CHAPTER-I

INTRODUCTION TO POLYMORPHISM
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INTRODUCTION

Most of the compounds in their solid state are known to exist in distinctly different physical states. This behavior in elements is termed as "allotropy", while in compounds, it is known as polymorphism.¹

Polymorphism is derived from the greek words, (poly = many, morph=form) specifying the diversity of nature, is a term used in many disciplines.² Polymorphism is the ability of a substance to crystallize into different crystalline forms. These crystalline forms are called polymorphs or crystalline modifications. Polymorphs have the same chemical properties but they differ in a few physical properties. The best-known example of polymorphism is carbon, which can exist in the form of graphite or as diamond.³ Polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and / or different conformations of the molecules in the crystal lattice. Amorphous forms consist of disordered arrangements of molecules that do not possess distinguishable crystal lattice.⁴ As a result, the polymorphic solids have different unit cells and hence display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties.⁵
Different solid phases, like true polymorphs, solvates and amorphous forms occur during crystallization or pharmaceutical processes. The process of transformation of one polymorph into another is a phase transition, which may occur on storage or during processing. If the phase transition is reversible, the two polymorphs are enantiotrops and if it is irreversible, then the two polymorphs are monotrops and only one form is stable whatever the temperature may be. In case of solvates, the phase transitions are more complex since several phases or forms are involved. All thermodynamically “unstable” forms may behave like stable forms outside the phase diagrams for kinetic reasons. They are therefore called “metastable” forms.  

Polymorphs may differ in their melting and sublimation temperatures, heat capacity, conductivity, volume, density, viscosity, crystal hardness, crystal shape, color, refractive index, solubility, dissolution rate, stability, hygroscopicity, processability and solid state reactions. The consequences of polymorphism and pseudo-polymorphism are found in many steps of manufacture and storage of drug substances and drug products. This impact is so high that the International conference on harmonization (ICH) requires proper investigations and analytical methods for drug substance and drug products following a decision tree. The details of the decision tree are incorporated below.
DECISION TREE: INVESTIGATING THE NEED TO SET ACCEPTANCE CRITERIA FOR POLYMORPHISM IN DRUG SUBSTANCES AND DRUG PRODUCTS

1. Co-exist polymorph screen on drug substance
   - Yes: Further test for forms
     - e.g.: X-ray Powder Diffraction
     - DSC / Thermogravimetry
     - Microscopy
     - Spectroscopy
   - No: Further test or acceptance criteria for drug substance

2. Do the forms have different properties?
   - No: Drug product safety, performance or efficacy affected
   - Yes: Set acceptance criteria for polymorph content in drug substance
     - Note: Can be satisfied only if technically possible

3. Does drug product performance testing provide adequate control of polymorph ratio changes (e.g., dissolution)?
   - Yes: Establish acceptance criteria for the relevant performance test(s)
   - No: Monitor polymorph form during validation of drug product

4. Does a change occur which could affect safety or efficacy?
   - No: No need to set acceptance criteria for polymorph change in drug product
   - Yes: Establish acceptance criteria which are consistent with safety and/or efficacy
PREPARATION OF POLYMORPHIC FORMS

The concept of different crystalline modifications arise under varied experimental conditions demands the use of a diverse medley of crystallization approaches to explicate the polymorph spectrum. Currently, the polymorph screen is a jumbled affair based mostly upon hit and trial basis. Crystallization from solution (single solvent or solvent mixtures) and non-solvent methods such as sublimation, thermal treatment, desolvation, processing (grinding) and crystallization from melting are the commonly used traditional approaches for polymorph screening. A meticulous consideration of the factors of solvent recrystallization like solvent polarity, degree of supersaturation, temperature along with the cooling profile, additives, seeds, pH and agitation rate aids in elucidating the complete polymorphic picture of the drug.\(^9\)

However, the traditional crystallization methods are exhaustive, time consuming and may be liable to miss metastable forms having an energy difference of less than 10 kJ/mole, as observed in the case of paracetamol and chlorthalonil.\(^10\) Therefore, innovative techniques allowing generation of ‘crystal mutants’ would prove to be of high value.

Newer crystallization strategies, such as laser-induced crystallization, capillary crystallization and sono-crystallization, target the nucleation stage. Though currently in limited use, these can competently contribute to polymorph screening. These techniques, by use of unusual reaction conditions (e.g. ultrasound and laser as a source of energy), are capable of bringing fortuitous surprises. As previously mentioned, nucleation is more energetically demanding than crystal growth – hence accelerating this stage can have a remarkable influence on the crystallization rate.
Despite the profound importance of controlling the crystalline form of compounds for applications from material science to drug delivery, there exists no general method for producing all of the energetically reasonable polymorphs of a given compound. In fact, there is no guarantee that the modification with the lowest free energy has ever been obtained. This creates a troubling situation particularly for pharmaceutical researchers trying to employ a given solid form for studies such as bioavailability and dosage formulation and a point of legal exposure for companies whose intellectual property can be threatened by the unexpected discovery of new polymorphs for a drug substance. Therefore, much effort has been extended to create tools for controlling crystallization with varying degrees of success.

Current approaches for discovery and selection of polymorphic forms of a compound include crystallization with tailor made soluble additives, epitaxial growth, laser induced nucleation, crystallization in capillaries, confinement within porous materials and more traditional methods, such as varying solvent, temperature, and extent of supersaturation. Most high throughput polymorph generation techniques are limited to combinatorially changing solvent, temperature, and supersaturation conditions.

Crystallisation in the pharmaceutical industry is most often carried out batch-wise. The techniques used are cooling, evaporation, drowing-out, and reaction crystallizations. Normally, the crystallization will be carried out as unseeded crystallization, relying on spontaneous nucleation and the modification it entails. In a large number of cases, this will be an unstable modification, as is predicted by Ostwald's rule of stages. However, an unstable form is prone to a phase transformation either
while the product is still in suspension during work-up, or even during storage, although the later transformation is rarely observed. Instead of relying on the modification formed under spontaneous nucleation, control can be exercised on the modification formed. One of the most straightforward techniques is the control of the nucleation process via seeding.¹⁹

The importance of polymorphism and solvate formation in the crystallization of organic compounds are widely recognized with in the industry and academic communities.²⁰ This is particularly true for the pharmaceutical sector where two polymorphs of the same drug compound may have different physical properties, e.g. solubilities, melting points, density, hardness, or colour and may have dramatically different properties that affect processability.²¹ Intellectual property can also become an issue for the pharmaceutical companies who develop and market new drug products, where challenges to patents have been made on the basis of the discovery of a new polymorph. The search for polymorphs is therefore an area of intense activity. Generally the techniques used for polymorph screening involve recrystallizations from a wide range of solvents under a variety of conditions, and high-throughput robotic screening is increasingly being used. Almost all studies that seek to explore polymorphism and solvate formation are performed under ambient pressure. The only exceptions are a few processes that use supercritical liquids (such as carbon dioxide) as solvents.²²
IDENTIFICATION OF POLYMORPHS

A battery of analytical techniques is available. Each technique has its advantages and disadvantages. X-ray diffraction is the most useful technique since it is directly related to the crystal structure, which is the characteristic of polymorphs.23

A proper monitoring of polymorphs and pseudo-polymorphs in pharmaceuticals has to follow the ICH guideline for polymorph screening, identification, isolation and characterisation of different phases in order to select the target solid form of the drug substance and also to optimize robust processes. Analytical methods for the study of polymorphism and their main features includes Differential scanning calorimetry (DSC), microcalorimetry, solution calorimetry, thermogravimetry (TG), moisture sorption / desorption isotherms, FT-IR, FTIR-ATR (Fourier transform infrared spectroscopy-attenuated total reflectance), Raman, Solid state NMR, X-ray diffraction, solubility, microscopy, SEM. Several automated analytical techniques with high sensitivity, best-coupled techniques including X-ray diffraction and spectroscopy, or thermogravimetry with FT-IR are necessary for such a challenging task. Quantitative methods require generally pure samples of polymorphs for routine analysis.

X-ray powder diffraction (XRD) is one of the most powerful technique for qualitative and quantitative analysis of crystalline compounds. The technique provides information that cannot be obtained by any other way. The information obtained include types and nature of crystalline phases present, structural make-up of phases, degree of crystallinity, amount of amorphous content, microstrain, its size and orientation of the crystallites.
IMPORTANCE OF POLYMORPHISM

Polymorphism is a keyword of considerable importance in the life sciences research and more so in the pharmaceutical industry. It abridges the fact that a solid compound can exist in different crystalline forms that can have different physical properties. To ensure no variations in the product to be due to different solid-state properties, care must be taken in selecting the most appropriate solid-state form for the substance and in ensuring a reproducible production of this form.24

Although new routes of administration for pharmaceutically active therapeutic agents continue to be developed, most compounds are still administered as a solid dosage form.25 Any defining characteristic that might affect the stability or availability of the drug substance in a solid dosage form should be monitored and controlled.26 So, the physical characterisation of solids has become an extremely important area in pharmaceuticals.27 Important investigations into solid-state phenomena can center on questions of chemical reactivity, where attention is focused on the solid-state reactions that occur in bulk drugs or in their dosage forms.28 An equally important area of solid-state pharmaceutics is the study of the crystallographic properties of a given compound. Indeed, crystallography studies are sometimes carried out solely with the intention of determining possible variations in the structural aspects of solid forms of drugs.29

As concerns the pharmaceutical industry, it has been shown that more than half of the drug substances described in monographs crystallize in more than one solid state form being it either polymorphs, solvates or both.30 The solid state form of a drug substance can influence a variety of properties, namely the solubility and rate of dissolution or the chemical stability or stability against excipients. Thus, the regulatory bodies require an
exhaustive search for polymorphic forms of a drug substance. The manufacturer is required to make a substantiated choice for one of the forms, or a defined mixture of forms. Changes in the polymorphic form of the batches produced are seen as indicative of changes in the production process, also requiring the reproducible crystallization of a certain solid form.

The choice of the solid form of a new drug substance is up to the applicant and should be made by considering all aspects, such as chemical stability and stability with excipients, dissolution behaviour and bioavailability, and last but not least thermodynamic stability of the solid form its ease and reproducibility of production.

The latest trend that has, of late, crept into the pharmaceutical industry is the studies on polymorphism in drugs and the difference in the potency of different polymorphic forms of a given drug. Polymorphic forms would include different physical forms, crystalline and non-crystalline (amorphous forms). This has especially become very interesting after observing that many antibiotics, antibacterials, tranquilizers, etc., exhibit polymorphism and that one or some of the polymorphic forms of a given drug exhibits superior bioavailability and consequently shows much higher activity compared to other polymorphs. Ranitidine, Sertraline, Frentizole are some of the important examples of pharmaceuticals, which exhibit polymorphism. Polymorphism in drugs is a topic of current interest and is evident from the host of patents being granted. To cite a few, US 5700820 discloses six polymorphic forms of Troglitazone, US 5248699 discusses about five polymorphic forms of Sertraline hydrochloride, while European patent EP 014590 describes four polymorphic forms of Frentizole. European
Polymorphism plays an important role in active pharmaceutical ingredients as they play a key role in the variation of the physical characteristics like solubility, dissolution, bioavailability, bioequivalence, manufacturing process and stability.

The solid-state properties of a drug substance can have a significant influence on the solubility of the drug substance. Since polymorphic forms differ in their internal solid-state structure, a drug substance that exists in various polymorphic forms can have different aqueous solubilities and dissolution rates. When there are differences in the solubilities of the various polymorphic forms, such differences can have a potential effect on drug product bioavailability (BA) and bioequivalence (BE).

For a drug product whose absorption is only limited by its dissolution, large differences in the solubilities of the various polymorphic forms are likely to affect bioavailability / bioequivalence. On the other hand, for a drug whose absorption is only limited by its intestinal permeability, differences in the solubilities of the various polymorphic forms are less likely to affect BA/BE. Furthermore, when the solubilities of the polymorphic forms are sufficiently high and drugs dissolution is rapid in relation to gastric emptying, differences in the solubilities of the polymorphic forms are unlikely to affect BA/BE.

Although the different polymorphs have same chemical composition, their solid-state properties are generally different as a consequence of their different crystal structures. In recent years, there has been considerable interest within the industry in being able to find and characterize as many polymorphs as possible of the active
molecule of the interest (for example, a drug or pigment) so that the polymorph with the most desirable properties for the targeted application can be selected. It is then essential that the desired polymorph can be produced reliably and reproducibly on scale-up and that it remains stable during subsequent processing and storage. Given these issues, the quest to produce and fully characterize all accessible polymorphs of a given drug substance has become an area of intense activity within pharmaceuticals and other industries.\textsuperscript{40}

For the other polymorphs, structure determination must be carried out using powder X-ray diffraction data. While structure determination from single-crystal X-ray diffraction data is now essentially routine (provided that the appropriate single crystals could be grown), carrying out complete structural determination from powder X-ray diffraction data is substantially more challenging, particularly in the case of molecular solids.\textsuperscript{41a-d}

In recent years, polymorphism, specifying the diversity of nature, is widely observed in pharmaceutical compounds.\textsuperscript{42} Differences in their physico-chemical and mechanical properties led to the emergence of stringent characterisation, quality control measures of these altered solid-state forms in active pharmaceutical ingredients (APIs) during filing of New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs).\textsuperscript{43}

The process of reproduction of polymorphs significantly varies with the presence of impurities in the starting material used, reaction parameters like cooling conditions, rate of addition of anti-solvent, speed of rotation etc. These factors may differ from lab to scale-up. Some times the conditions may be well accepted for the production of
targeted polymorph in laboratory studies and the conditions may require further tuning in scale-up.\textsuperscript{44} Crystallization in the pharmaceutical arena is a means of 'giving birth' to new polymorphs.\textsuperscript{45} Due to varied functional behaviours, polymorphs can also be termed 'crystal mutants'.\textsuperscript{46} Scientists working on pre-formulation have a critical role in elucidating multiple solid-state forms of the API by using a thorough and rapid polymorph screen.

POLYMORPHISM-AN IP PERSPECTIVE

Polymorphism now becomes the part of intellectual property for the industry in particular pharmaceutical industry. Latest trend clearly reveals that identification of polymorphs in drug substances and its characterisation are essentially a part of their drug development. Academic institutions also now involved in studying the polymorphism in various organic compounds in particular drug substances to extend their innovations.

The thrust is to prepare new polymorphs and thereby filing patents to protect the innovations. Innovator companies (companies that involve in the identification of novel chemical moieties which are suitable as drugs) try to protect the stable polymorph to extend the life of the product. Similar, generic companies (companies that involve in the development of process / formulation of existing drugs for reduction in cost and enter into the market after the marketing exclusivity of the drugs expires) will explore studies to identify novel polymorphs, which are suitable for formulation. However, it has now become the part of pharmaceutical industries to explore the absence of protected polymorphs in their targeted form.

The importance of identification and protection of polymorphic forms can be particularly observed in the drug substances. Various polymorphs of different drugs are
protected in patents by different pharmaceutical industries. Few active pharmaceutical ingredients, which are also known as drugs containing different polymorphic forms are described in Table 1.
<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Name of the Drug</th>
<th>Chemical Name</th>
<th>Structure of the Drug</th>
<th>Therapeutic activity [From Merck Index, Volume 13]</th>
<th>Polymorphic forms known</th>
<th>Amorphous form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Alendronate sodium</td>
<td>(4-amino-1-hydroxybutyridene) bisphosphonic acid monosodium salt trihydrate</td>
<td><img src="structure1.png" alt="Structure" /></td>
<td>Bone resorption inhibitor (P.44, Ref: 227)</td>
<td>Twelve</td>
<td>Known</td>
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<tr>
<td>2.</td>
<td>Aripiprazole</td>
<td>7-[(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril</td>
<td><img src="structure2.png" alt="Structure" /></td>
<td>Antipsychotic (P.134, Ref: 791)</td>
<td>Twenty seven</td>
<td>Known</td>
</tr>
<tr>
<td>3.</td>
<td>Atorvastatin Calcium</td>
<td>βR-SR-3-(4-Fluorophenyl)-δ, δ, dihydroxy-5-([1-methyl]ethyl)-3-phenyl-4-([phenylamino) carbonyl]-1H-pyrole-1-heptanoic acid, calcium salt (2:1) trihydrate</td>
<td><img src="structure3.png" alt="Structure" /></td>
<td>Anti-hyperlipoproteinemic (P.148, Ref: 865)</td>
<td>Forty two</td>
<td>Known</td>
</tr>
<tr>
<td>4.</td>
<td>Candesartan Cilexetil</td>
<td>(+)-1-((cyclobexyl)carbonyl)-ethyl-2-ethoxy-1-[2′-[(N-benzyl-1H-tetrazoli-5-yl)bisphenyl-4-y]methyl] benzimidazole-7-carboxylate</td>
<td><img src="structure4.png" alt="Structure" /></td>
<td>Antihypertensive (P.291, Ref: 1747)</td>
<td>Forty two</td>
<td>Known</td>
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</tr>
<tr>
<td>7. Dutasteride</td>
<td>17β-[(2,5-Bis(trifluoromethyl)phenyl)carbamoyl]-4-aza-5α-androst-1-en-3-one</td>
<td>Treatment of benign prostatic hyperplasia (P.612, Ref: 3504)</td>
<td>Three</td>
<td>Known</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Fexofenadine Hydrochloride</td>
<td>(+)-4-[[1-hydroxy-4-[4-(hydroxymethyl)methyl]-1-piperidinyl]banyl][alpha,alpha-dimethyl benzeneacetic acid hydrochloride</td>
<td>Antihistaminic (P.718, Ref: 4104)</td>
<td>Fifteen</td>
<td>Known</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>Molecular Structure</td>
<td>Description</td>
<td>Quantity</td>
<td>Known</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>Finasteride</td>
<td><img src="image1" alt="Molecular Structure" /></td>
<td>Treatment of benign prostatic hypertrophy, antialopecia agent</td>
<td>Five</td>
<td>Known</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Montelukast sodium</td>
<td><img src="image2" alt="Molecular Structure" /></td>
<td>Antiasthmatic</td>
<td>Two</td>
<td>Known</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Nateglinide</td>
<td><img src="image3" alt="Molecular Structure" /></td>
<td>Antidiabetic</td>
<td>Thirty seven</td>
<td>Known</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Oxtcarbazepine</td>
<td><img src="image4" alt="Molecular Structure" /></td>
<td>Anticonvulsant</td>
<td>Four</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Risedronate sodium</td>
<td><img src="image5" alt="Molecular Structure" /></td>
<td>Bone resorption inhibitor</td>
<td>Ten</td>
<td>Known</td>
<td></td>
</tr>
</tbody>
</table>
PRESENT WORK

The increasing incidence of polymorphic studies to a large number of organic compounds in particular active pharmaceutical ingredients and its importance in the academic and industry point of view has prompted the studies on the development of polymorphs for various active pharmaceutical ingredients. Therefore, it has been considered worthwhile to explore polymorphic forms in different active pharmaceutical ingredients and eventually test them with the available analytical tools. Further, the studies also have been done to find out the variations of the polymorphic forms available in the prior art / literature with the ones identified. The analytical tools which are considered for the characterisation includes powder X-ray diffractometry, infrared spectrometry, differential scanning calorimetry, thermogravimetric analysis, moisture content analysis by karl-fischer method, solubility studies etc. which are readily available and easy to perform.

Selection of Active pharmaceutical ingredients for the study

We have selected Olanzapine, Doxazosin mesylate, Nevirapine and Risperidone to study the polymorphism.

Olanzapine and Risperidone are superior active drugs, which are known as antipsychotics, indicated for the treatment of schizophrenia and bipolar disorders. Having the greater efficacy over the related drugs, these drugs have become the market leaders in their therapeutic category and have significant sales in the regulated markets (markets which are stringent in terms of drug approvals).
Doxazosin mesylate is one of the ideal candidates in the category of antihypertensives. It shows a great structural similarity to the older representatives of this class, Prazosin hydrochloride and Terazosin hydrochloride. The two latter active substances are used primarily in the treatment of high blood pressure, but, in the case of Doxazosin mesylate, there is an additional indication, namely, the treatment of benign prostate hyperplasia. Unlike Prazosin and Terazosin, Doxazosin is used therapeutically not the hydrochloride but as the mesylate, that is, as a salt of methane sulfonic acid.

Nevirapine, an antiviral drug, a non-nucleoside inhibitor of HIV-1 reverse transcriptase is useful for the treatment of HIV-1 infection in humans and acts by a mechanism distinct from that of nucleoside analogs such as Zidovudine. Treatment of HIV infection has now become a serious concern across the globe.

Having the advantages mentioned above and availability of these drugs at our research centre also encouraged us for selecting these moieties for our present studies.

Chapter-II covers the various polymorphic forms of Olanzapine, an antipsychotic drug, which were prepared using different methods and were characterized by the above-mentioned analytical tools. Few of the resulted polymorphic forms were also studied with respect to their stability.

Chapter-III describes the preparation of various polymorphic forms of Doxazosin mesylate, an antihypotenstion drug through different methods and were characterized by the above-mentioned analytical tools. Few of the polymorphic forms were also studied for their stability.
Chapter-IV provides the preparation of various polymorphic forms of Nevirapine, an antiviral drug. The resulted products were characterized by using above-mentioned analytical tools.

Chapter-V presents the preparation of thermally stable crystalline form of Risperidone, an antipsychotic drug. Various analytical tools were utilized to characterize the products produced.

The results of our investigation on polymorphism described in the chapters provide an insight into the preparation and characterisation of novel and stable polymorphic forms in various active pharmaceutical ingredients.


