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EFFECT OF POLYMORPHISM ON THE DRUG PRODUCT DEVELOPMENT

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ABSTRACT

Polymorphism plays a significant role in various aspects of drug product development, such as chemical and physical stability, solubility, dissolution, bioavailability, bioequivalence, and manufacture. To ensure quality, safety, and efficacy of pharmaceuticals, careful consideration should be given during drug product development. In order to achieve consistent bioavailability over the shelf life of a drug substance and under diverse storage conditions, the most thermodynamically stable form of the drug substance must be selected. Getting a comprehensive understanding of low-solubility drug absorption requires studying polymorphism. Pharmaceutical formulation begins with investigating drug polymorphism. Pharma is increasingly focusing on polymorphism for formulations and regulatory considerations for solid pharmaceuticals. A comprehensive overview of polymorphism is provided here, including physical characteristics, classification, characterisation, synthesis methods, and strategies to enhance solubility.

KEYWORDS: Polymorphism, Monotropes, Enatiotropes, Conformers, Solvates, Hydrates.

INTRODUCTION

A polymorph is a range of shapes or forms derived from the Greek word polymorph, which means many. There are two or more crystal phases of a substance that can consist of molecules arranged or conforming differently in the crystal lattice, which is known as polymorphism.[1-4] Most drugs have poor water solubility, which reduces their bioavailability. Amorphous dispersions, nano crystal dispersions, and co-crystal synthesis were studied to improve the solubility and bioavailability of drugs. Bioavailability can be improved by polymorphism. It is possible to improve product stability by using polymorphic form modification in addition to drug bioavailability management. It is generally more stable for metastable forms to transform to thermodynamically stable forms in a relatively short period of time, but in general, metastable forms are more stable than sable polymorphic forms. Due to this, it is important to monitor the polymorphic transition during formulation manufacturing and the dosage form throughout its shelf-life, in order to ensure that product quality and bioavailability are not significantly affected.[5,6] Analyzed polymorphic forms of drugs are shown in Table 1.

Table 1: List of Various Drugs Studied for Polymorphism.[1,7,8]

S.No.	Drug	No of polymorph	Bioavailable form	Advantages and significance
1	Cortisone acetate	5	I	Stable
2	Methylprednisolone	2	I	Higher dissolution
3	Sulphamethoxydiazine	3	III	Water stable form
4	Oxy tetracycline	2	Form B	Dissolution rate is high
5	Ritonavir	2	Form II	Stable
6	Ranitidine HCL	4	Form II	Stable
7	Levodopa	2	Form I	Stable
8	Paracetamol	2	II	Good compressibility
9	Indomethacin	3	I& II	Higher therapeutic efficiency

10	Chloramphenicol Palmitate	3	II	Thermodynamically stable and better
11	Phenylbutazone	5	IV	Most stable form
12	Sulfathiazole	3	I	Stable
13	Atenolol	2	I	Stable
14	Pramocaine	2	I	More stable
15	Amobarbitol	2	II	Dissolution rate is high

Polymorphism classification

There are two types of polymorphs: monotropes and enatiotropes, based on the temperature and pressure ranges at which they are stable. In polymorphism, one form remains stable at all temperatures below its melting point while the rest are unstable. Monotropes are systems of monomorphs, and the two polymorphs are monotropes of one another. A change from an unstable to a stable form doesn't reverse at all temperatures. Due to this, no region of stability can be found on the pressure-temperature graph for other unstable polymorphs. During reversible polymorphism, you have enantiotropes, which are polymorphic forms with enantiomorphic properties. Below a certain temperature and pressure, one form is stable while the other is unstable. Neither polymorph has a melting point higher than the transition temperature, otherwise no phase transition would occur.[9,10] Polymorphs can be crystalline, amorphous, solvates, hydrates, or co-crystals depending on their pattern of arrangement or associated solvent.[11] It has a different arrangement of molecules in the crystal lattice in crystalline form than it does in three-dimensional form. A crystal solid usually has well-established properties and is highly stable. Crystalline drugs are commonly used. There are no distinguishable crystal lattices in amorphous materials because they consist of random arrangements of molecules. Supercooled liquids are also called pseudosolids. Crystalline solids are usually more stable and dissolve faster than amorphous solids. A solvate means that the crystal lattice is saturated with a solvent in stoichiometric or nonstoichiometric amounts. A solvate called a hydrate is incorporated with water. It is made up of molecules, typically active pharmaceutical ingredients and co-crystals (conformers), that are crystalline materials (Figure 1).

Various method for preparation

An API and its excipients must be completely solid-state characterized before polymorphic transitions can occur spontaneously or induction of some specific conditions can occur. Polymorphic transitions have therefore been induced by many different methods. Polymorphs can be prepared using the following methods.[12]

1. Vacuum Sublimation

A substance sublimates into a gas when it transitions directly from its solid phase to its gas phase. Based on their sublimation temperature, this technique only applies to thermally stable compounds. Various static and dynamic vacuum variations are commonly used to induce crystallization. Many ways can be used to induce temperature gradients in a small amount of sample sealed under a vacuum in a reactor. At a pressure of around 10-2 mm of Hg, a temperature of 250°C can easily be employed. A crystal grows from the reactor's wall to its center. A polymorphic form IV of carbamazepine was developed.[13-15]

2. Vapour Diffusion

As a drop is placed on the underside of a microscope coverslip, the concentrated drug solution is applied. Over the high precipitant concentration solution, silicon oil seals the cover slip with the hanging drop. Compared with drug solutions, precipitant solutions have lower vapour pressure. After the drop reacts with the solvent, the solvent diffuses towards the reservoir and crystallizes within hours to weeks.[16]

3. Rota evaporation method

By utilizing a rotary evaporator, it evaporates solvent. Rotary evaporation is used to remove the solvent from the drug saturated solution. Utilizing air drying at different temperatures to produce different polymers.[17]

4. Slow cooling approach

Often, polymorphic drugs with a boiling point between 30 and 90°C are prepared using this technique. During this method, the solute is heated above the boiling point of the solvent to produce the saturated solution. A stopped tube containing the solvent is connected to a Dewar flask containing water at just below its boiling point. For obtaining more soluble polymorphic forms, leave the flask in this condition for several days.[18,19]

5. Solvent diffusion technique

The method is used when the available drug amount is small or sensitive to air or solvents. It involves placing a solution in a tube, and then dropping down the slide of the tube a less dense solvent. API crystallizes at the interface due to slow diffusion of solvent.[20]

Polymorph characterization

There have been several techniques used to identify the different polymorphic phases of a compound, providing a powerful tool for identifying and isolating each phase.

Table 2: List of analytical techniques for characterization of polymorph.[7,21-23]

S.No	Technique	Significance
1	Powder X-Ray Diffraction (PXRD)	Standard for phase identification, usually show a significant difference among crystal forms
2	Single crystal X-ray Diffraction	Ultimate phase identification (ID) in depth understanding of structure
3	Differential scanning calorimetry (DSC)	Small sample size, information on phase transition, information on interference with recipients
4	Thermogravimetry Analysis (TGA)	Quantitative information on the stoichiometry of solvates / hydrates
5	Fourier Transforms Infrared Spectroscopy (FT-IR)	Identification of the drug present and distinguishing between solvates and anhydrous form.
6	NCAR IR (NIR)	Complementary phase ID method, ability to penetrate through containers ability to show different states of water
7	FT-Raman	Used to identify or characterize and estimate the purity of co-crystalline phases.
8	Solid state nuclear magnetic resonance (SSNMR)	Complimentary phase ID method, local environment of atoms
9	Polarized microscopy	Information on crystal morphology and size, qualitative information on crystallinity. Complimentary information on phase transition
10	Hot stage microscopy	Complimentary information on phase transition
11	Solvent sorption	Excellent for detection of low level of amorphous phase, defining the liability of hydrates
12	Optical microscopy	To study solid state properties, crystallinity, refractive index, and particle size & shape of different polymorphs

Factors affecting polymorphism[1]

1. Effect of temperature and humidity

Arrhenius' activation theory states that storing drugs at higher temperatures accelerates their physicochemical reactions. Polymorph conversion can also be induced by humidity. The solid surface is catalyzed by humidity. Polymorph stability, phase conversion barriers, and stress generally determine the conversion reaction. Drugs should be manufactured and stored at controlled temperatures.

2. Effect of grinding

Particles are reduced by grinding. Micromorphs that are unstable. Surface area increases when materials are ground, which affects how they dissolve and bioavailability. It is important to keep in mind that compound stability increases with grinding time, since weakened bonding crystals and water molecules encourage hydrolysis.

3. Photostability

Depending on their polymorphic form, polymorphs may react differently to light. There is a profound difference between solid and liquid states in terms of how atoms are arranged. As a result, they show different photostability when exposed to light. Light-resistant containers are used to pack these photo-sensitive drugs.

4. Effect of solvent

Solute and solvent interactions form clusters or groups in a solution. A crystal lattice is formed by this interaction. Polymorphs can be formed by various crystallization processes, such as diffusion, vacuum sublimation, solvent evaporation. These polar, dipolar, aprotic, protic, aromatic, or non-polar solvents can form Lewis-acidic, Lewis-basic, dipolar, aprotic, protic polymorphs. Solvents or water are incorporated into the crystal lattice of polymorphs, converting them into solvates or hydrates.

5. Effect of compression

Most pharmaceuticals do not undergo phase transformation when compressed between 40 MPa and 200 MPa during the tableting process. When pressure increases, phase transformation occurs in the crystal, forming polymorphs.

Application of polymorphism in pharmaceuticals[24,25]

1. **Purification of drugs:** Recrystallization of drug substances is the traditional technique for separating impurities.
2. **Better processing characters:** Changes the flow property and compressibility of the drug by changing its micrometric properties
3. **Enhanced physical stability:** Tablet hardness and suspension stability are both heavily influenced by crystal forms. In addition, using dehydrating agents like glycerol and absolute alcohol will increase the stability of compounds.
4. **Handling of drugs:** Various operations occur during crystallization, including transportation and storage.
5. **Better chemical stability:** An example of a product that is less stable than its crystalline salt is amorphous penicillin G, whereas its crystalline salt is more stable.
6. **Improved bioavailability:** Several drugs have a greater effectiveness when they are crystalline. The gastric fluids do not dissolve penicillin G immediately. Thus, the drug will be more bioavailable.
7. **Sustained release:** For sustained release dosages like protamine zinc insulin, size and shape are also crucial factors.

CONCLUSION

For improving dissolution rate and bioavailability of low solubility drugs, polymorphism needs to be studied. As the understanding of APIs advances, it is no longer only the chemical purity/integrity that is the sole factor influencing formulation. Physicochemical properties and therapeutic outcomes are influenced by the physical arrangements of constituents in the crystal lattice. It is imperative to study polymorphic forms as much as other branches of pharmaceutical sciences because they guide API/excipient form selection. Hence, pharmaceutical companies should carefully analyze polymorphism for every drug they are developing.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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