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"AN OVERVIEW: POLYMORPHISM AND ITS APPLICATIONS IN DRUG DEVELOPMENT PROCESS"

Belsarkar A.S.[1*], Shinde A.D[2]., Sonawane S.P[3]

[1]Department of Pharmaceutics, SVPM'S College of Pharmacy, MalegoanBk, Baramati-422608, Dist-Pune, Maharashtra, India.

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Abstract:

The physical properties, characterization, and uses of polymorphism are highlighted in this article. Polymorphism is important in pharmaceutical compounds and it's important to research and development of drug and drug discovery. Polymorphism in pharmacological substances is well known for its prevalence and relevance. During medication discovery and development, it is critical to plan and pick the appropriate form from the start. This review introduces the basic concepts of Polymorphism in pharmaceutical compounds and also vibrational spectroscopy in polymorphism applications and study of crystal polymorphism, cocrystals, physicochemical characteristics and uses, polymorphism research methods, Chemical stability and polymorphism, polymorphisms effect on drug substance and drug administration product polymorphism's impact on bioavailability, solubility, and dissolution bioequivalence (BA) and bioequivalence (BE) polymorphism's impact on drug product manufacturing, etc. Hence this study topic is undertaken for detail insights of phenomena of polymorphism and its relevance in drug development process.

Key words: *Polymorphism, Crystallization, Bioavilability ,API, Polymorph.*

Corresponding author:

Belsarkar A.S

Department of Pharmaceutics, SVPM'S College of Pharmacy, MalegoanBk,

Baramati- 422608, Dist-Pune, Maharashtra, India.

apurvabelsarkar5@gmail.com, *Contact : 9975395395*

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INTRODUCTION:

Polymorphism is a scientific term for similar phenomena in compounds. “AGUIAR ETAL” invented the term polymorphism in 1967. Solids can be crystalline or amorphous depending on their interior structure. Polymorphisms occur when a substance exists in several crystalline forms. Polymorph comes from the Greek terms 'poly', which means numerous, and 'morph' , which means form. As a result, polymorphism refers to a chemical substance's several structural configurations [34]. Polymorphism can be divided into two categories: monotropy and enantiotropy. Only one polymorph is stable in a monotropic system at any temperature below the solid's melting point. Different polymorphs in an enantiotropic system may be more stable than others in different temperature ranges [25].

A transition temperature exists for an enantiotropic system, which is defined as the temperature at which two polymorphs have the same free energy. Understanding the thermodynamic and interconversion connections between polymorphs is therefore essential for solid state characterization. There is growing interest in polymorph, which is partly due to increased financial pressures on pharmaceutical businesses and a clearer understanding of the impact polymorphs can have on bioavailability, manufacturability, and product stability. The physicochemical features of the drug molecule have an impact on the drug's performance. Pharmaceutical procedures such as milling, mixing, filtering, washing, drying, tableting, and dissolution can be affected by the form and particles of solid drugs [25]. In contrast, one polymorph is stable within a particle of other chemicals [34]. Physical qualities such melting point, solubility, dissolving rate, hygroscopicity, and stability differ between polymorphs of the same active pharmaceutical ingredient (API) [25]. For the study of polymorphs and solvates, a variety of physical characterization methods have been developed, with many researchers opting for the traditional approaches of crystallography, microscopy, thermal analysis, and solubility studies. The capacity to successfully synthesise and reproduce certain stable polymorphs is closely linked to drug development efficiency and speed, manufacturing process robustness, and, ultimately, API stability and quality [25].

Polymorphism and solvate formation have long been known to have pharmacological consequences, since it has been recognised that different crystal structures of a chemical entity can have varying solubilities, stabilities, or bioavailabilities. Polymorphism occurs often in organic molecules, and a large number of polymorphic medicinal compounds have been identified and catalogued. Pharmaceuticals, agrochemicals, pigments, and explosives all benefit from polymorphism [24].

Introduction to polymorph:

To this seemingly easy question, the literature offers a variety of definitions, all of which are based on McCrone'sstatement from 1965: "A polymorph is a solid crystalline phase of a substance that results from the possibility of at least two distinct configurations of that compound's molecules in the solid state." Rosenstein and Lamy proposed an alternate description in 1969: "A substance is considered to exhibit polymorphism when it may exist in more than one crystalline state."

This allows for a wide range of interpretations, including solvates. "If these (solids made of only one component) can exist in multiple crystal lattices, then we speak about polymorphism," says. "Polymorphs means the different crystal forms, belonging to the same or different crystal systems, in which the identical units of the same element or the identical units of the same compound, or the identical ionic formulas or identical repeating units are packed differently," Even a high school student understands the fundamental differences between graphite and diamond: In fact, this example is often used to demonstrate how structure affects property.Many similar examples of structure were known to chemists. Even when chemistry was in its infancy, property connections were discovered. Most science students today have internalised the phrase "graphite and diamond are allotropes." They are aware that elements have allotropes, and that this is a common occurrence Allotropism is a term used to describe a phenomenon. What about mixtures? The current situation scientifically, the phenomena in compounds is discussed in this article. Polymorphism is a term used to describe the diversity of a person's DNA.

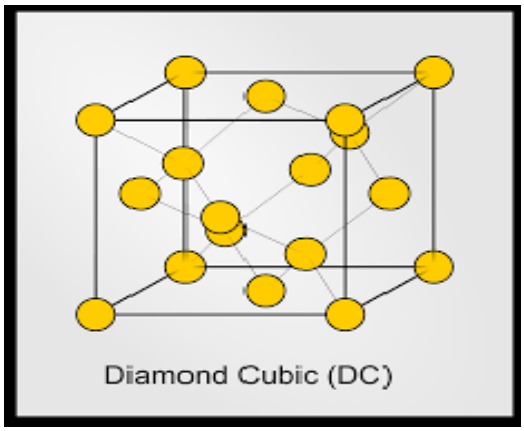

Figure 1: Diamond Cubic

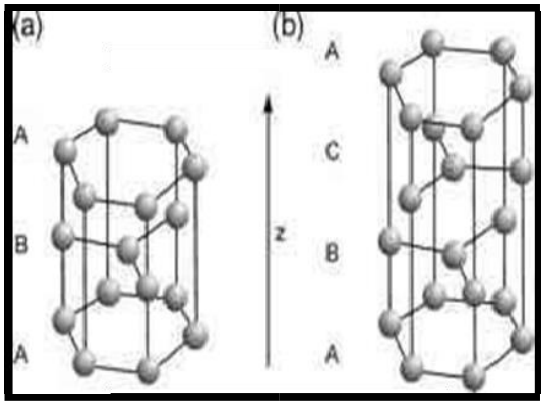

Figure 2: Cubic

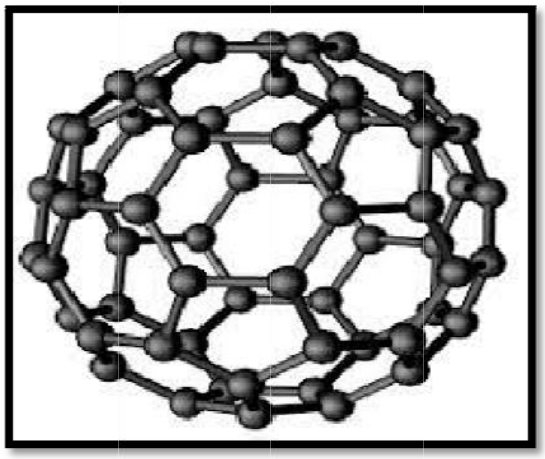

Figure 1: Fullerene

Polymorphic Changes in Pharmaceuticals: Identification Research Methods and tools [22,23]:
To identify various polymorphic phases of a chemical, a variety of approaches have been used. Each of these methods may be successful in identifying the phase, but when used together, they give a formidable tool for detecting and isolating each crystalline alteration.

Microscopy:
Optical Crystall graphy-Biles discusses optical crystallography and its application to polymorph detection in his study of crystallography. Depending on the influence of light transmission in different directions through the crystals, distinct polymorphs of a crystal may belong to one of two classes. There are two types of classes: isotropic and anisotropic. The velocity of light, or the refractive index that depends on it, is the same in all directions in isotropic crystals, however in anisotropic crystals, there may be two or three distinct light velocities or refractive indices.

Different polymorphs will belong to different crystal systems and have different sets of refractive indices due to their intrinsic structures. Biles studied the optical crystallographic characteristics of prednisolone and hydrocortisone polymorphs.

Hot Stage Method:
The polarising microscope with a hot stage (or cold stage) is an excellent tool for polymorphism research.

An experienced microscopist can quickly determine.
(a) hether polymorphism exists;
(b) the degree of stability of the metastable forms;

(c) transition temperatures and melting points;
(d) transition rates under all temperature and physical conditions; and
(e) whether polymorphism should be pursued as a path to a better dosage form using this combination.

X-Ray Powder Diffraction:
X-ray diffraction patterns made consisting of peaks in certain places and varied intensities are characteristic of crystalline materials in powder form.

Using the Bragg equation,nX = 2d sin 0,

where the wavelength of the X-ray source is known, the spacing values (d distance) for the different planes of the crystal can be derived from the 20 values of these peaks. Each crystal lattice powder pattern is unique to a particular polymorph. X-ray powder diffraction has an advantage over other identification procedures in that it examines the sample as it is (after size reduction), requires very few samples, and the material can be retrieved because the approach is nondestructive. Because the diffraction peaks for mixtures of substances are additive, caution is required [15,32].

Infrared-Spectroscopy:
Only solid samples (such as mineral oil mulls or potassium bromide pellets) can be used to identify various polymorphs using IR spectroscopy, because polymorphs of a substance in solution exhibit identical spectra.

IR spectroscopy has been employed by several researchers to investigate polymorphism. Kendall claims that the technique is both quantitative and qualitative, in addition to being quick. The IR absorption spectra for distinct polymorphs of estradiol-17p were converted to a single spectrum when they were triturated as a mull for different time intervals.

Differential Thermal Analysis:
Heat loss or gain resulting from physical or chemical changes in a sample is recorded as a function of temperature in differential thermal analysis (DTA) as the substance is heated at a constant pace.

Phase transitions produce exo- and endothermic increases in enthalpy. Endothermic effects are produced by fusion, boiling, sublimation, vaporisation, crystalline structure inversion, solid-solid transition,and water loss, for example, whereas exothermic effects are produced by crystallisation. The capacity to compute the temperatures of transition from one polymorph to the next is one of the benefits of DTA. Guillory determined the transition temperatures of methyl prednisolone and sulfathiazole polymorphs using DTA.

Dilatometry:
The melting Behaviour of Theobroma oil was studied using dilatometry, which measured the specific volume of both rapidly and slowly cooled Theobroma oil as a function of bath temperature.

Differential Scanning Calorimetry:
The heat of transition and the rate of heat flow are both measured using DSC. Because all transitions in pharmaceutical materials include heat transfer, DSC is the universal detector for monitoring a wide range of transitions (into the sample in endothermic events and out of the sample for exothermic events). The sample andreference are kept at the same temperature in this procedure, and the heat flow required to maintain temperature equality is calculated.

This is accomplished by putting separate heating elements in the sample and reference cells, and controlling and measuring the rate of heating by these elements. DSC plots are shown by differential heating rates (W/sec, J/sec) vs temperature. The area beneath the DSC peak is proportionate to its height.

Chemical Stability and Polymorphism:
There have been several cases where the chemical stabilities of various crystalline phases of the same molecule have differed. When chemical instability arose in some batches of an experimental corticosteroid, one of the scientists noticed it while working with aqueous solutions of the substance. The presence of two distinct polymorphs was confirmed using X-ray diffraction on the raw starting material batches. When the chemical stability of these polymorphs was investigated further, it was discovered that one of them was light-sensitive. Batches with this crystal form then dissolved over time, yielding lower results than the other batches. This chemical sensitivity could be caused by occluded solvents or absorbed mother liquor, the latter of which could affect chemical stability, or in the case of polymorphs, by differing light absorption patterns.

The patterns would be slightly different, and one would have to absorb a frequency that induces

photochemical breakdown. Crystalline potassium penicillin, for example, can tolerate dry heat for several hours without breakdown. The amorphous forms lose a lot of activity under similar settings. "If one wants to deposit penicillin on a solid, such as in tablet coating, this feature is critical." Application from a solution in a volatile solvent would certainly result in more instability, whereas deposition of a crystalline suspension, even in a very fine stage of subdivision, would be predicted to result in more stability" When chemical stability is a concern, meticulous monitoring during the manufacturing process is required to ensure that the intended polymorphic form is attained.

Polymorphism's Effect on Drug Substance and Drug Administration Product Polymorphism's impact on Bioavailability, solubility, and dissolution Bioequivalence (BA) and Bioequivalence (BE):

For a medication whose absorption is solely restricted by its dissolution, large changes in the apparent solubilities of the various polymorphic forms are likely to impact BA/BE. For a medication whose absorption is only limited by intestinal permeability, changes in apparent solubilities of the various polymorphic forms are less likely to impact BA/BE.

Furthermore, when the apparent solubilities of the polymorphic forms are sufficiently high and drug dissolution is rapid in respect to gastric emptying, changes in the solubilities of the polymorphic forms are unlikely to alter BA/BE. The many physiological parameters that regulate the rate and extent of drug absorption, such as gastrointestinal motility, drug dissolution, and intestinal permeability, decide whetherchanges in apparent solubilities of the various polymorphic forms can alter drug product BA/BE. In this case, the Biopharmaceutics Classification System (BCS) provides a valuable scientific framework for regulatory judgments involving drug substance polymorphism.

Polymorphism's Impact on Drug Product Manufacturing:

The effect of polymorphism on pharmaceutical processing is also influenced by the formulation and manufacturing method. The active ingredient's solid-state qualities will almost certainly be crucial in the direct compression manufacturing of the therapeutic product, especially if it makes up the majority of the tablet mass. When the product is created by wet granulation, however, the solid-state features of the active ingredients are often concealed by the ensuing granulation, and the solid-state properties of the active ingredient are less likely to affect the creation of the therapeutic product [21].

Despite the polymorphism effect on pharmaceutical manufacturing, the ability to consistently create a drug product that meets applicable in-process controls and release standards is the most essential factor. When polymorphic forms of the drug material are exposed to a variety of production procedures, including as drying, milling, micronization, wet granulation, spray drying, and compaction, phase conversion might occur. Exposure to external variables such as humidity and temperature can also be induced through polymorph conversion [35]. In general, the extent of conversion is determined by the relative stability of the polymorphs, kinetic barriers to phase conversion, and applied stress.When phase conversion occurs consistently as part of a validated manufacturing process with well-understood and regulated important manufacturing process variables and when drug product BA/BE has been demonstrated, phase conversion is generally not a cause for worry.

Polymorphism's Effect on Stability:

Analytical tools should be used to investigate the forms' thermodynamic stability. In general, the form with the lowest free energy is the most thermodynamically stable at a given temperature and pressure. The remainder of the forms are said to be metastable.At normal temperature and pressure, a metastable form may remain intact or transition to a thermodynamically more stable form. In general, the less soluble version is more stable. Changes in some of the physical properties of the chemical may result in changes in other important aspects such as bioavailability, manufacturability (also known as processability), and so on when converted to a thermodynamically more stable state[35].

Different physical and chemical (reactivity) traits can be found in polymorphs. The polymorphic with thehighest thermal stabilityduring drug development, the polymorphic form of a pharmacological substance is frequently chosen because it has the least potential for conversion to another polymorphism form and has superior chemical stability. A metastable form, on the other hand, can be chosen for a variety of reasons, including increased bioavailability. Because an ANDA applicant must show that the generic medicine goods arestable enough.

Polymorphism Research:

By far the most used tool for studying polymorphism is the polarising microscope. Although X-ray diffraction is useful, the others indicated are more useful for routine quality control, such as DTA, or for elucidating molecular distinctions between polymorphs, such as NMR [36]. The remainder of this work will be devoted to microscopical techniques. A comprehensive phase diagram, preferably plotted as a solubility- temperature diagram, and composition diagrams for all solid phases of the drug with all other components of theformulation should be included in the entire characterisation of a chemical. The following are some of the questions the investigator must be able to answer:

a) How many different polymorphic forms are there?
b) What are the relative degrees of stability for all of the polymorphic forms, and how stable are the metastable forms?
c) Is a noncrystalline glass state possible, and if so, is it stable enough to be used as a dosage form?
d) Is it possible to stabilise any metastable forms?
e) What are the ranges of temperature stability for each?
f) How soluble are each of the forms?
g) How do you make pure and stable crystals of each form?
h) Will the more soluble metastable form, such as micronized or tableted, survive processing?
i) Does the medicine form a molecular addition compound with any other chemical component duringprocessing or final formulation?
j) If so, what are its physical characteristics, such as stability?
k) If so, what are its physical qualities, such as stability, solubility, and melting point, andcan it exist in a desirable metastable polymorphic or glass form?

CONCLUSION:

The impact of drug substance and polymorphs on pharmaceutical development is centred on drug substance solubility and drug product dissolution. Once a polymorphism has been discovered in the literature, the pharmacological ingredient in question must be analysed, and formulations based on its solubility can be created. When it comes to substances with low solubility, the formulation must be designed to minimise the impact of polymorphism on dissolving and bioequivalence. Identifying the drug candidate's lowest energy crystalline polymorph throughout development is always a good idea in this case. If metastable or amorphous forms are employed in the formulation of a medicinal product, chemical stability can be improved by carefully selecting excipients and other ingredients and procedure of formulation. This review article can be more helpful for researchers those are mostly involved in bulk manufacturing of API as well as, the formulation and development department present in pharmaceutical R&D.

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List Of Abbreviations:

1	Mg	Milligram
2	J/Sec	Joule per second
3	W/Sec	Watt per Second
4	cm	Centimetres
5	API	Active Pharmaceutical Ingredients
6	IR	Infrared-Spectrocsopy
7	DSC	Differential Scanning Calorimetry
8	BCS	Biopharmaceutical Classification System
9	NMR	Nuclear Magnetic Resonace
10	ANDA	Abbrevated new drug applications

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