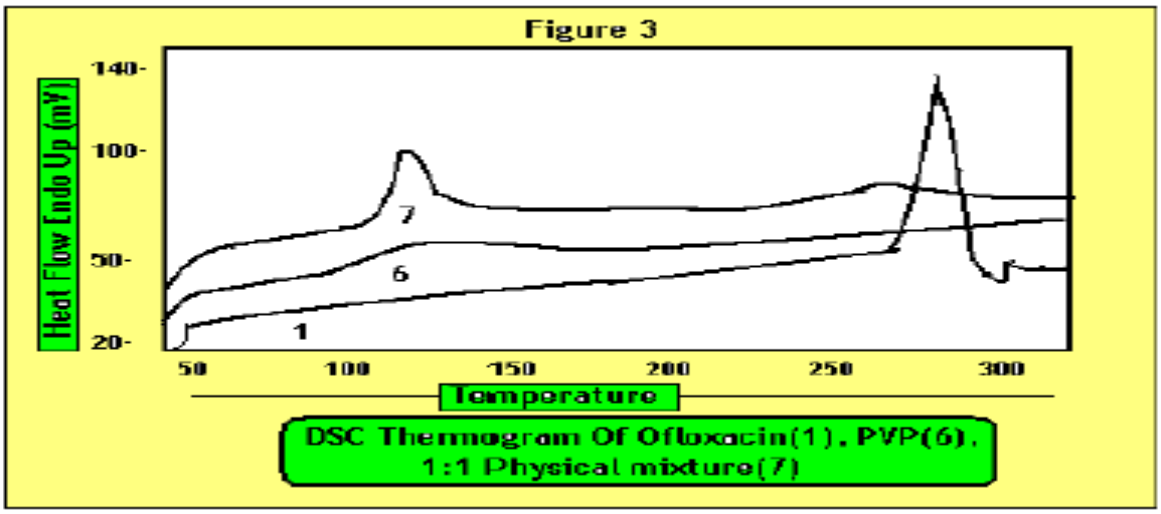
Trace 3 (Physical mixture of Ofloxacin & Lactose) shows absence of peak at 278.33 0C and slight pre shift in Lactose peaks.

DSC RESULT—INCOMPATIBLE



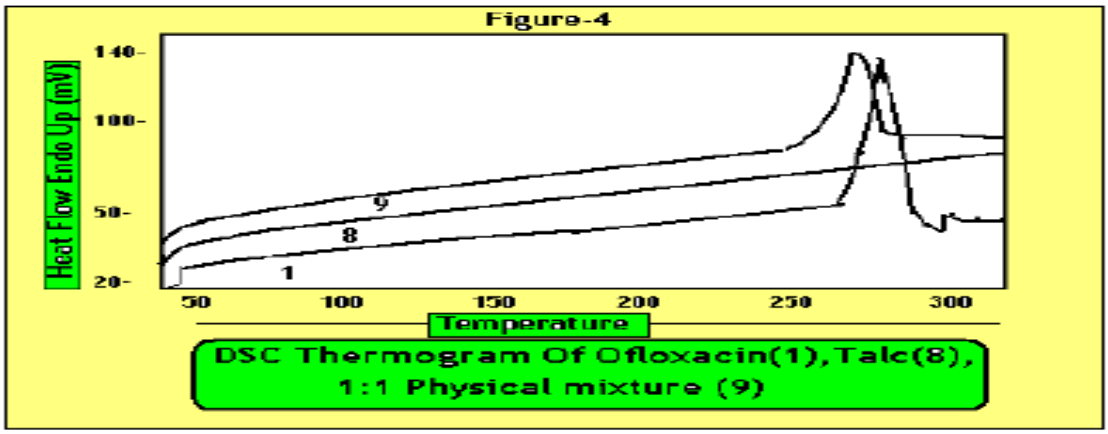
Trace 5 (Physical mixture of Ofloxacin & Starch) shows an early onset at 268.37 0C.

DSC RESULT—COMPATIBLE



Trace 7 (Physical mixture of Ofloxacin & PVP) shows no change in position of endothermic peak for PVP but there is increase in peak area and size & shape of peak for Ofloxacin is also decreased.

DSC RESULT-- INCOMPATIBLE



Trace 9 (Physical mixture of Ofloxacin & Talc) shows combine features of each component but there are evident changes in onset.

DSC RESULT—COMPATIBLE

DSC Study of Ascorbic acid P'ceutical formulations

Excipients: Sod. Crosscarmellose, MCC, Lactose

• Thermal stability was performed on ascorbic acid std. samples, binary mix. Of ascorbic acid & excipients, under N2 & air atmospheres.

• IR & X-Ray Diffractometry: No chemical interaction

• However thermal stability of pharmaceutical formulations is different.

• Temp. of beginning of thermal degradation for Ascorbic acid is lowered of about 50C for MCC & 100C for Na-crosscarmellose & Lactose.

Such facts must be considered for storage planning of tablets.

ADVANTAGES OF DSC OVER TRADITIONAL METHODS

1. Fast – (no long term storage of mixture is required prior to evaluation.

2. Reliable

3. Very less sample required (few mg.)

LIMITATIONS

1. If thermal changes are very small, DSC can_t be used. Therefore, it should always be supported by some non-thermal methods like TLC or FT-IR or XRPD.

2. DSC can not detect the incompatibilities which occur after long term storage.

DIFFERENTIAL THERMAL ANALYSIS

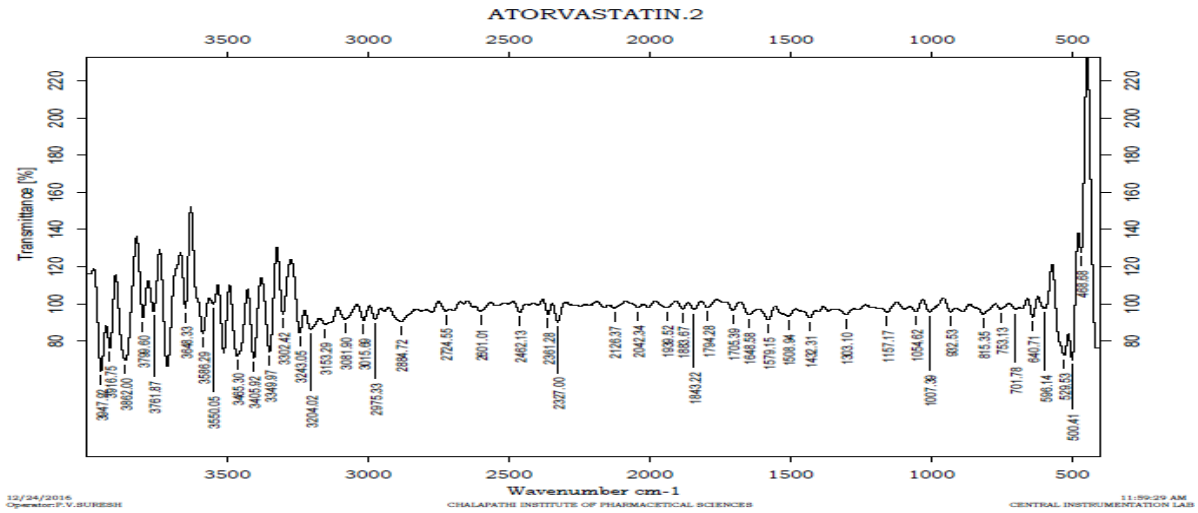
- **Drug :** Enalepril maleate
- **Excipients**(Directly compressible diluent)**:**

(1) Avicel
(2) Spray dried lactose
(3) Emcompress
(4) A-tab

FORMULATION	RESULT OF DTA (interaction)	SHELF LIFE	INFERENCE
F_1 (Avicel)	+	3 ½ month	Least suitable
F_2 (Spray dried lactose)	—	1 yr and 3 month	Ideal
F_3 (Emcompress)	+	8 month	Not recommended
F_4 (A-tab)	+	9 ½ month	Not recommended

FOURIER TRANSFORM INFRARED SPECTROSCOPY

Fourier-transform infrared (FTIR) spectroscopy was performed on each of the samples to determine the structure of the organic compounds and to identify the presence of specific functional groups within a sample. Furthermore,drug-polymer interactions were examined using the resulting spectra. Spectra are obtained by passing infrared radiation through a sample and determining what fraction of incident radiation is absorbed at a particular energy. The energy of a peak in the spectrum corresponds to the frequency of vibration of part of the sample compound.3-5mg of composite sample was added to approximately 100mg of KBr. The mixture was then ground to a fine powder using a mortar and pestle, and transparent discs were formed using a pellet press. The discs were then placed in the FTIR spectroscopy apparatus, and spectra were collected. The range of collected spectra was 4000-500cm^{-1}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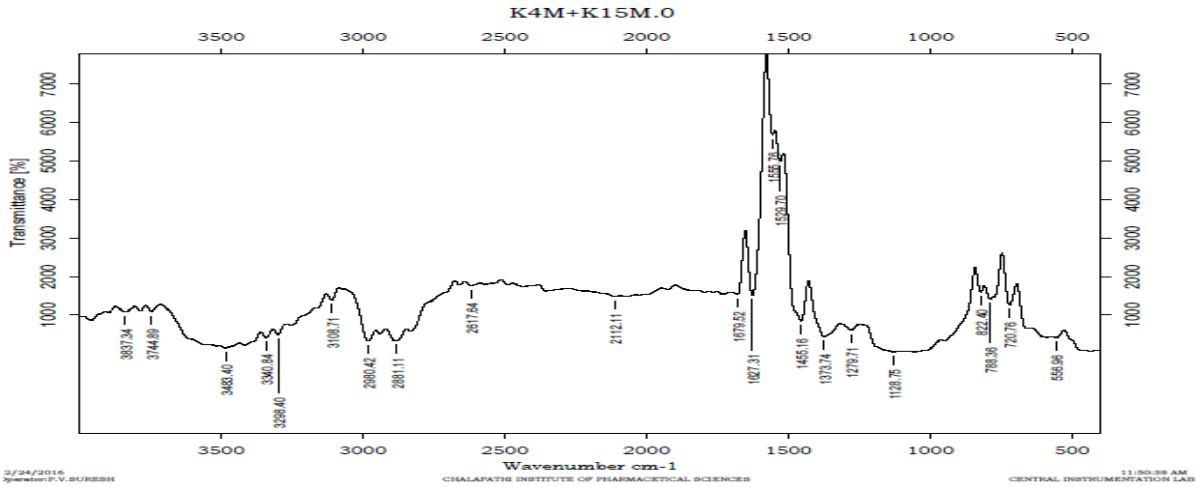
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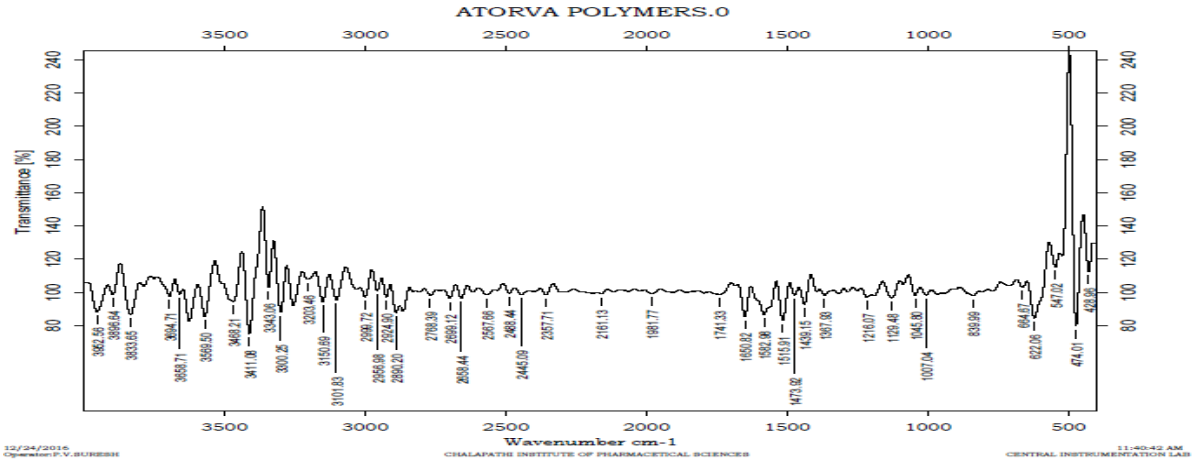
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CHROMATOGRAPHY

TLC: Thin Layer Chromatography

HPTLC: High Performance Thin Layer Chromatography

TLC is generally used as confirmative test of compatibility after performing DSC.

Because if sample undergo negligible thermal changes, it will difficult to detect by thermal method.

- In TLC, Stationary phase consist of powder adhered onto glass, plastic or metal plate.
- Powders commonly used are Silica, Alumina, Polyamide, Cellulose & Ion exchange resin.
- Solution of Drug, Excipient & Drug: Excipient mixture are prepared & spotted on the same baseline at the end of plate.
- The plate is then placed upright in a closed chamber containing the solvent which constitutes the Mobile phase.
- As the solvent moves up the plate, it carries with it the material.
- The materials that have stronger affinity for S.P. will move at slower rate.
- The material is identified by its Rf value.
- The position of the material on the plate is indicated by spraying the plate with certain reagents or exposing the plate to UV radiation.
- If there is no interaction between drug & excipient, the mixture will produce two spots.
- The Rf value of which are identical with those of individual drug & excipient.
- If there is interaction, the complex formed will produce a spot. The Rf value of which is different from those of the individual components.

Radio labeled technique

Highly sensitive method but the cost of carrying out the method ,as well as the availability of well established other techniques and methods, this method is generally not preferred. It is important when the API is radio-active.

Method is carried out by using either **3H or 13C.**

B. CHEMICAL CHARACTERISTICS

1) Hydrolysis
2) Oxidation
3) Photolysis

Hydrolysis

This is the most common degradation pathway since water plays an important role in many processes especially in solution but also in solid systems where it may be present albeit at low concentrations. Hydrolysis occurs via a nucleophilic attack of the water molecule on labile bonds with susceptibility dependent on the bond type and decreasing from

lactam > ester > amide > imine.

This can be influenced by pH if the molecule is ionizable with maximum instability in the ionized form, since it has the greatest solubility and therefore exposure. This leads to a change in hydrolysis reaction rate with pH with the shape of the pH/hydrolysis curve related to the underlying chemical processes. If the solvent is not water, solvolysis is also possible if the solvent and compound react.

Oxidation

Oxidation is an environmental phenomenon requiring oxygen (or an oxidizing agent), light, and trace metals capable of catalyzing the reaction. If molecular oxygen is involved, the reaction is generally rapid and termed ―auto-oxidation.‖ Chemically, oxidation is classed as a loss of electrons, which requires an electron acceptor, or oxidizing agent, which could be, for example, iron undergoing a ferric (Fe3+) to ferrous (Fe2+) change.

Oxidation reactions generally involve free radical chain reactions, and the initial free radical may arise through thermal or photolytic bond cleavage or a redox process involving a trace metal ion. Once formed the radical can then be propagated, catalyzed by the metal ions present, until a suitable chemical inhibitor (antioxidant) or termination reaction intervenes. Oxidation reactions usually produce highly colored degradation products, which can be detected by eye before chemical detection is possible. Many drugs undergo oxidation; for example, adrenaline produces adrenochrome, which is intensely pink, and degradation is initiated by free radicals induced by light and further catalyzed by multivalent metal ions.

Photolysis

If the compound absorbs light, it is absorbing energy with the potential to break or rearrange bonds, produce light emission such as fluorescence or phosphorescence, or increase temperature. Light energy is inversely proportional to wavelength, therefore UV light (220–370 nm) with the shortest wavelength has the highest energy. Photodegradation is therefore dependent on the wavelength of the light and also its intensity. Most degradation

occurs through UV light, which is present in sunlight (290–1750 nm) and also artificial lighting such as fluorescent tubes (320–380 nm). Prevention of photodegradation is achieved by suitable light opaque packaging such as foil wraps or amber glass.

CONCLUSION

The preformulation phase is a critical phase in establishing the properties that will allow suitable risk assessment for development of a formulation. Decisions made on the information generated during this phase can have a profound effect on the subsequent development of those compounds. Therefore, it is imperative that preformulation should be performed as carefully as possible to enable rational decisions to be made. 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. The last activity performed in pre-formulation studies is the compatibility studies, wherein the physical and chemical stability of the drug molecule is studied in presence of excipients This knowledge can be useful in developing various types of formulations of any drug. Stability studies in solution will indicate the feasibility of parental or other liquid dosage form and can identify methods of stabilization.

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