Presentation on

“Polymorphisam in APIs”

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POLYMORPHISM

When a substance exists in more than one crystalline form, the different form are designated as polymorphs and the phenomenon as polymorphism.

Need to study polymorphism

• Depending upon their relative stability, one of the several polymorphic form will be physically more stable than others.

• Stable polymorph represents the lowest energy state, highest melting point and least aqueous solubility.

• Metastable form represent the higher energy state, lower melting point and high aqueous solubility .

• Metastable form converted to the stable form due to their higher energy state.

Types of polymorphism.

Enantiotrophs:-

If one form stable over certain pressure and temperature range, while the other polymorph is stable over different pressure and temperature range.

Monotrophs:-

only one polymorph is stable at all temperature below the melting point, with all other polymorph being unstable.

Pseudopolymorphism

The phenomenon in which solvent molecules get incorporated into crystal lattice of solid are known as **solvates.** This solvates exist in different crystal form called **pseuodopolymorph and** the phenomenon is called as **Pseudopolymorphism .**

Solvatomorphism

Those unit cells differ in their elemental composition through inclusion of one or more molecule of solvent is called as solvatomorphisam.

Method To Identify Polymorphism

Optical crystallography:

• Use in the identification of polymorphs crystal

• Isotropic examine that velocity of light is same in all direction

• Anisotropic crystal have 2 or3 different light velocities or refractive indices.

• Video recording system and polarizing microscope fitted during according to heating and cooling stage for investigating polymorph.

Applications

• To study degree of stability of metastable form.

• Transition temperature

• Melting point

• Rate of transition under various thermal and physical condition.

Hot stage microscopy

• Fluid stage transformation as a function of temperature is observed

• Silicon oil stage microscopy is used for detection of pseudopolymorph.

Application:

• In the study of solid-state active pharmaceutical ingredients (APIs), EXCIPIENTS and pharmaceutically relevant polymers and lipids.

X- ray diffraction method

• It provide the most complete information about solid state (identification & description)

• This method is based on the scattering of x-ray by crystals

• By this method one can identify crystalline forms of given compound.

• In an X-ray diffraction, a crystal is mounted on a goniometer and gradually rotated while being bombarded with X-rays, producing a diffraction pattern of regularly spaced spots known as **reflections.**

• It is tedious time consuming so it is not used or unsuitable for routine use.

Application:-

• Many materials can form crystals—such as salts, metals, minerals, as well as various inorganic, organic and biological molecules.

Differential Thermal Analysis (DTA)

• The advantage is that the sample size required is only 2-5mg .

• DTA measures the temp difference between sample and reference as a function of temperature or time when heating at constant rate.

• A DTA consists of a sample holder comprising thermocouples, sample containers ,ceramic or metallic block; a furnace; a temperature programmer; and a recording system.

• The key feature is the existence of two thermocouples connected to a voltmeter.

• One thermocouple is placed in an inert material such as Al2O3, while the other is placed in a sample of the material under study.

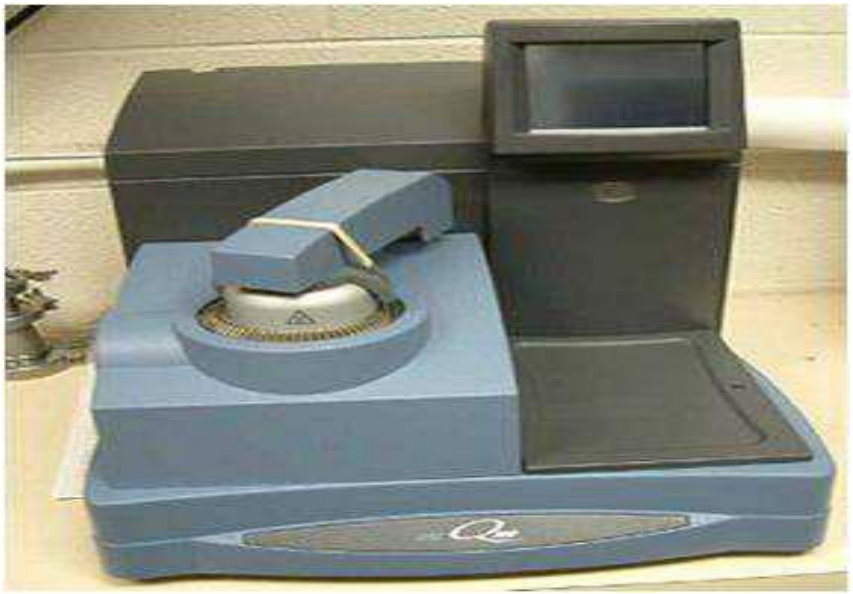
Differential Scanning Calorimetric (DSC)

• DSC is also like to DTA except that the instrument measures the amount of energy required to keep the sample at the same temperature as the reference.

• When no physical or chemical changes is occurring within the sample then there is neither a temperature change nor the need to input energy to maintain an isotherm.

• Samples that may be studied by DSC or DTA are: Powders, fibers , single crystals, polymer films, semi-solids.

• DSC measures endothermic and exothermic transitions as a function of temperature.



Applications of DTA / DSC

1. To determine the purity of a sample
2. To determine the number of polymorphs and ratio of each polymorph
3. To determine the heat of solvation .
4. To determine the thermal degradation of a drug or excipients .
5. To determine the transition temperature of a polymer.

Thermo Gravimetric Analysis (TGA)

•It determines the changes in weight in relation to change in temperature of a sample.

• As many weight loss curves look similar, the weight loss curve may require transformation before results may be interpreted.

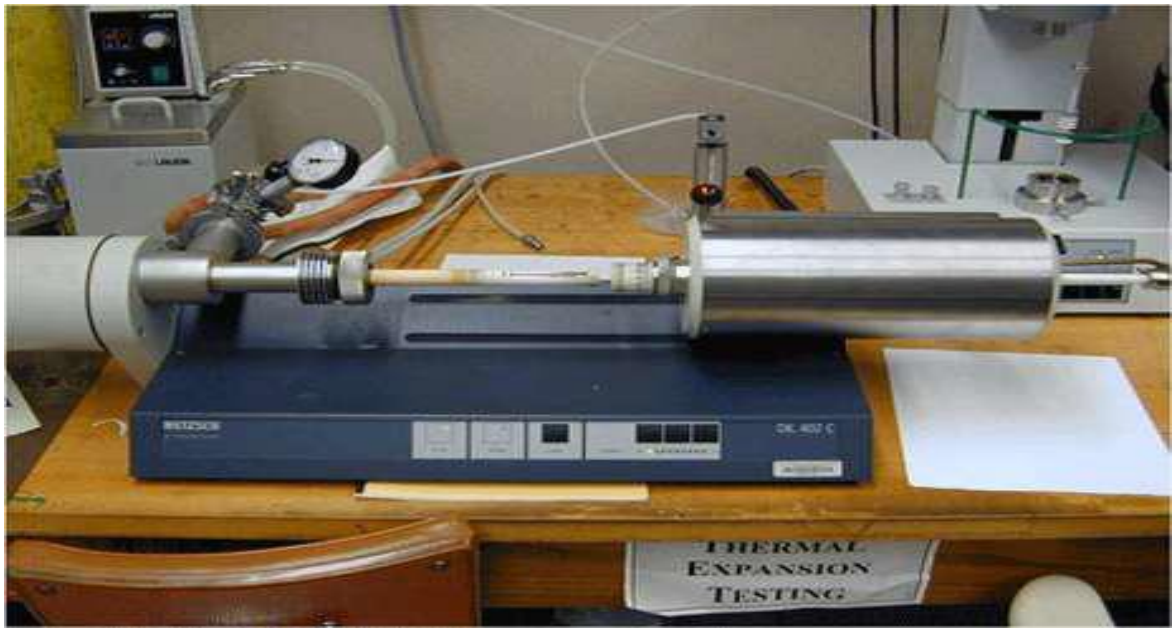
Applications

•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.

Dilatometry

- Measure change in volume caused by thermal or chemical effect.
- Using dilatometry the melting behaviour of Theobroma Oil was studied.
- Extremely accurate but tedious , time consuming and not widely used.



Melting point

Methods of preparation of polymorphs in APIs.

A) Crystallization

- From solution
- By using cooling techniques
- By using seeding techniques
- Evaporative crystallization
- By using anti-solvent
- By using ultrasound
- Capillary crystallization
- Crystallization by using additives

B) Mechanochemical methods

❖Grinding

❖Cryogenicgrinding

C) Other methods

❖Thermal methods

❖Sublimation

❖Slurrying