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Research Article

Thermal And X Ray Crystallographic Study in Formulations

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Abstract

Thermal techniques and X ray crystallography are useful techniques that have been successfully applied in the pharmaceutical industry to reveal important information regarding the physicochemical properties of drug and excipient molecules such as polymorphism, stability, purity, formulation compatibility among others and used to determine the arrangement of atoms of a crystalline solid in three dimensional spaces respectively. In pharmaceutical industries drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. For high resolution were used to get an insight on solid state properties of the drug and evaluate drug-excipient compatibility this analytical techniques are mainly used. This article contains considerations and interpretation of the graphical data obtained from these techniques.

Keywords: Incompatibility, Excipient, Thermal analysis, X ray Diffraction

Introduction

Thermal analysis And X-ray crystallography has been employed in research and development of small molecules pharmaceuticals for many years. Small molecule active pharmaceutical ingredients (API) and excipients can crystallize as polymorphs which can have different solubilities and stabilities. Changes in solubility and stability can lead to changes in the bioavailability of the molecule [1]. Using X-ray crystallography in identifying the polymorphic form of a crystalline active pharmaceutical ingredient is well established in the literature [2] A branch of X-ray crystallography, powder X-ray diffraction, has been used to "fingerprint" a specific solid form of the crystalline API, so that any solid form changes can be identified throughout product development and commercialization[3, 4] .For small molecules, crystalline form changes can have a large impact on the bioavailability of the molecule because of the changes in solubility. In bio therapeutic formulation development crystalline changes in the formulation matrix can have an impact on the stability of the formulated product and Thermal Analysis (TA) is a group of techniques that study the properties of materials as they change with temperature. In practice thermal analysis gives properties like; enthalpy, thermal capacity, mass changes and the coefficient of heat expansion. Solid state chemistry uses thermal analysis for studying reactions in the solid state, thermal degradation reactions, phase transitions and phase diagrams.

THERMAL TECHNIQUES: [1, 2, 3, 4, 5]

Thermal analytical techniques, in which a physical property is monitored as a function of temperature or time while the analyte is heated or cooled under controlled conditions, are fundamental techniques for characterisation of drugs and drug products. The first method developed by Le Chatelier in 1887 was Differential thermal analysis. Due to different information delivered, thermal techniques are complementary to other analytical techniques. For pharmaceutical applications the methods used are,

Differential scanning calorimetry (DSC)
Differential thermal analysis (DTA)
Thermo gravimetric analysis (TGA)
Thermo mechanical analysis (TMA).

DIFFERENTIAL SCANNING CALORIMETRY:

Transformations are taken place when material is heated. These transformations are connected with heat exchange. DSC measures these transformations and also temperature of thermal phenomenon during a controlled change of temperature.DSC measures the amount of energy absorbed or released by a sample when it is heated or cooled, providing quantitative and qualitative data on endothermic (heat absorption) and exothermic

(heat evolution) processes.Only non-corrosive samples can be analyzed in this very sensitive instrument. No organic or other materials containing F, Cl, Br, or I may be submitted for DSC analysis without our knowledge. The customer must either tell us what the material is or at least that it is non-corrosive to metals and assume responsibility for possible replacement of a $3000 DSC cell if a cell is destroyed as a result of the analysis of their sample. Or, you may have us perform such analysis as may be needed to determine what the material is and whether it can be analyzed in the DSC. Sometimes a higher temperature DSC to which we have access may be able to handle somewhat more corrosive samples in the lower temperature range.he sample is placed in a suitable pan and sits upon a constantan disc on a platform in the DSC cell with a chromel wafer immediately underneath. A chromel-alumel thermocouple under the constantan disc measures the sample temperature. An empty reference pan sits on a symmetric platform with its own underlying chromel wafer and chromel-alumel thermocouple. Heat flow is measured by comparing the difference in temperature across the sample and the referencechromel wafers.

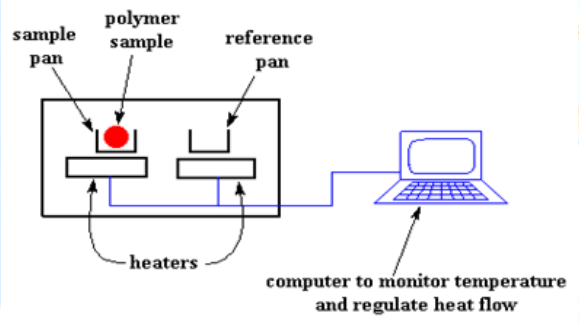


Fig no.1 Schematic principle diagram of Differential scanning calorimetry

Temperature can range from -120°C to 725°C, though an inert atmosphere is required above 600°C. The temperature is measured with a repeatability of ±0.1°C. We have access to a higher temperature DSC/DTA instrument capable of a maximum temperature of 1500°C, though it has slightly lower sensitivity at temperatures below 725°C. Pans of Al, Cu, Au, Pt, alumina, and graphite are available and need to be chosen to avoid reactions with samples.Atmospheres: nitrogen, air, oxygen, argon, vacuum, controlled mixed gases.

Calorimetric Specifications:

1. Sensitivity: 6 μW/cm
2. Precision: 1%
3. Baseline noise: ±5 μW
4. Baseline stability: 20 μW (ambient to 200°C); 400 μW (ambient to 600°C)
5. Maximum power output is 300W
6. Sample size: from 0.5mg to 100mg.
7. Samples can be encapsulated in aluminium pans using a pan press
8. Used to determine the thermal properties of plastics, adhesives, sealants, metal alloys, pharmaceutical materials, waxes, foods, lubricants, oils, catalysts, and fertilizers.

Applications of Differential Scanning Calorimetry

a. Metal alloy melting temperatures and heat of fusion.
b. Metal magnetic or structure transition temperatures and heat of transformation.
c. Intermetallic phase formation temperatures and exothermal energies.
d. Oxidation temperature and oxidation energy.
e. Exothermal energy of polymer cure (as in epoxy adhesives), allows determination of the degree and rate of cure.
f. Determine the melting behavior of complex organic materials, both temperatures and enthalpies of melting can be used to determine purity of a material.
g. Measurement of plastic or glassy material glass transition temperatures or softening temperatures, which change dependent upon the temperature history of the polymer or the amount and type of fill material, among other effects.
h. Determines crystalline to amorphous transition temperatures in polymers and plastics and the energy associated with the transition.
i. Crystallization and melting temperatures and phase transition energies for inorganic compounds.
j. Oxidative induction period of an oil or fat.
k. May be used as one of multiple techniques to identify an unknown material or by itself to confirm that it is the expected material.
l. Determine the thermal stability of a material.
m. Determine the reaction kinetics of a material.
n. TMA can also be used to measure glass transition temperatures, melting temperatures, crys-

talline phase formation temperatures, and crystalline to amorphous transition temperatures. It is often more sensitive to detecting the transition, but cannot measure the energy of the transition as DSC does. It also may measure the temperature more accurately when sample thermal conductivity is low or its dimensions are large since DSC has to have a higher rate of temperature change commonly to detect the transitions.

Differential thermal analysis (DTA):[3]

Differential thermal analysis is a thermo analytic technique, similar to Differential Scanning Calorimetry DSC. In DTA, the material under study and an inert reference are made to undergo identical thermal cycles, while recording any temperature difference between sample and reference. This differential temperature is then plotted against time, or against temperature (DTA curve or thermogram). Changes in the sample, either exothermic or endothermic, can be detected relative to the inert reference. Thus, a DTA curve provides data on the transformations that have occurred, such as glass transitions, crystallization, melting and sublimation. The area under a DTA peak is the enthalpy change and is not affected by the heat capacity of the sample.

A DTA consists of a sample holder comprising thermocouples, sample containers, a ceramic or metallic furnace, a temperature programmer; and a recording system. The basic configuration is the two thermocouples are connected in a differential arrangement and connected to a high gain low noise differential amplifier. One thermocouple is placed in an inert material such as Al2O3, while the other is placed in a sample of the material under study. As the temperature is increased, there will be a brief deflection of the voltage if the sample is undergoing a phase transition. This occurs because the input of heat will raise the temperature of the inert substance, but be incorporated as latent heat in the material changing phase.

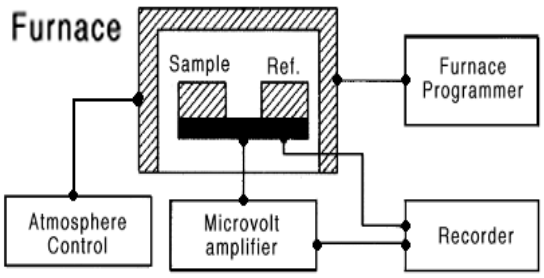


Fig no.2 Schematic principle diagram of Differential thermal analysis (DTA)

In today's market most manufactures no longer make a DTA but rather have incorporated this technology into a Thermogravimetricanalysis(TGA), which provides both mass loss and thermal information. With today's advancements in software, even these instruments are being replaced by true TGA-DSC instruments that can provide the temperature and heat flow of the sample, simultaneously with mass loss.

Applications

1. A DTA curve can be used only as a finger print for identification purposes but usually the applications of this method are the determination of phase diagrams, heat change measurements and decomposition in various atmospheres.
2. DTA is widely used in the pharmaceutical and food industries
3. DTA may be used in cement chemistry, mineralogical research and in environmental studies.
4. DTA curves may also be used to date bone remains or to study archaeological materials.

Thermogravimetric Analysis (TGA):[4]

Thermogravimetric analysis or thermal gravimetric analysis (TGA) is a type of testing that is performed on samples to determine changes in weight in relation to change in temperature. Such analysis relies on a high degree of precision in three measurements: weight, temperature, and temperature change. As many weight loss curves look similar, the weight loss curve may require transformation before results may be interpreted. A derivative weight loss curve can be used to tell the point at which weight loss is most apparent. Again, interpretation is limited without further modifications and deconvolution of the overlapping peaks may be required.

TGA is commonly employed in research and testing to determine characteristics of materials such as polymers, to determine degradation temperatures, absorbed moisture content of materials, the level of inorganic and organic components in materials, decomposition points of explosives, and solvent residues. It is also often used to estimate the corrosion kinetics in high temperature oxidation.Simultaneous TGA-DTA/DSC measures both heat flow and weight changes (TGA) in a material as a function of temperature or time in a controlled atmosphere. Simultaneous measurement of these two material properties not only improves productivity but also simplifies interpretation of the results. The complementary information obtained allows differentiation between endothermic and exothermic events which have no associated weight loss (e.g., melting and crystallization) and those which involve a weight loss (e.g., degradation).

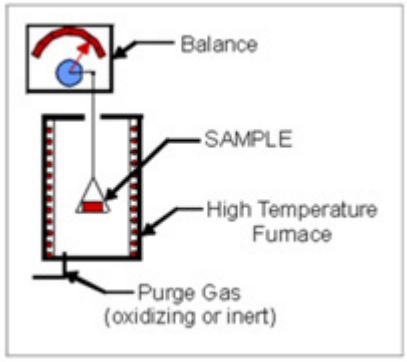


Fig no.3 Schematic principle diagram of Thermo gravimetric Analysis (TGA)

The analyzer usually consists of a high-precision balance with a pan (generally platinum) loaded with the sample. The pan is placed in a small electrically heated oven with a thermocouple to accurately measure the temperature. The atmosphere may be purged with an inert gas to prevent oxidation or other undesired reactions. A computer is used to control the instrument.

Analysis is carried out by raising the temperature gradually and plotting weight against temperature. The temperature in many testing methods routinely reaches 1000°C or greater, but the oven is so greatly insulated that an operator would not be aware of any change in temperature even if standing directly in front of the device. After the data is obtained, curve smoothing and other operations may be done such as to find the exact points of inflection.

A method known as hi-resolution TGA is often employed to obtain greater accuracy in areas where the derivative curve peaks. In this method, temperature increase slows as weight loss increases. This is done so that the exact temperature at which a peak occurs can be more accurately identified. Several modern TGA devices can vent burn off to an infrared spectrophotometer to analyze composition.

Applications of Thermogravimetryanalysis:

1. Determining the purity and thermal stability of both primary and secondary standards.
2. Investigating the correct drying temperatures and the suitability of various weighing forms for gravimetric analysis
3. Direct application to analytical problems
4. Determining the composition of alloys and mixtures
5. Thermogravimetry is a valuable technique for assessing the purity of materials.

Thermo mechanical analysis (TMA) [5]

Thermo mechanical analysis (TMA) easily and rapidly measures sample displacement (growth, shrinkage, movement, etc.) as a function of temperature, time and applied force.Traditionally, TMA is used to characterize linear expansion, glass transitions, and softening points of materials by applying a constant force to a specimen while varying temperature. For expansion measurements, a probe rests on a sample on a stage with minimal downward pressure. Other constant force experiments include measurement of penetration, bending, tension, shrinkage, swelling, and creep (sample motion measured as a function of time under an applied load).

Sample Chamber: The easily accessible chamber is located in the centre of the furnace. Both temperature and atmosphere can be controlled. In addition an optional mass flow controller is available for purge gas regulation. The gas tight cell can be evacuated and allows you to measure under a defined atmosphere. Only such a system can provide definitive information concerning the samples sensitivity to oxidation.

Furnace: The TMA Platinum Series comes with a robust and reliable furnace. Its customized design

enables rapid heat up and cool down times and an excellent heating rate control over the entire temperature range.

Applications of Thermo mechanical analysis (TMA)

TMA applications are in many ways the simplest of the thermal techniques. We are just measuring the change in the size or position of the a sample. However, they are also incredibility important in supplying information need to design and process everything from chips to food products to engines. Because of the sensitivity of modern TMA, it is often used to measure Tgs that are difficult to obtain by DSC, for example those of highly cross-linked thermosets.

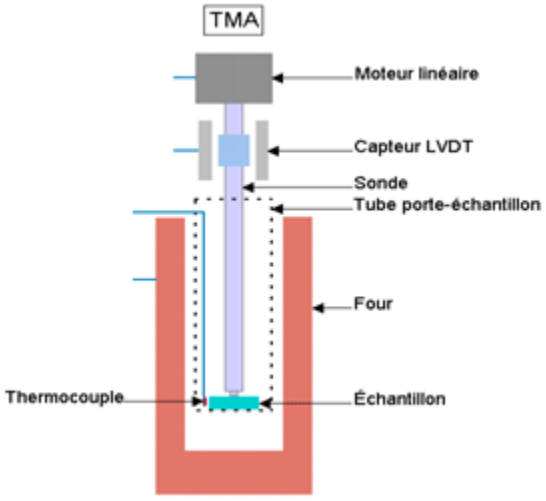


Fig no.4 Schematic principle diagram of Thermo mechanical analysis (TMA)

Considerations and interpretation of the graphical data obtained from these techniques[4]

The energy of the isolated system remains constant and the energy exchange of the system must be equal but opposite in sign to the entry of the environment (First law of thermodynamics, conservation of energy). This is the basis for endothermic and exothermic reaction. Based on the assumption that the system is closed, any reaction carried inside calorimeter can be subdivided into small reversible steps (Hess' law of summation). It defines the internal energy, dU, as the sum of change in heat that has been transferred to the system, dq and work done dW.

$$dU = dq + dw$$

When operated at constant pressure equation can be written as

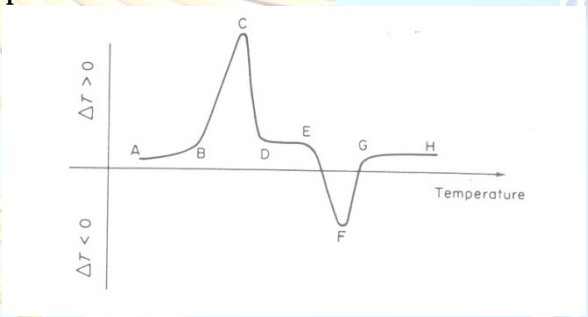
$$dH = dU + Pdv \text{(At constant pressure)}$$

Thus the enthalpy is effectively equal to the heat added or lost from the system, and changes in enthalpy can be measured directly in a calorimeter as dq (heat flow). The heat exchange dqis equal to the change in enthalpy dH, which is related to heat capacity, C_P:

$$dq = dH = \int_{T_2}^{T_1} Cp\, dT$$

The increase in temperature of the system (from T_1 to T_2) is a function of its capacity. If C_P is large, then the transfer of given amount of heat system results in only a small temperature increase.

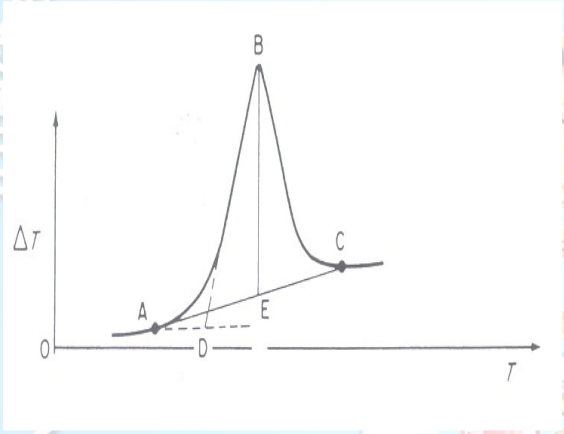
Interpretation Of DTA/DSC Curves-Onset Temperature: [6]



Part of an idealised DTA curve is given above a small thermal lag normally develops between sample(s) and reference material (r) due to mainly to the thermal capacity of S. So there is gradual increase of ΔT with temperature T initially (AB) until begins to undergo an exothermic effect at B. point B where the begins to deviate from the baseline correspond to onset temperature at which the exothermic effect is first detactable.The peak temperature C corresponds to maximum rate of heat evolution detected. It does not represent the max. Rate of reaction nor the completion of exothermic process. Further more the position of C is influenced significantly by experimental factors, such as heating rate so the position of peak C is less useful than it may first appear. Now to proceed he exothermic causing peak BCD is completed at same temperature between C and D the record

returning to baseline D note the levels of base line AB Sand DE above the abscissa are different.

Account for the Difference In Baseline Level:
It is due the fact that the heat capacity of sample has changed as a result of exothermic process.
From Fig.4 we see that the onset of an endothermic process is indicated by the downward movement of baseline at E giving endothermic peak EFG to which the similar comments about peak temperature significance (at F) also apply.When the endotherm is complete, stable thermal phase is indicated by baseline GH.Again a change in heat capacity is indicated by baseline GH and DE are not on the same level.
Extrapolated onset temperature:
It is a temperature which corresponds to the point of interception(D) of the tangent (drawn at the point of max.



Slope of the leading edge (AB) of the peak,and extrapolate baseline (AD). A and C represents point where the curve begins to deviate from baseline, i.e. A is the onset temperature. Good agreement has been reported between experimental melting point temperatures, the later being determined by the extrapolated onset technique.

Factors affecting DTA/DTA curves:
Sample factors:
Amount of sample-the peak areas are proportional to the mass of sample involved in thermal transition
The choice depends on the nature of analytical-problems. If we want to measure thermal effects which are small in magnitude, e.g. second order or glass transition (T_g) temperature in polymers we shall need to use more sample than we need for the measurement of large thermal effects eg melting point . Normaly the sample wt. required by modern instruments will be in the range 1-10 mg.
Small amounts of sample:

- Yield maximum resolution of peaks,
- Yield based qualitative results,
- Yield most regular peak shapes,
- Permit best thermal contact with sample container,
- Allow efficient removal of volatile decomposition products,
- Minimize thermal gradient within sample,
- Permit use of higher heating rates,

Whereas *larger amount of samples:*

- Allow detection of small thermal effects more readily,
- Provide more precise quantitative measurements,
- Produce greater quantity of volatile for subsequent evolved gas analysis (EGA) if required

Heating Rate:

- Smaller samples allow use of higher rates of heating eg 10°C/min or more.
- Larger samples requires lower heating rates eg 5°C/min or less.
- Thermal gradients are obiviously to be a more problem with larger samples.
- Increase in heating rate results into,
  (1) Increases the procedural peak temperature.
  (2) Deacrease the resolution between two adjacent peak.

Particle Size:
Fine particles are generally preferable and use particles of uniform size.
Sample Packing:
Since tight packing may impede interactions with atmosphere and allows also escape of volatilities so reproducible methods of packing is desirable. Eg tapping with rod.

Diluents:
Glass beads, powedered alumina, iron fillings are used which do not react with sample but modifies properties like,
Reduce the peak area associated with sample.
To bulk up a small sample.
Modify heat capacity and thermal conductivity of sample.

(3) Atmosphere around sample:

(4) Flowing gas is preferable around sample rather than static- which is liable to degradation also the volatilities by products get sweeped out.

(5) Let us consider the case of calcium oxalate monohydrate

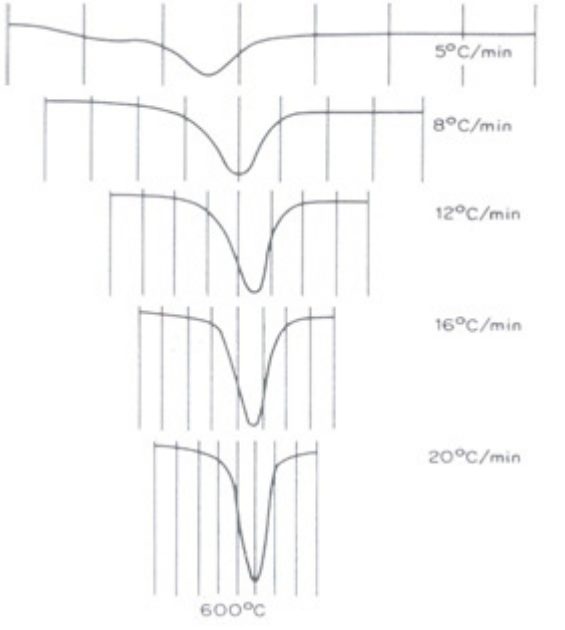


Fig no.5 Variation of peak temperature of kaolin with rate of temperature increase.

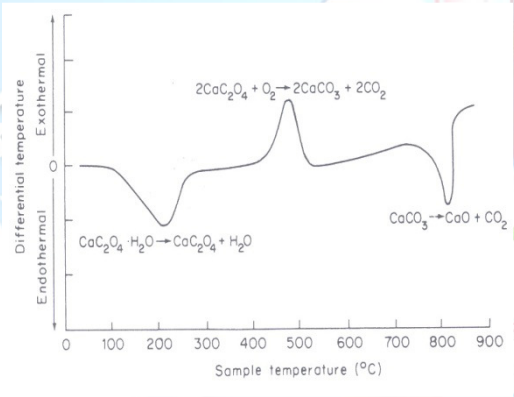


Fig No.6 DTA record of $CaC_2O_4.H_2O$ in the presence of O_2; the rate of temperature increase was 8°C/min

There are two endotherms corresponding to following reactions

$CaC_2O_4.H_2O \longrightarrow CaC_2O_4 + H_2O$ (200°C)

$CaCO_3 \longrightarrow CaO + CO_2$ (800°C)

(**The intermediate reaction is exothermic in air, but endothermic in nitrogen)**

Relevant chemical equations,

$CaC_2O_4 \longrightarrow CaCO_3 + CO$ (IN NITROGEN) endothermic

OR

$2CaC_2O_4 + O_2 \longrightarrow 2\ CaCO_3 + 2\ CO_2$ (IN OXYGEN) exothermic

So again sample atmosphere is of critical importance in determining the nature of the thermal process.

Oxidation of $COCO_2$ doesn't affect the wt. changes in the TG record (which monitors residuewt. and not volatiles). However for DTA/DSC experiment it is endothermic-exothermic effects which are recorded and not weight changes. For this reason temperature taken of reaction is between 400-500°C.

Factor – variations in	Effect – to cause	Recommendation:
Heating rate	Changes in peaks	Use a low heating rate
Location of thermocouple	Irreproducible curves	Standardise thermocouple location
Atmosphere around sample	Changes in the record	Use flow of inert gas
Amount of sample	Changes in peaks	Standardise sample weight
Particle size of sample	Irreproducible curves	Use small, uniform particle size
Packing characteristics of sample	Irreproducible curves	Standardise packing technique
Sample container	Changes in peaks	Standardise container

Table No.1 some common factors that influence DTA record.

DTA/DSC in polymers: [4, 6]

Effect of additives on polymer properties may also be investigated, as,

Glass transition temperature(Tg):

Second order transition (because it is relatively small in magnitude) which causes change in heat capacity and hence shift in base line. Below Tg polymer looses its flexible working behaviour.

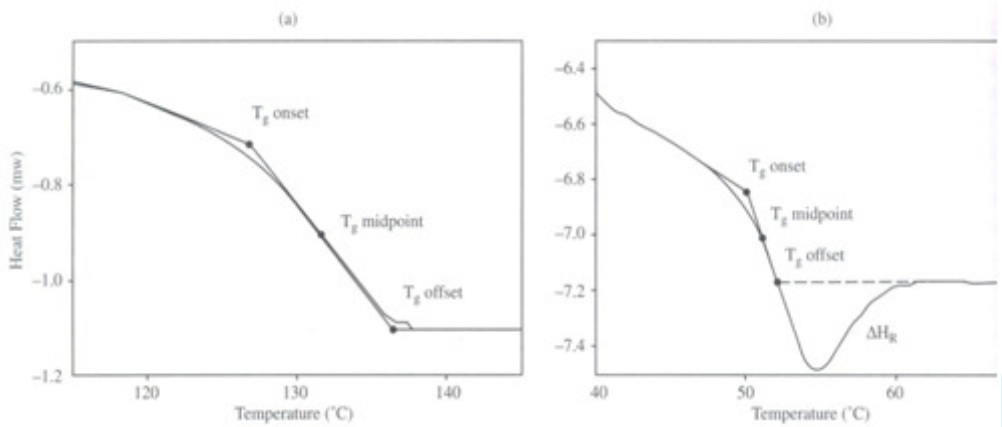


Fig no 7 (a) Glass transition(T_g) temperature of miscible blend of MK-591 with 10% PVP (b) T_g of sucrose with enthalpic relaxation endotherm and enthalpy(ΔH_R)

Amorphous State study:

Amorphous compounds are characterised by T_g..For amorphous substances, there is no melting point, and the change of slope occurs at the so-called last Transition Temperature.

These compounds are unstable thermodynamically and are characterised by T_g by DSC is seen as increase in heat capacity,

$$\Delta Cp = Cp_{liq} - Cp_{glass}$$

Where Cp_{liq} is heat capacity of liquid and Cp_{glass} heat capacity of glassy phase.

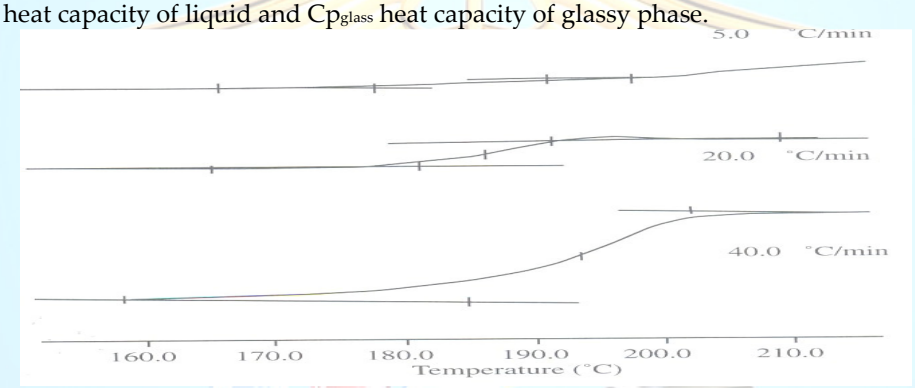


Fig No. 8 Quality control excipients by Tg. Example of Carbopol 974 P. Second DSC run in order to eliminate water and relaxation: influence of heating rate.

Tg is measured either at its onset or midpoint as shown in above fig.7. Above this temperature amorphous substance retains some properties of liquid, e.g. molecular mobility and is termed **rubbery.**

Crystalline state study:

If physical properties of crystalline substance is plotted against temperature sharp discontinuity occurs at melting point. Above Tg the increase in molecular mobility facilitate spontaneous crystallization with an exothermic enthalpy change after the Tg. Let us consider the case of blend of polyethylene (PE), high density (HD) and low density (LD).

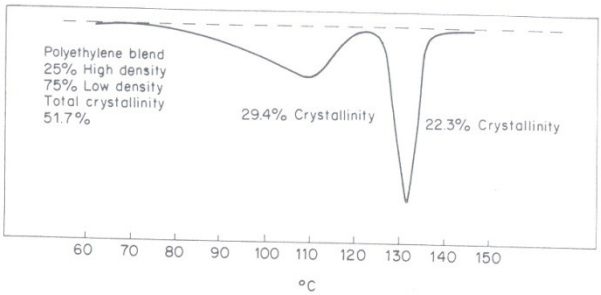


Fig No.9 Analysis of powder blend by DSC

We can see that the two forms are easily distinguished by two well separated endotherms. The HD melts at about 125-135^{0}C, LD melts between 85-115^{0}C. Note the different shapes of the two peaks- reflecting difference in chain length and branching. It is possible to measure the degree of crystallinity of each form as well as fusion from the peak.

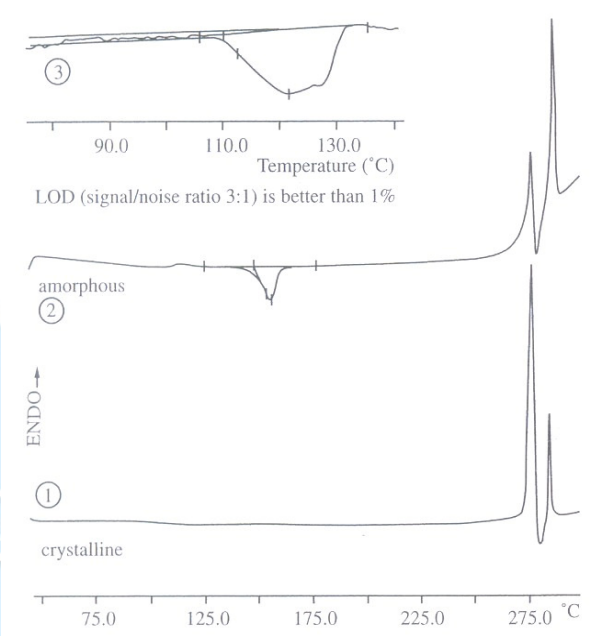


Fig10 Determination of amorphous content at 20K/min 1) Crystalline sample, 2) Amorphous sample, 3) exothermic of sample containing 4% amorphous.

Commonthermal events that can be detected using calorimetric technique:[4]

Endothermic:

Fusion- melting of substances

Melting is the first order endothermic process by which compound takes in a net quantity of heat (molar heat of fusion)

Vaporisation- evaporation of liquid and semisolid excipients

Sublimation-removal of frozen water during lyophilisation

Desorption –drying of wet granulation

Exothermic:

Crystallisation- solvent vapour induced crystallisation of amorphous excipients.

Precipitation- formation of salt forms of drug substances.

Other:

Glass transition, dissolution, complexation.

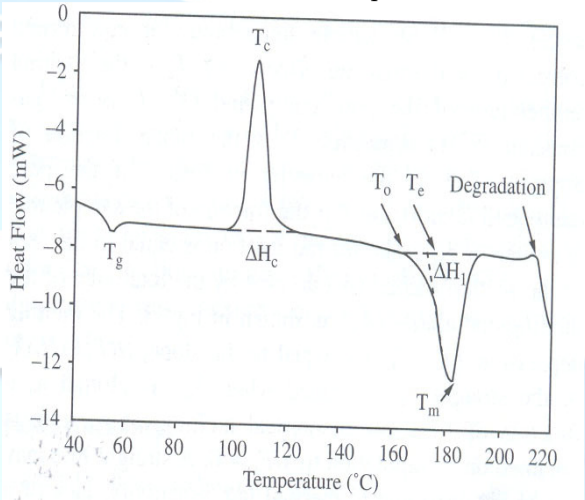


Fig no.11 DSC scan of sucrose T_g glass transition temperature, $T_c$recrystallization endotherm Temperature, ΔH_c enthalpy, t_o onset of melting, $T_e$extrapolated melting onset, T_m enthalpy of fusion, ΔH_f onset of degradation at 10K/mole.

X-ray Diffraction (XRD):[1, 2, 3, 7]

The discovery of X-rays in 1895 enabled scientists to probe crystalline structure at the atomic level. X-ray diffraction has been in use in two main areas, for the fingerprint characterization of crystalline materials and the determination of their structure. Each crystalline solid has its unique characteristic X-ray powder pattern which may be used as a "fingerprint" for its identification. Once the material has been identified, X-ray crystallography may be used to determine its structure, i.e. how the atoms pack together in the crystalline state and what the interatomic distance and angle are etc. X-ray diffraction is one of the most important characterization tools used in solid state chemistry and materials science. We can determine the size and the shape of the unit cell for any compound most easily using X-ray diffraction.

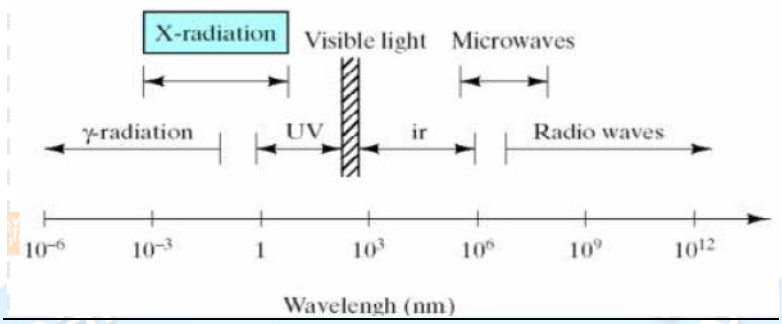


Fig 12 Electromagnetic radiations. X ray represents 0.1nm/ 1Å.

Production of X rays:

X-rays are produced by bombarding a metal target (Cu, Mo usually) with a beam of electrons emitted from a hot filament (often tungsten). The incident beam will ionize electrons from the K-shell (1s) of the target atom and X-rays are emitted as the resultant vacancies are filled by electrons dropping down from the L (2P) or M (3p) levels. This gives rise to Ka and Kb lines.

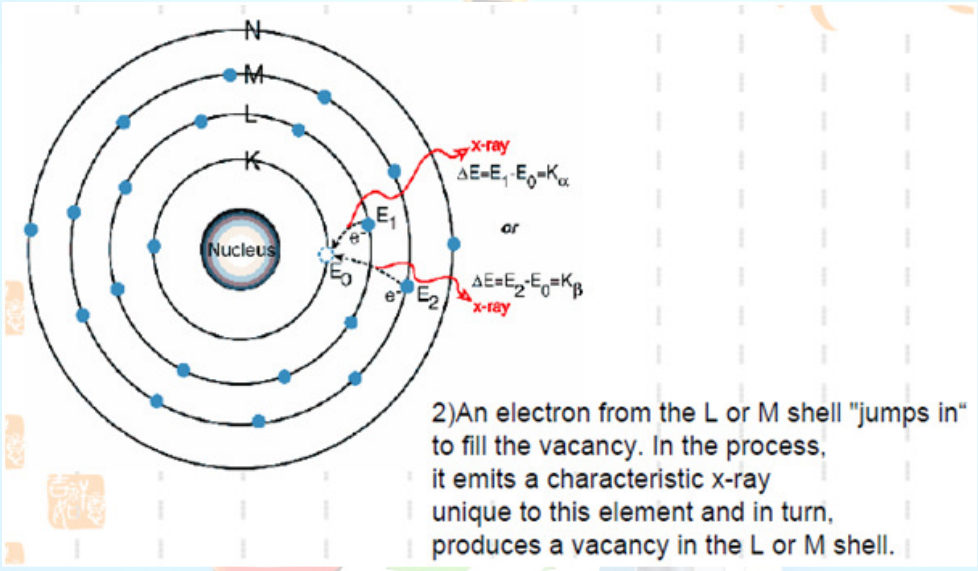
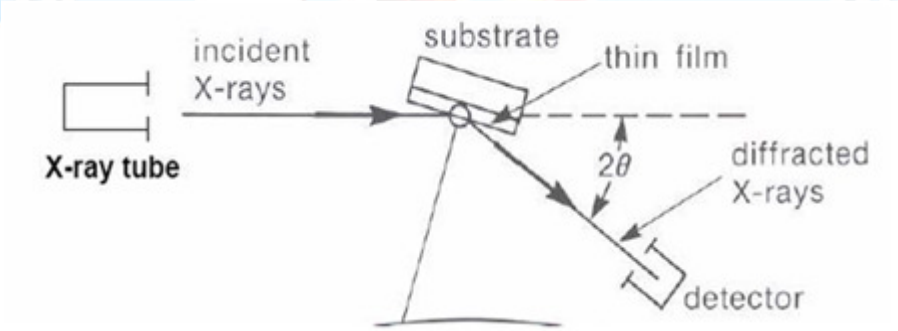
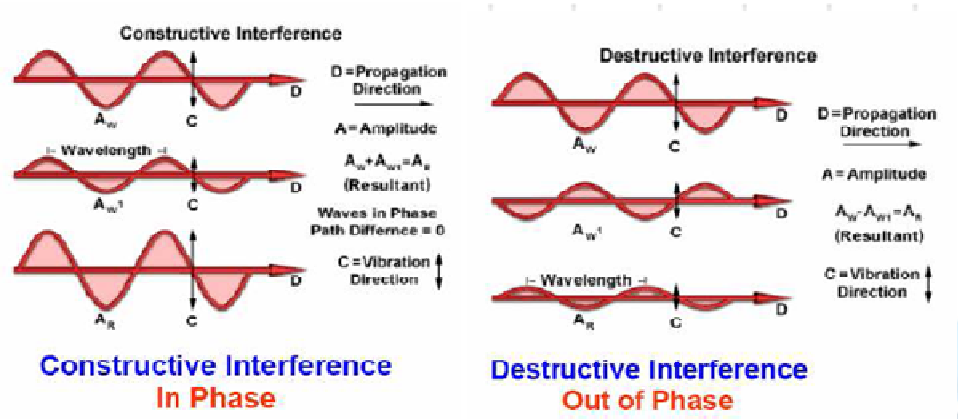


Fig 13 Production of X ray

Basic Features of Typical XRD: [11]

Experiment:





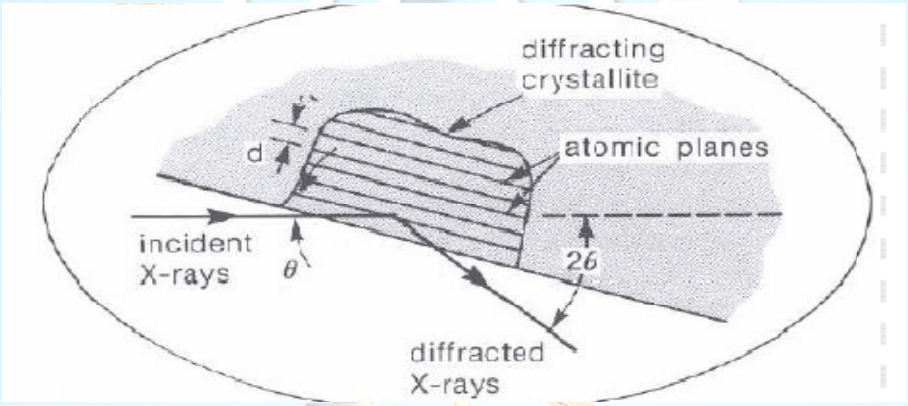
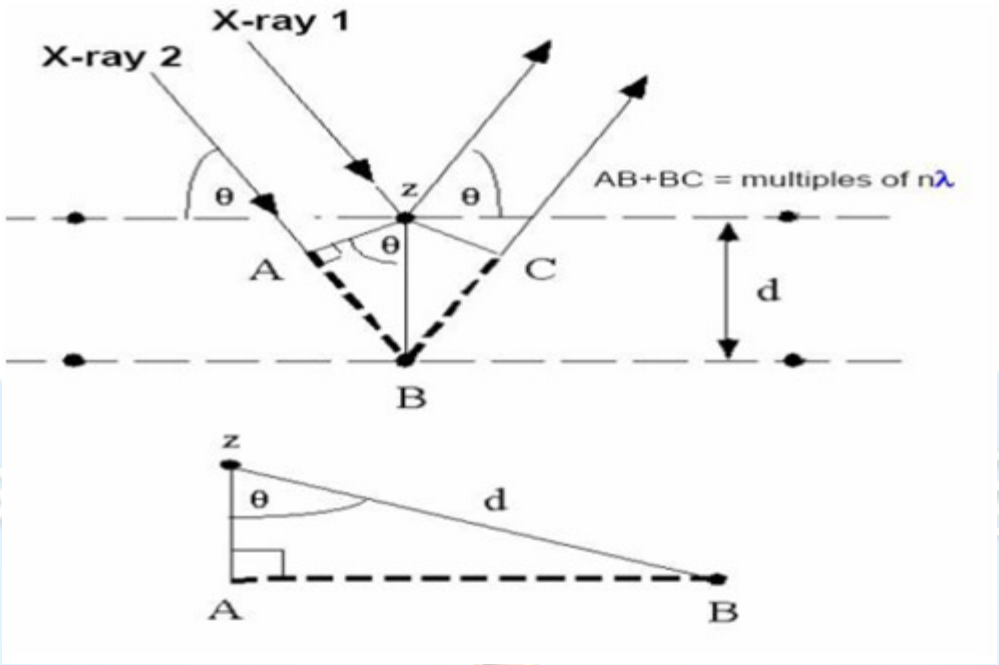


Fig 14 Instrumentation of XRD

X-ray Diffraction:

Bragg's Law $n\lambda = 2d \sin\theta$

- The variable d is the distance between atomic layers in a crystal.
- variable λ is the wavelength of the incident X-ray beam.
- n is an integer.
- θ angles of incidence.
- Diffraction occurs occurs only when bragg's law satisfies condition for constructive interference.



$N\lambda = AB + BC$

$AB = BC = d \sin\theta$

Therefore $n\lambda = 2d \sin\theta$; This is Bragg's law.

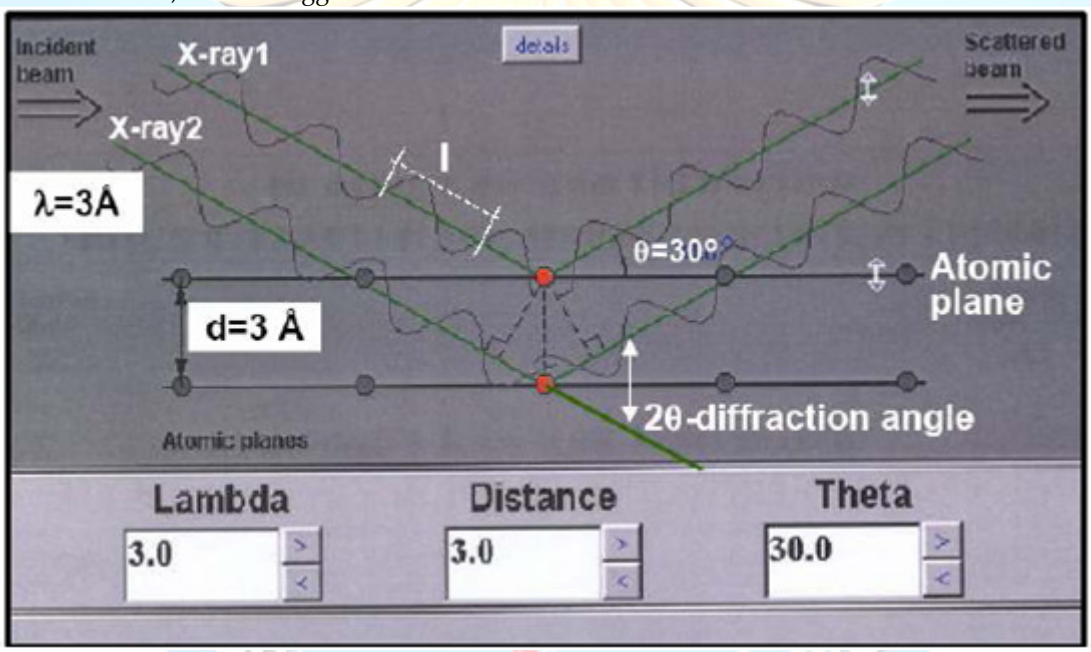


Fig 15 Planes satisfying Bragg's condition

This observation is an example of X-ray wave interference. It was direct evidence for the periodic atomic structure of crystals.

There are various applications based on line profile, eg study of preferred orientation, determination of particle size.

One of the important application in pharmaceutical is,

Polymer Analysis: [8]

Polymers are not highly absorbing to x-rays. The dominant experiment is a transmission experiment where the x-ray beam passes through the sample.

This greatly simplifies analysis of diffraction spectra for polymers but requires somewhat specialized diffract meter from those commonly used for metallurgy.

Elementary crystallography:[7]

For all seven crystal system, it is possible to derive mathematical relationship between unit cell parameter, interplanar spacing and miller indices,

$$\boldsymbol{d = \frac{a}{\sqrt{h^2 + k^2 + l^2}}}$$

Let us consider particular family of plane and examine the corresponding values of $h^2 + k^2 + l^2$

The nine families of planes are as

Hkl	100	110	111	200	210	211	220	221	300	etc.
$h^2 + k^2 + l^2$	1	2	3	4	5	6	8	9	9	

We will notice from above that no 7 is missing, this is called a forbidden no. It doesn't matter what integer values you give to h, k, l, $h^2 + k^2 + l^2$, can never equal. The next two forbidden nos are 15 and 23.

Note that 221 and 300 both gives $h^2 + k^2 + l^2$= 9 this implies that reflections from them overlapped .

If we take Braggs equation put n=1 then combine it with equation we get

$$\boldsymbol{\sin^2 \theta = \frac{\lambda^2}{4a^2}(h^2 + k^2 + l^2)}$$

Now for particular X ray powder pattern λ and a are constant,

$$\boldsymbol{\sin^2 \theta \propto h^2 + k^2 + l^2}$$

This relationship enables us to recognise the powder pattern of primitive cubic substance. We simply measure the positions of the lines from low to high Braggs angle, derived θ values, and then compute $\sin^2 \theta$ values if these are in the ratios of 1:2:3:4:5:6:8 etc. , then we must have the pattern of a primitive cubic material .

Having established these sequences, sequence of no's, we can then assign miller indices. This is called indexing the pattern.

Examples in pharmaceutical drug & excipients:[3, 7, 8]

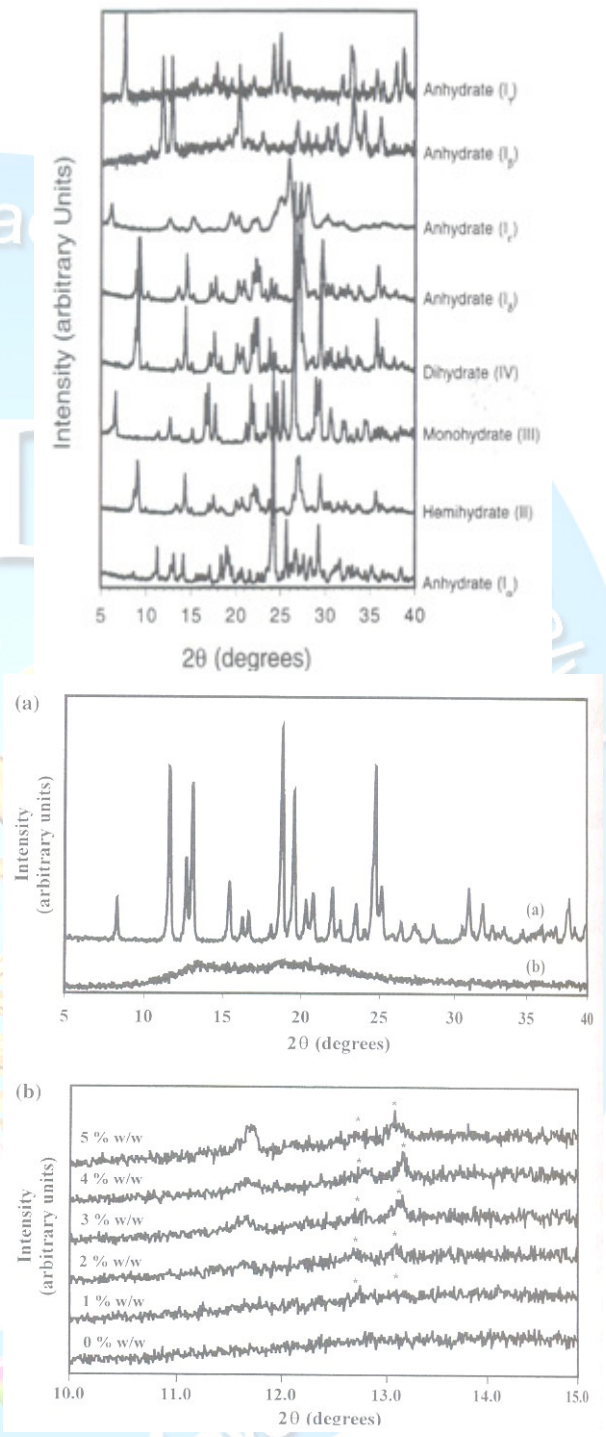


Fig no. 16 XRD pattern of (1) different solvate (2) amorphous and crystalline sucrose.

Information that we get from powder X-ray diffraction

1. Lattice parameters
2. Phase identity
3. Phase purity

4. Crystallinity
5. Crystal structure
6. Percent phase composition

Conclusion:

X-Ray Crystallography is a technique for examining the structure of a regular crystal. It only works on substances that can be crystallized. An x-ray source is aimed at the crystal, and the diffraction pattern that is created as the x-rays strike the crystal are studied. In much the same way that you can infer the structure of an object by looking at its shadow, the diffraction pattern can be used to infer the structure of the crystal.n practice thermal analysis gives properties like; enthalpy, thermal capacity, mass changes and the coefficient of heat expansion. Solid state chemistry uses thermal analysis for studying reactions in the solid state, thermal degradation reactions, phase transitions and phase diagram. These two methods are mainly used in a preformulation study for formulation of pharmaceutical products.

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