

# **THERMAL ANALYSIS**

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# Thermal analysis

## INTRODUCTION

Definition:

Thermal method of analysis are group of techniques in which changes in physical and /or chemical properties of a substance are measured as a function of temperature, while substance is subjected to controlled temp programme.

**Thermal analytical methods can measure the following physical properties,**

- 1) WEIGHT LOSS ON DRYING
- 2) ENTHALPY
- 3) TEMP
- 4) GAS EVOLUTION
- 5) ELECTRICAL CONDUCTIVITY
- 6) OPTICAL CHARACTERISTIC
- 7) MAGNETIC PROPERTIES
- 8) CHANGES IN FORM IN DIMENSION
- 9) VISCOELASTIC PROPERTIES OF SUBSTANCE

## ROLE OF THERMAL ANALYSIS IN PREFORMULATION

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

### Classification of Thermal Analytical Technique

Physical properties	Name of technique	Instrument used
1) MASS	A) THERMOGRAVIMETRY	THERMO BALANCE
	B) EVOLVED GAS ANALYSIS	EVOLVED GAS DETECTOR
2) TEMP	DIFFERENTIAL THERMAL ANALYSIS(DTA)	DTA APPRATUS
3) ENTHALPY	DIFFERENTIAL SCANNING CALORIMETRY(DSC)	DIFFERENTIAL CALORIMETER
4) MECHANICAL PROPERTIES (DIMENSION, VISCOELASTIC PROPERTIES)	A) THERMO MECHANICAL ANALYSIS	TMA APPRATUS
	B) THERMODILATOMETRY	DILATOMETER
5) ACOUSTIC CHARACTERISTIC	A) THERMO ACOUSTIMETRY	
	B) THERMOSONIMETRY	
6) OPTICAL CHARACTERISTIC	THERMOPTOMETRY	
7) MAGNETIC SUSCEPTIBILITY	THERMOMAGNETOMETRY	
8) ELECTRICAL RESISTANCE OR CONDUCTION	THERMOELECTROMETRY	

#### OTHER THERMAL ANALYSIS

- 1) **Thermophotometry:** measures light intensity
- 2) **Thermoluminescences:** measures light emitted by sample
- 3) **Thermomicroscopy:** visual examination of phase transformation
- 4) **Microthermal analysis:** measures thermal conductivity
- 5) **Differential mechanical analysis:** measures modulus, damping & viscoelastic behaviour
- 6) **Emanation thermal analysis:** measures release of radioactive emanation from a substance as a function of temperature.
- 7) **Thermoparticulate analysis:** measures release of particulate matter from a substance.

Combined techniques:

#### A) COMBINATION WITH THERMOGRAVIMETRY

- 1) FOR BETTER INTERPRETATIONS
  - A) TG-DTA
  - B) TG-DSC
- 2) FOR IDENTIFICATION OF GAS INVOLVED IN THERMAL ANALYSIS
  - A) TG-IR
  - B) TG-GC-MS

C) TG-MS

**B) COMBINATION WITH DSC**

A) DSC-THERMOMICROSCOPY

B) DSC-FTIR

C) DSC-TEM

d)DSC-X-RD

**GENERAL PRINCIPLE INVOLVED IN THERMAL TECHNIQUE**

**1) THERMOGRAVIMETRY**

**PRINCIPLE:** Tg is a technique in which a change in the weight of a substance is recorded as a function of temperature or time.

Instrument: Instrument used for thermogravimetry is thermobalance

→ Major components of a Thermobalance

- 1) Sample container ,usually shallow platinum crucible.
- 2) Furnace Assembly
- 3) Automatic recording Balance(Micro balance)

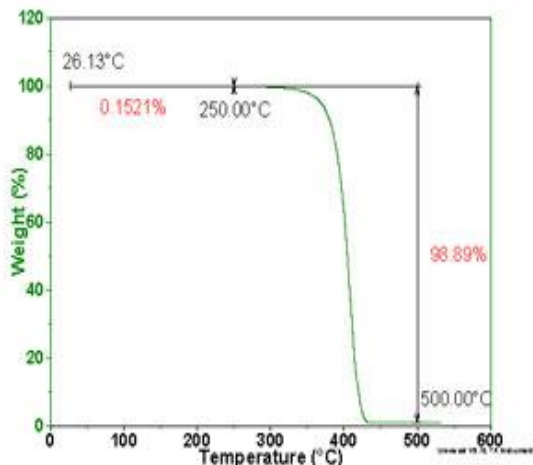
Factors affecting Thermogravimetry analysis are

- 1) heating rate
- 2) furnace atmosphere
- 3) crucible geometry
- 4) sample characteristic

Data recorded in form of curve known as **Thermogram**.

Thermograms can be divided into two portions:

- 1) Horizontal portion: indicate region where there is no weight loss.
- 2) Curved portion: indicate regions of weight loss.



## 2) Differential Thermal analysis (DTA)

**PRINCIPLE:** A Technique in which the temperature difference between a substance & a reference material is measured as a function of temperature, while the substance & reference are subjected to a controlled temperature programme.

- The Difference in temperature is called as Differential temp( $\Delta t$ ) is plotted against temp. or a function of time.
- Physical changes usually result in Endothermic peak, whereas chemical reactions those of an oxidative nature are exothermic.
- Endothermic reaction (absorption of energy) includes vaporization, sublimation, and absorption & gives downward peak.  
Exothermic reaction (liberation of energy) includes oxidation, polymerization, and catalytic reaction & gives upward peak.

## 3) Differential scanning calorimetry

**PRINCIPLE:** It is a technique in which the energy necessary to establish a zero temp. difference between the sample & reference material is measured as a function of temp.

☞ Here, sample & reference material are heated by separate heaters in such a way that their temp are kept equal while these temp. are increased or decreased linearly.

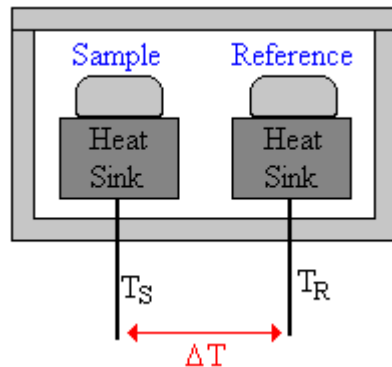
**Endothermic reaction:** if sample absorbs some amount of heat during phase transition then reaction is said to be endothermic. In endothermic reaction more energy needed to maintain zero temp difference between sample & reference.

E.g. Melting, boiling, sublimation, vaporization, desolvation.

**Exothermic reaction:** if sample released some amount of heat during phase transition, then reaction is said to be exothermic. In exothermic reaction, less energy needed to maintain zero temp difference between sample & reference.

E.g crystallization, degradation, polymerization.

## INSTRUMENT



### Ideal DSC curve:

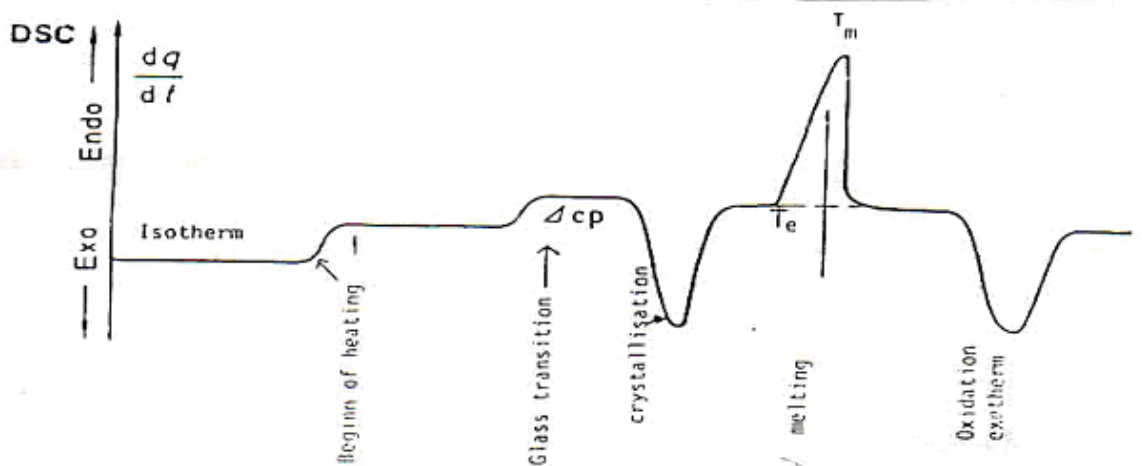


FIG. 1 Typical transitions observed in DSC:  $T_e$  = extrapolated onset,  $T_m$  = peak maximum.

- DSC is widely used to measure glass transition temp & characterization of polymer.
- **Glass Transition temp( $T_g$ ):** Temp at which an amorphous polymer or an amorphous part of crystalline polymer goes from hard, brittle state to soft, Rubbery state.

## 4) THERMO MECHANICAL ANALYSIS

PRINCIPLE: A Technique in which changes in dimension of substance are measured as Function of temp.

- TMA is useful for the measurement of changes in shape (volume or dimension), penetration characteristic & viscoelastic properties of different material as a function of controlled temp elevation.

## 5) THERMOMICROSCOPY

- This Technique also known as Hot stage microscopy.
- This Technique essentially involves the observation of a sample through a microscope fitted with a stage that can be heated or cooled at a controlled rate
  
- By This Method we can Determine
  - a) investigation of the changes according to heat
  - b) melt crystallisation
  - c) detection of melting
  - d) crystal transformation
  - e) crystal pseudomorphs
  - f) sublimation
  - g) desolvation

## 6) MICROCALORIMETRY

**PRINCIPLE:** Calorimetric technique deals with the measurement of heat evolved or absorbed by chemical or physical process.

- \* Isothermal & adiabatic calorimetry are the diff ways of measuring the heat of samples maintained at constant temp.
  - The output of the instrument is measured by the rate of heat exchange ( $dq / dt$ ) as a function of time.

## INNOVATION IN THERMAL ANALYSIS

### a) Multielemental scanning thermal analysis(MESTA)

- Method for the identification & characterization of solid substance.
- Simple,rapid,sensitive,alternative for routine examination of solid sample.
- Principle: Volatile components in the sample are carried to a high temp combustion tube where the C, N, S are oxidized to their respective oxides & detected by the detector.

#### **ADVANTAGE:**

- SIMPLE
- Cost effectiveness of MESTA make it a promising tool for routine chemical analysis of solid substance.

### b) MICROTHERMAL ANALYSIS



- Microthermal analysis is a relatively new technique that combines the resolution of an **Atomic force microscope (AFM)** with **thermal conductivity** measurement.
- MTA is useful for polymorph analysis. In this technique thermal conductivity is measured as a function of temp.
- MTA used for
  - Identification of components in compressed tablet
  - Analysis of tablet coats.

**c) Modulated DSC:**

- Also called as oscillating DSC.
- Advantage of modulated DSC over traditional DSC method
  - Increased sensitivity
  - Increased resolution
  - Separation of complex transitions
  - Measurement of crystallinity.

**d) ROBOTIC SYSTEM**

- Most companies nowadays introduces to the robotic system with autosampling, data manipulation.
- Also increased efficiency of analysis & increased accuracy.

**e) DYNAMIC MECHANICAL ANALYSIS**

- Here the mechanical response of a sample is measured as it is deformed under oscillating load against temp/time.
- Here, **Dynamic Modulus** and /or **damping** of a substance under oscillatory load is measured.

**f) FAST SCAN DSC**

- ☞ **FAST SCAN DSC** distinguishes melting, melting degradation, sublimation, & thermal stability of drug.
- ☞ Useful for stability study.
- ☞ Stability of drugs is based on a comparison of their thermal properties at various heating rates.

**Application of thermal analysis in pre formulation**

**1. characterization of hydrates and solvates**

Pre formulation studies is to identify the ability of drug to take up water and characterize the state of this water because this information is relevant in developing strategy for the process and storage of dosage form.

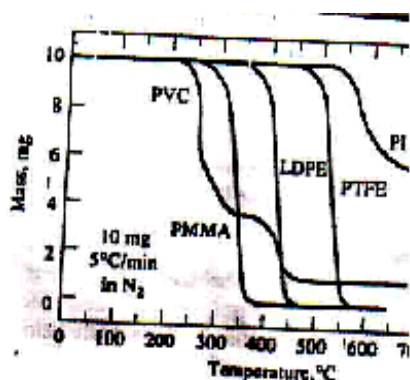
- ☞ TGA provides an important tool to characterize & quantify the moisture content in pharmaceutical material.

## 2. study of polymer

**TGA:** Thermogravimetric methods are largely limited to decomposition & oxidation reaction & to such physical process like vaporization, sublimation, desorption.

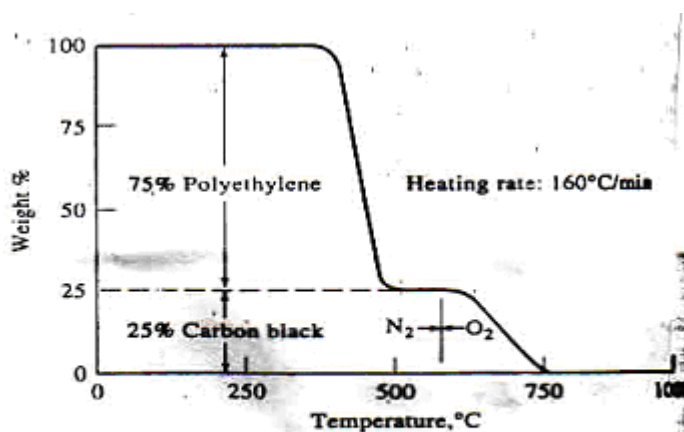
### Qualitative analysis:

Most important application of thermogravimetric methods are found in study of polymers. Thermogram provides information about **decomposition mechanism** for various polymeric preparation. In addition, the **decomposition** patterns are characteristic for each kind of polymer & in some case can be used for identification purpose.



### Quantitative information

- Thermogram is also used for quantitative analysis of a polymeric material.
- Example: **polyethylene** mixed with **fine carbon black** to inhibit degradation from exposure to sunlight. This analysis would be difficult by most other method.



**Figure 31-4** Thermogravimetric determination of carbon black in polyethylene. (From J. Gibbons, Amer. Lab., 1981, 13, (1), 33. Copyright 1981 by International Scientific Communications, Inc.)

### 3. Detection of impurity

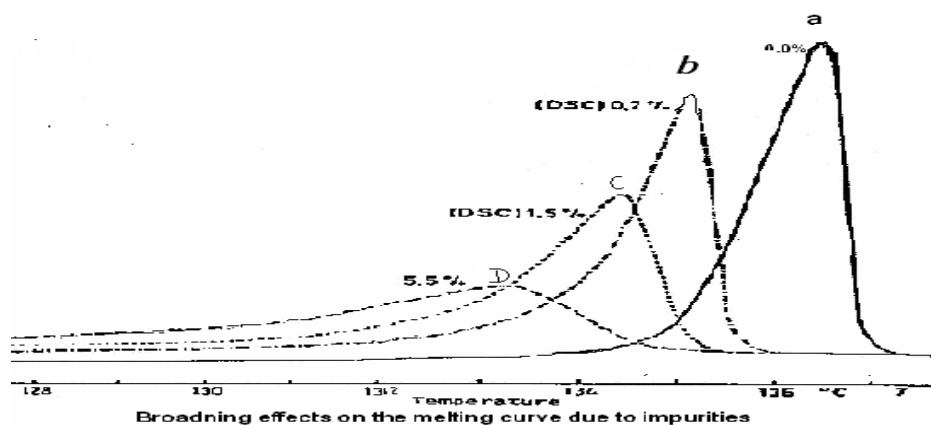
Thermal analytical system can be used for detection of impurities in pharmaceutical ingredient by recording **TG Thermogram & DTA or DSC curves**. This curves could be then be compared with the curve of reference standard . **Any abnormal mass changes on TG curve & irregular endotherm or exotherm peaks on DTA or DSC curve** would indicate the presence of impurity.

#### Basic of any calorimetric purity method

A sharp melting endotherm indicates the relative purity where as broad asymmetric curve suggest impurity. The presence of minute amount of substance broadens its melting range & lowers its mp.

Compare to other thermal methods, DSC is best method for detection of impurity.

Eg. **DSC of phenacetin.**



**4. Polymorphism** is the tendency of a substance to crystallize in different crystalline modification.

The all thermodynamic parameter in the polymorphism substance is different like melting, sublimation temperature, kinetics, stability, solubility, heat capacity, crystal hardness & shape which are extremely important for the dosages form.

During preformulation, it is important to identify the polymorph that are stable & also imp. to determine whether polymorphic transition are possible within the temp. range used for stability studies, processing (drying, milling, mixing. granulation etc.) & storage.

Eg. **Mannitol** occurs in **four forms**, all melting at the same temp. & they are non hygroscopic, only **form B** shows a small endotherm exotherm process.

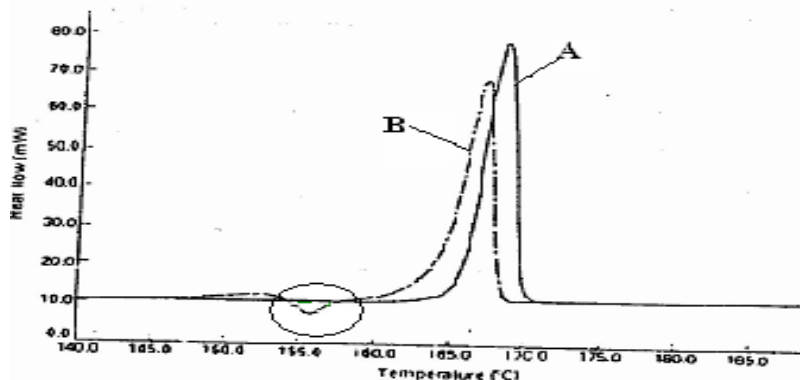


FIG — DSC curves of two mannitol polymorphs.

## 5. Prediction of stability of drug

- **Stability test** is one of the tests which req. the longest time in drug development.
- For a quick release of new drugs to the market, it is difficult to estimate stability speedy from exact information in preliminary stability tests.
  - Thermal analysis is a ideal technique to solve this problem.

### ADVANTAGES OF THERMAL ANALYSIS IN PREDICTION OF STABILITY

- a) This method is very **speedy**.
- b) It only takes two weeks to predict stability of a drug substance in detail.
- c) The operations are **simple**
- d) The method required very small quantity of drug substance & total amount of sample being necessary to predict stability is very little so method is used even at an early developmental stage when production scale is small.
- e) Furthermore the **accuracy & the precision** of prediction using the method are equivalent to or better than those of preliminary tests.
- f) This method is very widely applicable to
 

# Pharmaceutical intermediate	# Pharmaceutical excipient
# Agricultural chemical	# Pesticides
# Pharmaceutical raw material.	

### 6) Degree of crystallinity

- **Partial crystallinity** is also a type of **polymorphism**.
- **The degree of crystallinity was** determined by solution calorimetry.
- **Principle of solution calorimetry**

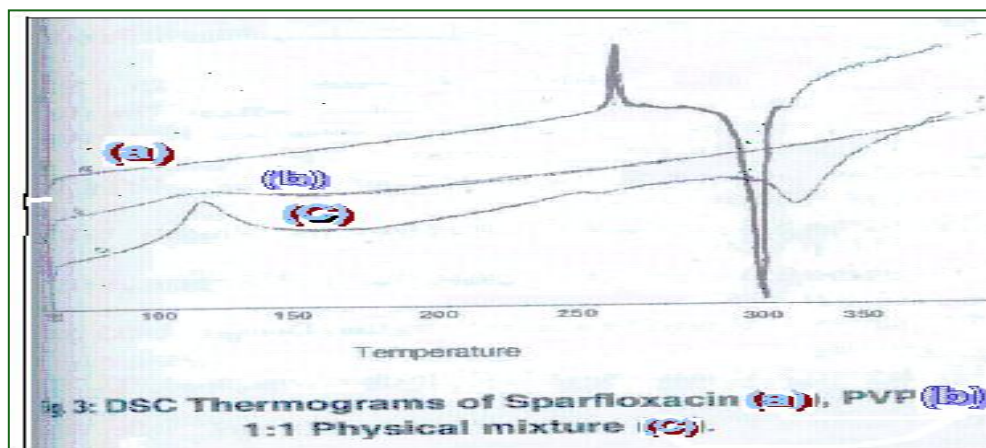
- Basis on the fact that for many solids the amorphous form is higher in energy than the crystalline form. The heat of solution of the amorphous form is expected to be more exothermic than the crystalline form.
- The percentage of crystallinity (pc) may be determined in a partially crystalline sample according to the following equation.

$$PC = \frac{100(\Delta H \text{ sample} - \Delta H \text{ amorphous})}{\Delta H \text{ crystal} - \Delta H \text{ amorphous}}$$

where, sample is partially crystalline material  
amorphous is 100% amorphous standard & crystalline is 100% crystal standard.

#### 7) COMPATIBILITY STUDY OF DRUG WITH EXCIPIENT.

- The early detection of **Drug excipient Incompatibility** is vital in pharmaceutical industry to **avoid costly material wastage & time delays**.
- **DSC & TGA** with the support of **x-ray diffraction & infrared spectroscopy** are used as screening technique for the compatibility testing of drug with excipient.



#### E.g. DRUG EXCIPIENT COMPATIBILITY STUDY

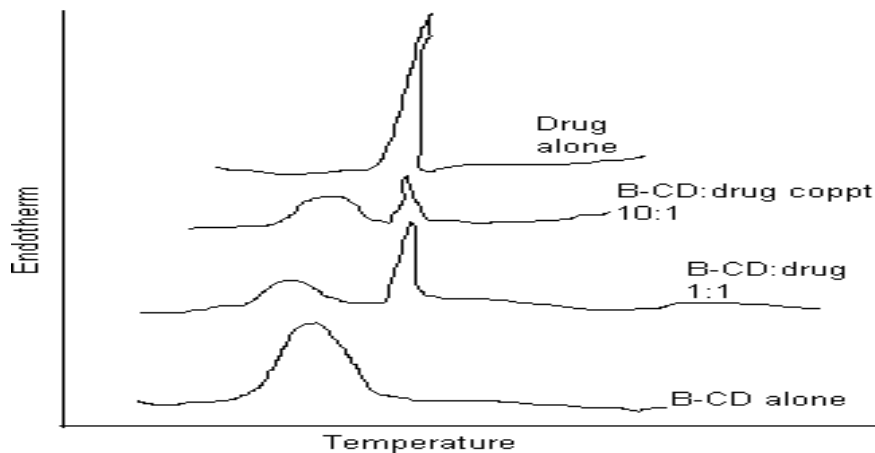
a) DSC of sparfloxacin

- b) DSC of pvp
- c) DSC of 1:1 physical mixture of Drug:pvp

**Conclusion**– incompatibility

Reason: Absence of melting endotherm & exotherm is broad.

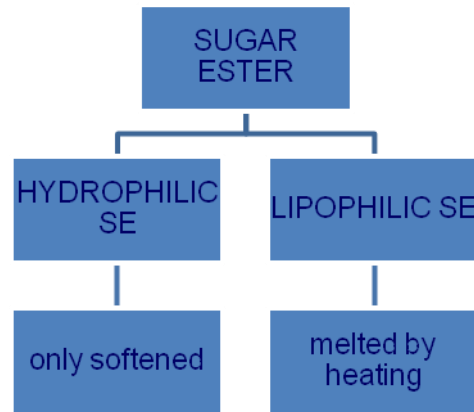
## 8) STUDY OF COMPLEXES & INCLUSION COMPOUNDS



- The **Disappearance of the DSC peak** of the drug is the proof of Complexation in solid state.
- Figure shows, that no complexation was obtained for a drug with  $\beta$ -cyclodextrin.

## 9) Study of Thermal behaviour Sugar ester.

- They have wide range of **HLB value** so they can be used as **surfactant** or **penetration enhancer**.
- Aim of this study, to measure thermal properties of Sugar ester & to differentiate sugar ester with HLB.
- Thermal properties are measured with **modulated DSC**, & combined with **HOT STAGE MICROSCOPY** to visualized changes in sample during heating.

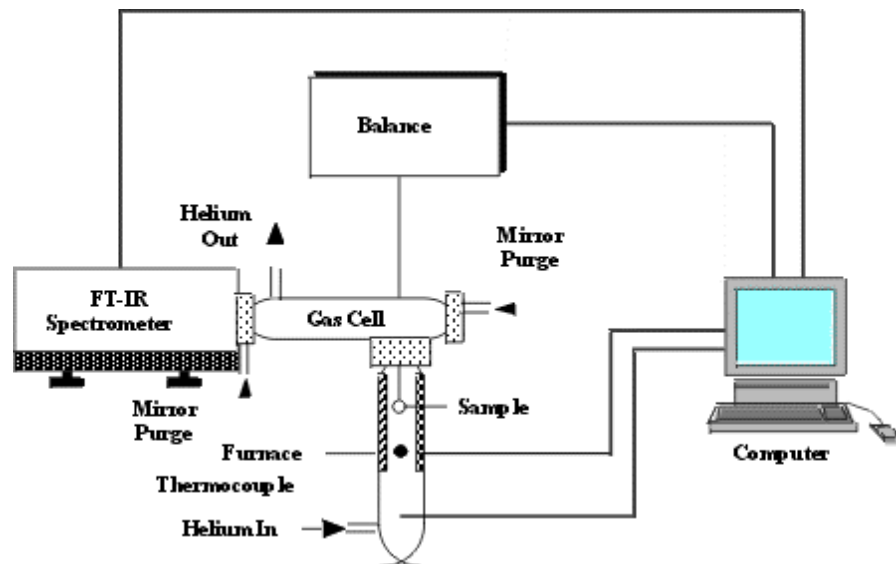


### MINOR APPLICATIONS

- DSC is a valuable tool in choice of suppository base.
- In study of polymer composition ,miscibility & individual characterization.
- Study of tablet coating
- Determinations of melting point. etc
- Determination of moisture content in drug.
- Checking technological quality grade of disintegrate.
- Study of solid drug dispersion.
- Determination of drying temp. for different excipients.

### GENERAL PRINCIPLE & APPLICATION OF FTIR SPECTRUM & X-RAY DIFFRACTION METHOD.

- Generally ,this technique are not consider as thermal technique, But if used in specific condition then this technique are classified as thermal technique.
- A) Fourier transform infrared spectroscopy(FTIR)
- Fourier transform infrared spectrometers can be single beam or Double beam.
  - Commercial FTIR spectrometers are of single beam. A double beam instrument is designed to compensate for atmosphere.
  - In most IR spectrometer ,the optical components are manufactured in sealed & desiccated compartment with a goal of reducing water & carbon dioxide interference.



**ADVANTAGE:**

- Simple
- Accurate
- Sensitive
- Speedy

**DISADVANTAGE:**

- 1) Generally not used alone.
- 2) Gives peak at same wave number,  
Eg. so not differentiate polymorph.

**B) X-RAY POWDER DIFFRACTION**

☞ X-RAY powder Diffractometry is used to characterize spray dried & crystalline material & the binary mixtures.

**PRINCIPLE:** x-ray are Diffracted & order of this diffraction is measured in form of graph.

☞ Diffraction occurs as a result of the interaction of radiation with electron of atom.

☞ **Why only x-ray are used?**

Because x-rays have wavelengths of about the same magnitude as the distance between the atoms or molecules of crystal.

🌐 **Theory** – Crystals to be examined are reduced to a fine powder and placed in a beam of monochromatic x-rays.

-- Each tiny crystal is oriented at random with respect to the incident beam.



- The crystals diffract x-ray similar to a diffraction grating.
- $\lambda$  related to  $\theta$  and  $d$  by bragg's equation:

$$n \lambda = 2 d \sin \theta$$

where,  $n$  = order of diffraction

$d$  = interatomic distance

$\theta$  = angle of incidence

- Diffraction occur as a result of the interaction of radiation with electron of atom.
- when Bragg's condition is fulfilled, a peak is detected.

### Application:-

- **For structure determination:**

- **Identification Of Impurity:**

☞ X-ray diffraction pattern of any specimens match with standard.  
Presence of Additional lines on the photograph of specimen, indicate the

presence of impurity.

e.g In cosmetic talc, the contaminant tremolite (a potentially carcinogen )

can be detected by x-ray diffraction technique.

- **Characterization of polymorphism:**

☞ Polymorphs having different lattice arrangement & give different x-ray Powder diffraction spectrum., so it is easily characterize by this technique.

- **Characterize spray dried & crystalline material.**

- **For particle size analysis.**

### Limitations of Thermal analysis

- 1) low sensitivity for transitions involving small energies.
- 2) The interpretation of the curves & DSC studies should always Include several conditions & replicate.
- 3) Impurity consisting of molecules of same size, shape, & character as those of the major component are not detected by DSC, Because these impurity fit into the matrix of the major component without disruption of lattice forming solid solution or inclusion ,such impurity are not detected by DSC.
- 4) TGA used to studies hydrates & moisture study is not always reliable.

- 5) Thermal analysis are affected by number of factors like
- a) Sample weight
  - b) Particle size
  - c) Heating rate
  - d) Atmospheric condition
  - e) Instrumental factor
  - f) Furnace atmosphere
  - g) Crucible geometry

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