The International Journal Of Engineering And Science (IJES)
|| Volume || 5 || Issue || 6 || Pages || PP -29-34|| 2016 ||
ISSN (e): 2319 – 1813 ISSN (p): 2319 – 1805

Evaluation of Various Polymorphs by Different Techniques and Their Characterization A Review

K.P.Kadam[1], R.P.Chavan[2]

[1]*Research Scholar Of Shri Jagdishprasad Jhabarmal Tiberewala Univercity, Jhunjhunu, Rajasthan.*
[2]*Department Of Chemistry, Dnyanasadhana College [Thane] Maharashtra. Dnyansadhana College, Department Of Chemistry, Sathewadi Off. Highway, Thane (W)-400604.*

----------ABSTRACT----------

Polymorphism evolved out as a major point of attention for industry as well as regulatory agencies. Many pharmaceutical compounds exist in different crystalline forms and thus exhibit polymorphism. Polymorphism may affect Chemical and Physical Stability, Apparent Solubility, Dissolution, Bioavailability and Bioequivalence and Manufacturability of drug product, which require special attention during product development as it affects the quality, safety and efficacy of drug product. In addition to this, impact of polymorphism, monitoring and control of polymorphism and reporting scheme of polymorphic information in Abbreviated New Drug Application.

Keywords*: Polymorphisms, Carbamazepine, Enantiotropy, Monotropy, Dynamic allotropy, TGA, XRPD, S-NMR, DSC, FTIR.*

Date of Submission: 24 May 2016 Date of Accepted: 15 June 2016

I. INTRODUCTION

Evaluation of drug substances polymorphism play vital role in reformulation study because polymorphism gives impact on crystal lattices which may be modified drug behavior in pharmaceutical sector. Polymorphs are different crystalline forms of the drug substances that may be having different physicochemical properties such as solubility, dissolution rate, stability and bio availability. Polymorphism word found from Greek word poly means many and morphs mean shape. Thus it is defined as ability of a molecule exhibits in two or more than two crystalline phases. Theses crystalline phases have different arrangements or conformations of the molecules in the crystal lattice. Polymorphism play an important role in all of chemical research where full characterization of a material; has pivotal role in their uses such as Pharmaceutical, polymer, agrochemical, pigments and fine chemicals.

Important role of polymorphism in pharmaceutical.

1) It is an effective element in drug development.
2) Each drugs exhibits in different forms and each forms having their distinct chemical and physical properties like melting point, solubility, stability, dissolution rate, optical, electrical, and mechanical properties, vapor pressure and density.
3) These proportion are reflect with manufacturing of drug substances then drug product and then stability, dissolution rate, bio availability of drug product.
4) Polymorphism is very common among pharmaceutical substances and thermodynamic stability of polymorphs have influence on drug product pharmaceutical properties like bio availability, process ability and manufacturability.
5) Mostly polymorphic forms highly prone to temperature.
6) Major challenges in differentiating, isolation and characterization of polymorphs in pharmaceutical.

Application of polymorphism in pharmaceutical.

Purification of drugs:

Traditional technique is crystallization of drug substances to isolate impurities by recystallization.

Proper crystallization technique:

Crystallization has impact on micromerities of drugs like compressibility and wet ability.

Enhanced physical stability:

Crystalline forms play an important role in product properties such as suspension stability and hardness of tablets. This can be done by using dehydrating agent like dried absolute alcohol and glycerol, due to this stability of substances is enhance.

Handling of drug:

Drug is introduced in human body as a drug product thus handling of drug substances while formulation is also important and similarly the type of packing.

Better chemical stability:

Crystallization enhanced stability of product example like amorphous penicillin G is less stable than its crystalline salts. Similarly Amitryptyline is more stable in crystalline form.

Impact on bioavailability:

Some drugs show their drug properties in crystalline form like penicillin G. Its unwanted degradation in gastrointestinal fluid can prevent by using crystalline form.

Sustained release:

Size and shape of drug substance also play a vital role, when they are used as sustained release dosage e.g. Protamine zinc insulin.

Types of solids:

Solids are the one of the state of substance. It has definite shape, volume and weight. In this solid state atoms are bound together with bonds. Solids have regular or irregular arrangement of these atoms in molecule.

Crystalline solids:

It has regular three dimensional geometric structures. Arrangement of ions in crystalline solids is more stable. Bond and the bond length between different ions, molecules and atoms is uniform, due to this crystalline phase shows sharp melting point. Breaking of these bonds in the crystals while heating is uniform or at the unique time. The physical properties like thermal conductivity, refractive index, electrical conductivity and mechanical strength of crystals in solid crystals are different as per different directions. Crystalline solid is more stable than their other counter parts.

Amorphous Solids:

In this form bond and bond strength between two atoms is not uniform, thus it doesn't show uniformity in external structure. Due to this reasons, its melting point is not sharp. Amorphous solids expressed their melting point in range form.

Crystals are commonly having structure like cubic, Hexagonal, Tetragonal, orthorhombic, monoclinic and triclinic. This effective shape and size of molecule not only in drug substances but also in inorganic or metal solid, polymer and fine chemicals.

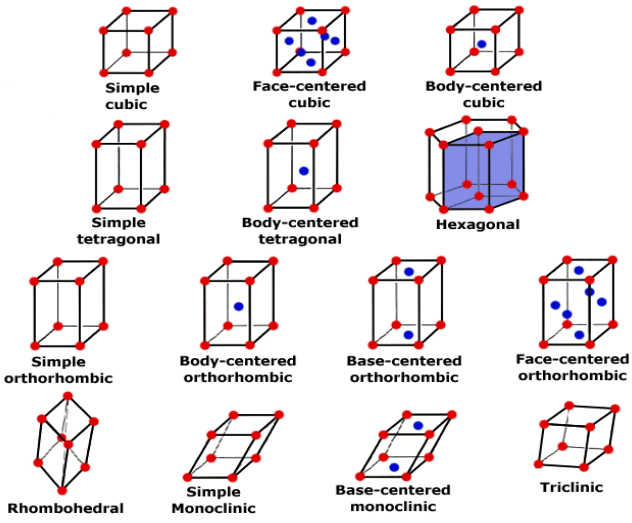


Fig1. Different crystalline shape.

4-Aminophenone is an antipyretic agent, it is called as paracetamol. Paracetamol is available in two polymorphic form (monoclinic and orthorhombic) and one hydrate form. Stability is also differ for each form thus in pharmacy mostly stable monoclinic form is used.

Carbamazepine is exhibits in three forms CBZ I, CBZ II and CBZ III (DH)

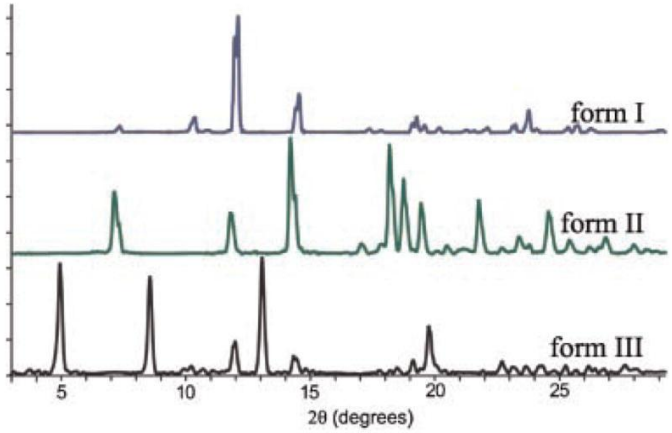


Fig.2a.PXRD of three forms of CBZ

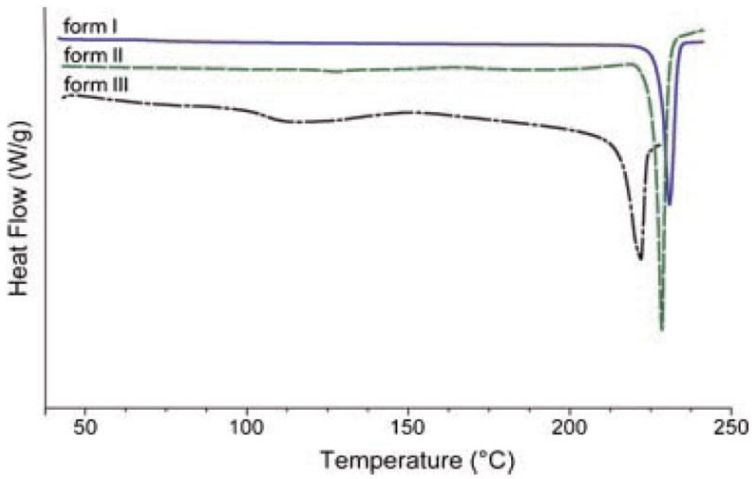


Fig.2b.DSC of three forms of CBZ

Physical properties which reflect on the parameters of crystal forms are given in following table.
Table No.1

Table No.1. Physical Properties that Differ for each Crystal Forms

Properties	**Parameters**
Packing properties	Molar volume and density, Refractive index Conductivity: electrical and thermal, Hygroscopicity
Thermodynamic properties	Melting and sublimation temperatures, Internal or structural energy, Enthalpy, Heat capacity, Entropy Free Energy and Chemical Potential, Thermodynamic Activity Vapor Pressure, Solubility
Spectroscopic properties	Electronic state transitions Vibration state transitions Nuclear spin state transitions
Kinetic properties	Dissolution rate Rates of solid-state reactions Stability
Surface properties	Surface free energy Interfacial tensions

	Crystal habit
Mechanical properties	Hardness Tensile strength

Methods used for authentic polymorphic forms:

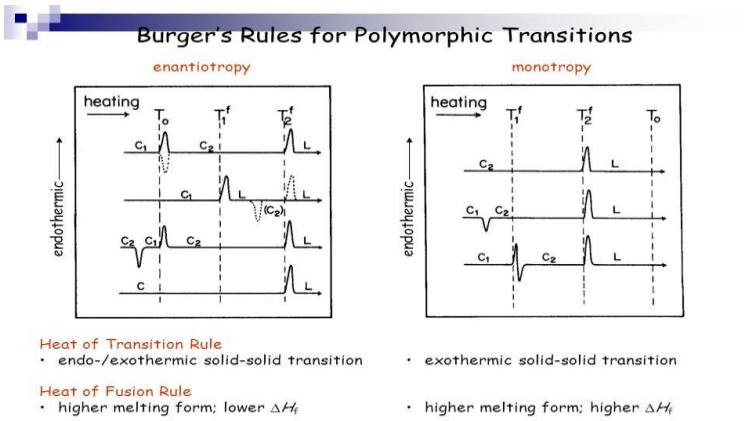
- Sublimation
- Crystallization by using mixture of solvents.
- Vapor diffusion
- Heating procedure
- Crystallization from melting
- Rapidly changing solution pH to precipitate acidic or basic substances
- Thermal desolvation of crystalline solvates
- By using some Additives
- Milling and Griding

Types of Polymorphism:

Enantiotropy:

In some cases one polymorphic form can change into another at a definite temperature when the two forms have a common vapour pressure. This temperature is known as the transition temperature. One form is stable above this temperature and the other form below it. When the change of one form to the other at the tranaisition temperature is revesible, the phenomenon is called Enantiotropy and the polymorphic forms enantiotropes.

For example, rhombic sulphur (α-sulphur) on heating changes to monoclinic sulphur (β-sulphur) at 95.6ºc (transition temperature). Also monoclinic sulphur, on cooling, again changes to rhombic sulphur at 95.6°C



Monotropy:

It occur when one form is stable and the other metastable. The metastable changes to the stable form at all temperature and the change is not reversible. Thus there is no transition temperature as the vapor pressures are never equal. This type of polymorphism is exhibited by phosphorus. For.eg. Nicergoline , a potent blocking agent for α-1-advenirecptors exhibits two forms Triclinic form (firm-I) and orthorhombic form (form-II). This triclinic form is stable at melting point 134°C, while orthorhombic form is melt at 120-122°C and transfer in to stable form.

Dynamic allotropy:

Some substance has several forms which can coexist in equilibrium over a range by the temperature. The separate forms usually have different molecular formulae but the known as dynamic allotropy, resembles enantiotropy transition point.

II. CHARACTERIZATION OF POLYMORPHS

A number of techniques have been used to identify different polymorphic phases of a compound of methods provides a powerful means for identification and isolation of each crystalline modification.

Optical microscopy:

It determines the optical properties (birefringence, indices of refraction, interference figure, dispersion color etc) and morphological properties of particles.

Scanning Electron Microscopy:
It determines surface topography and type of crystals (Polymorphism and crystal habit)
Hot Stage Microscopy:
The polarizing microscope fitted with a hot stage or cold stage is an extremely valuable tool for the characterization of polymorphic or solvate system.

Single Crystal X-ray Diffraction:
Single crystal X – ray diffraction provides the most complete information about the solid state. It will give information about the position of molecular groups within the crystal and thus actually defines the differences between the different forms.

Powder X – Ray Diffraction:
Crystalline materials in powder form give characteristic X –ray diffraction patterns made up of peaks in certain position and varying intensities.

Differential Scanning Calorimetric (DSC):
It measures the heat loss or gain resulting from physical or chemical changes within a sample.

Differential Thermal Analysis (DTA):
It monitors the difference in temperature existing between a sample and a reference as a function of temperature. It is useful in fusion, boiling, sublimation, vaporization; crystalline structure inversion, solid-solid transition, and water loss generally produce endothermic effects, and exothermic effects.

Thermo gravimetric analysis (TGA):
It is a technique that measures changes in weight that occur to a sample as function of temperature over time.

Fourier Transforms Infrared Spectroscopy (FT-IR):
It is the identification of the drug present and distinguishing between solvates and anhydrous form then for identifying polymorphs.

Raman Spectroscopy: It is established technique for identifying and differentiating
Pharmaceutical polymorphs.

Solid State NMR Spectroscopy:
It is used to study crystalline solids, as well as pharmaceutical dosage forms. It is used in the nature of polymorphic variations and molecular conformations.

III. CONCLUSION

Chemical structure and molecular formula of the crystalline and amorphous form of the same drug substances are same, but the physico-chemical properties are different such as melting point. Solubility, dissolution rate, stability and bio- availability. Formulation by using crystalline form is very difficult but it is quiet stable as compare to amorphous form on shelf life, thus mostly stable form gives preference at the time of formulation.

REFERENCES

[1]. Rahul P, Venugopalan P. Polymorphism – An Overview. Resonance 2009; 14(9):882-93.
[2]. Cesur S, Gokbel S. Crystallization Of Mefenamic Acid And Polymorphs. Crystal Research Technology 2008;43(7):720-8.
[3]. Harry G.Brittain. Polymorphism In Pharmaceutical Solids, 2nd Ed. New York: Crc Press; Pp.3 & 13, 2009.
[4]. Hosokawa K, Goto J, Hirayama N. Predicition Of Solvents Suitable For Crystallization Of Small Organic Molecules. Chemical And Pharmaceutical Bulletin, 2005;53(10):1296-9.
[5]. Manavalan R, Ramasamy C, Physical Pharmaceutics, 2nd Ed. Vignesh Publisher; 2004. P. 20 & 43.
[6]. B.S. Bahl,G.D.Tuli, Arun Bahl, Essential Of Physical Chemistry;Twenty-Fourth, Edition-1997;565
[7]. Panchagnula R, Sundramurthy P, Pillai O, Shrutidevi A, Yasvanth Ar. Solid State Characterization Of Mefenamic Acid. Journal Of Pharmaceutical Science, 2004;93(4):1019-29.
[8]. Vrecer F, Srcic S, Smid-Korbar. Investigation Of Piroxicam Polymorphism. International Journal Of Pharmaceutics, 1991;68: 35-41.
[9]. Gary N, Christopher Sf. Physico-Chemical Characterization Of The Orthorhombic Polymorph Of Paracetamol Crystallized From Solution. Journal Of Pharmaceutical Science 1998;87: 684-693.
[10]. Bauer, J.; Spanton, S.; Henry, R.; Quick, J.; Dziki, W.; Porter, W.; Morris, J. Ritonavir: An Extraordinary Example Of Conformational Polymorphism. Pharm. Res. 2001, 18, 859–866.

[11]. U.S. Food And Drug Administration. Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, And Controls Information. Available Online: Http://Www.Fda.Gov/Downloads/ Drugs/Guidances/Ucm072866.Pdf (Accessed On 4 September 2014).
[12]. Threlfall, T.L. Analysis Of Organic Polymorphs. A Review. Analyst 1995, 120, 2435–2460.
[13]. Haleblian, J.; Mccrone, W. Pharmaceutical Applications Of Polymorphism. J. Pharm. Sci. 1969, 58, 911–929.
[14]. Stahly, G.P. Diversity In Single- And Multiple-Component Crystals. The Search For And Prevalence Of Polymorphs And Cocrystals. Cryst. Growth Des. 2007, 7, 1007–1026.
[15]. Taylor, L.S.; Langkilde, F.W. Evaluation Of Solid-State Forms Present In Tablets By Raman Spectroscopy. J. Pharm. Sci. 2000, 89, 1342–1353.
[16]. Olimpia Maria Martins Santos, Polymorphism: An Evaluation Of The Potential Risk To The Quality Of Drug Products From The Famacia Popular Rede Propria, Bjps,Issn 1984-8250201
[17]. Marco Farias And Renato Carneiro, Simultaneous Quantification Of Three Polymorphic Forms Of Carbamazepine In The Presence Of Excipients Using Raman Spectroscopy, Molecules 2014, 19, 14128-14138; Doi:10.3390/Molecules190914128
[18]. P. Bashpa 1*, K. Bijudas 2, Anjali M Tom 3, P.K. Archana 4, K.P. Murshida 5, K. Noufala Banu 6 , K.R. Amritha 7, K. Vimisha 8, Polymorphism Of Paracetamol: A Comparative Study On Commercial Paracetamol Samples, International Journal Of Chemical Studies, Issn: 2321-4902.
[19]. Ye Sun,3,6 Lei Zhu,4 Tian Wu,5 Ting Cai,1 Erica M. Gunn,1 And Lian Yu1,2,6, Stability Of Amorphous Pharmaceutical Solids: Crystal Growth Mechanisms And Effect Of Polymer Additives, The Aaps Journal, Vol. 14, No. 3, September 2012 (# 2012)Doi: 10.1208/S12248-012-9345-6.
[20]. *Ethiraj Thiruvengadam And Ganeshan Vellaisamy, Polymorphism In Pharmaceutical Ingredients, World Journal Of Pharmacy And Pharmaceutical Sciences, Issn 2278 – 4357