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Research Article

Polymorphism

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Effect of Polymorphism on New Drug Formulation and Development: A Short Review

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The polymorphism of pharmaceutically active drugs has a major impact in the formulation, development and introducing it into the market. Manufacturing a stable and potent active pharmaceutical ingredient, is an important role of pharmacists, and it could be made by research and evaluation of polymorphs that might be probably studied on the drug. The objective of polymorphism and its application is to create a better product, and avoid manufacturing issues by studying the polymorphs of various drugs and the differences between their polymorphic forms. Polymorphism principally centers on solid pharmaceuticals and affects their characteristics such as melting point, boiling point, free energy, dissolution property, shelf life, viscosity, adsorption, bio availability, solubility etc., which may cause manufacturing difficulties of the drug. So, the data of polymorphism of drugs through various lab studies is essential to avoid them. In the case of production of a new drug, polymorphs of the drug have great influence from the production to the preclinical studies of the drug. Then the new drug enters the market after being subjected to tests which include considering the possible polymorphs of the drug and evaluating their stabilities for a longer shelf life and desirable therapeutic action. Polymorphism has been studied over more than 50 years and it still has a huge scope in the present and future of the pharmaceutical field.

Keywords: Polymorphism, Polymorphs, Active Pharmaceutical Ingredient, Bioavailability, Preclinical Studies

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Introduction

Polymorphism of Drugs: Polymorphism is the phenomenon of the existence of solids in more than one form due to their differences in molecular arrangement in the crystal lattice. It has a great influence on the melting point, boiling point, free energy, dissolution property, shelf life, viscosity, adsorption, bioavailability, solubility, etc., of the active pharmaceutical ingredient [1].

In formulation and development of a drug this concept is necessary for the design, approval, manufacturing, quality control, packing, storage, shelf-life, validation of a pharmaceutical product that is going to be on the market.

Example

1.Polymorphs of aspirin (acetylsalicylic acid)

Two forms: Form I and Form I at 100K, Form II is stable, but at room temperature, it reverts to Form I. polymorphism occurs when arrangement of methyl group differs [2].

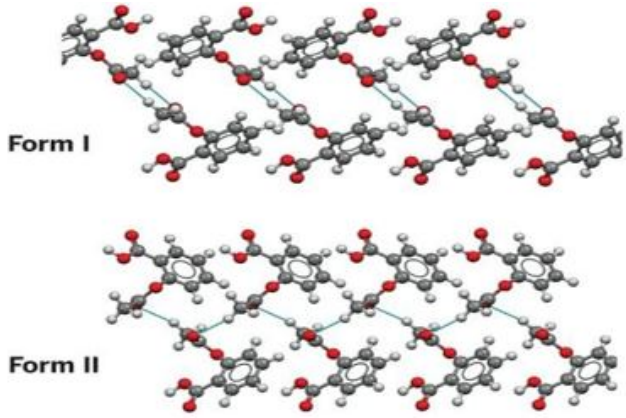

Fig:1 Polymorphism of aspirin

2.polymorphs of progesterone

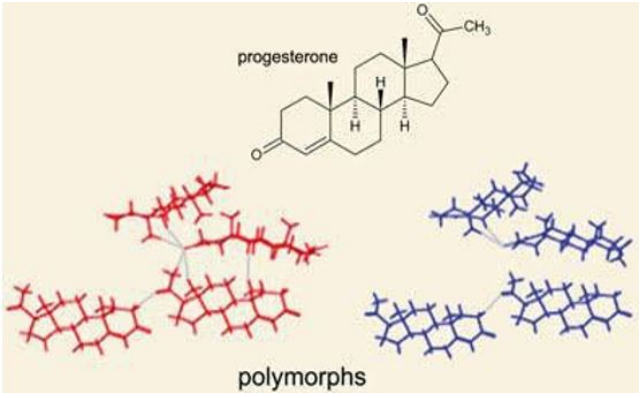

Fig:2 polymorphism of progesterone

Other examples include paracetamol, famotidine, ritonavir, chloramphenicol palmitate, sulfamerazine exhibits various polymorphs which have a significant importance in the study of polymorphs and polymorphism of pharmaceuticals. Polymorphs are chemically identical but differ in most physical properties.

Paracetamol has been used widely in the world for its anti-pyretic, analgesic and anti-inflammatory actions. Basically, it contains acetaminophen, which has two polymeric forms. One is monoclinic Form-I (P21/n), Form-II is orthorhombic (Pbca). Out of the two Form-I is more pharmaceutically stable, so it is marketed. Similarly, Famotidine is also found to exist in two different polymorphic forms, stable polymorphs A and metastable polymorph B. Other example is piroxicam a NSAID drug exist in three polymorphs form-I, II, and, III.

Various polymorphs exhibit different solubilities and dissolution rate could lead to non-equivalent bio availabilities.so most stable polymorphs are used to develop pharmaceutical products.

Table:1 Number of polymorphs of various active constituents

Drug	No of polymorph
Chloramphenicol Palmitate	2
Mefanamic acid	2
Oxytetracycline	2
Carbmazepine	4
Phenyl butazane	5
Sulfapyridine	7
Nabumetone	2
Terfenadine	3
Spiranolactone	6
Ritonavil	2
Lamivudine	2
Enalapril maleate	2
Ranitidine HCL	2
Terazosin HCL	3
Tolsemide	2
Warfarin VA	2
Cefurozime Axetil	2
Metaprotol tartarate paracetamol	2
2-Amino 5-Nitropyridine	3
Prednisolone tetra butylacetate	2
Primidone	2
Eztrene	3
Probucel	2
Ampicillin	3

Fig:3 Ritonavir tablets IP 100mg

History of Polymorphism on Drugs

Major developments of polymorphism on drugs was implemented in the late 19th century due to various incidents. The ritonavir drug incident is considered as the major influence to improve, adapt and overcome the phenomenon more deeply and for to be beneficial on an economical and in a pharmaceutical scale. In 1998, The active pharmaceutical component of Norvir capsules was discovered as Ritonavir. It was introduced as highly active antiretroviral therapy for HIV. It is also used in the combination of other HIV treatment drugs, which was successfully sold in the markets.

However, in 1998 the production of ritonavir was stopped due to changes occurred in the physical properties of the compound, the changed compound has a lower free energy resulting in solubility change and affected the bioavailability too. After a detailed research the problem was solved by introducing a new capsule version of the drug which overcame the sudden physical change. The reason for the change in the ritonavir drug is due to the polymerization of the drug into the body. This could be happens due to the temperature changes or due to use of combined drugs with ritonavir for synergy and additive effect [4]. Even Though the problem was solved it had a great impact on the patient, the market, the manufacturers and the U. S FDA (Food and Drug Administration). As, there are possibilities that a drug may show variation in its properties during storage and consumption. Therefore, it was realized that polymorphism is also an important factor which was necessary to be considered in the formulation of new drugs to avoid consumer and economical crisis.

Various Aspects of Drug Polymorphism

Types: Polymorphs are classified into two major types based on their stability to withstand a wide range of temperature and pressure.

1.Monotropic

2.Enantiotropic

Monotropic Polymorphism: Compounds which exhibit monotropic polymorphism contain one polymorph that is stable below the melting point and other polymorphs are metastable.

Example: Metolazone.

Enantiotropic Polymorphism: Compounds which exhibit enantiotropic polymorphism have polymorphs which are stable only at certain temperatures. Some polymorphs are stable at low temperatures and some could even be stable at high temperature ranges. [5]

Example: Acetazolamide.

Preparations: Polymorphs could be prepared by changing the physical conditions of their parent compound such as pressure, temperature, time, solvent, etc., There are also some methods/techniques to obtain the polymorphs of a compound.

Some of them are

1. Heating

2. Sublimation

3. Grinding and milling

4. Crystallization from melting

5. Rota evaporation

6. Slow cooling approach

7. Solvent diffusion technique

8. Vapour diffusion or vacuum methods

9. Crystallization by mixture of solvents

10. Rapidly changing solution Ph

11. Thermal desolvation of crystalline solvates by additives etc.,

Characterization: Various techniques have been used and still in research to identify different polymorphs and phases could be possible in a compound.

- Optical microscopy: It is used to determine the optical properties (indices of refraction, birefringence, dispersion color, interference etc.,) and other morphological properties.

- Scanning Electron Microscopy: It is used to determine the crystal type and topography.
- Hot Stage Microscopy: It is used to determine the solvate system of the
- It is done by setting the polarizing microscope on a hot stage.
- Single Crystal X-ray Diffraction: This method provides information about the solid state of the polymorphs. It is also used to determine the differences between polymorphs of the same parent compound by the molecular positional changes within the crystal lattice.
- Powder X – Ray Diffraction: This method identifies polymorphs by peak variation of intensities of powders when subjected into x-ray diffraction.
- Differential Scanning Calorimetric (DSC): It is used to measure the heat resulting from physical or chemical changes within a sample to identify the polymorph.
- Differential Thermal Analysis (DTA): This method monitors the difference in temperature existing between a sample and a reference as a function of temperature.
- Thermo gravimetric analysis (TGA): This method measures the changes in weight of the polymorph that occur to a sample as a function of temperature over time.
- Fourier Transforms Infrared Spectroscopy (FT-IR): This method identifies the polymorphs, drug presence and distinguishes between solvates and anhydrous compounds.
- Raman Spectroscopy: This method is an established technique for identifying and differentiating pharmaceutical polymorphs.
- Solid State NMR Spectroscopy: This method studies the crystalline solids, pharmaceutical dosage forms, molecular variations and nature of polymorphic variations.

Effect of Polymorphism on New Drug Formulation and Development

Various and diverse considerations are used when it comes to deciding the perfect polymorphs that are to be used to formulate and develop pharmaceutical products. Many are formulated and marked in crystalline form and often solvent incorporated in crystal lattice such as solvates.

When selecting a polymorph, it must be thermodynamically stable at various storage conditions and assured bioavailability, for example, the Form II polymorph of chloramphenicol palmitate is used as eye bactericidal that its original form due its high bioavailability.

Comparison between the bioavailability of Form-II is better than Form-I, even though Form-I is the identified drug, it's polymorph is used for its higher bioavailability. On preclinical and clinical testing decisions are made for which form and crystal of the API should be used for formulation and development. [7]

Identification of the polymorphic changes done by observing and studying the stability relationship of the solid phase which changes upon temperature, pressure, humidity etc., Difference in the lattice energy is associated with the dissolution rate and solubility. Variation in them affects the adsorption of the drug. Therefore, solids with high lattice free energy produces less stable polymorph which have high solubility, so metastable polymorphs are also used in the formulation of drugs. But it is advisable to use solids with low lattice free energy. Sometimes high soluble drug due to polymorphism cannot be for high bioavailability Eg;- ritonavir.

The properties of the drug are the main considered subject when it comes to formulating a drug. The properties may be physical, chemical, pharmacological, economical etc. But the solid state of the drug is also important and it should be considered properly because it has an influence on the solubility, dissolution, distribution, adsorption, absorption, metabolism, bioavailability, excretion of the drug. Not only to the consumer but also to the manufacturers, the state of the drug is important.

Issues such as precipitation, low melting point, poor quality, phase separation, less flow property, solidification of liquid dosages, compressing problem for solid dosage could occur in the manufacturing process if the properties of the compound are not well known. A pharmacist must follow proper GMP (good manufacturing process), so the properties of the drug and its polymorphs must be well studied by them to create a produce safe, efficient, and less toxic pharmaceutical products. Experimental and developmental studies on polymorphism must be implemented and known properly to avoid problem that may possibly occur in the future.

Summary

Polymorphism is a phenomenon of pharmaceuticals that exists in more than one form due to their differences in the molecular arrangement in their crystal lattices, mostly solids. This leads to variation in physical, thermodynamics, and kinetics of the drug properties. The ritonavir drug's polymorphism is an important incident in history which accelerated the studies of polymorphs of numerous drugs, and developing better drugs by studying the forms of drugs which have desirable properties. The polymorphs exist in stable and metastable forms but for drug formulation metastable forms are mostly used to maintain shelf life and solubility of the drug by converting to stable form whenever needed. The lab studies of polymorphism are achieved by numerous methods such as x-ray diffraction, Raman spectroscopy, NMR spectroscopy, process analytical technology (PAT) etc. With the help of these techniques, various research studies and properties of the drugs are observed and have a significant importance in drug development. The drug's performance greatly depends on its polymorph. Therefore, discovery and implement of more polymorphs may pave a new era for the drug developments in the near future.

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