CHAPTER-1

INTRODUCTION

Table of contents

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Description</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Phase transformation</td>
<td>4</td>
</tr>
<tr>
<td>1.2</td>
<td>Methods employed for preparation of polymorphs</td>
<td>5</td>
</tr>
<tr>
<td>1.2.1</td>
<td>Sublimation</td>
<td>5</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Crystallization from a single solvent</td>
<td>5</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Evaporation from a binary mixture of solvents</td>
<td>6</td>
</tr>
<tr>
<td>1.2.4</td>
<td>Vapour diffusion</td>
<td>6</td>
</tr>
<tr>
<td>1.2.5</td>
<td>Thermal treatment</td>
<td>7</td>
</tr>
<tr>
<td>1.2.6</td>
<td>Crystallization from the melt</td>
<td>7</td>
</tr>
<tr>
<td>1.2.7</td>
<td>Precipitation of basic or acidic substance by changing solution pH</td>
<td>7</td>
</tr>
<tr>
<td>1.2.8</td>
<td>Thermal de solvation of crystalline solvates</td>
<td>7</td>
</tr>
<tr>
<td>1.2.9</td>
<td>Growth in the presence of additives</td>
<td>8</td>
</tr>
<tr>
<td>1.2.10</td>
<td>Grinding</td>
<td>8</td>
</tr>
</tbody>
</table>
1. INTRODUCTION

The pharmaceutical applications of polymorphism have been reviewed by Haleblian [1]. Crystalline phase of a solid compound in the solid state is known to be a polymorph. The molecule itself may be of different shape in the two polymorphs, but that is not necessary and indeed, certain changes in shape (involving dynamic isomerism or tautomerism) involve formation of different molecules and hence do not constitute polymorphism. A polymorphism is the ability of any element or compound to obtain in many suitable forms. Different polymorphs of a compound are, in general, different in structure and properties in the same manner as the crystals of two different compounds. The properties of API’s solubility, melting point, density, hardness and crystal form modify the performance properties of a drug. Therefore, a knowledge of the behavior of the polymorphs in drugs is required.

The majority of pharmaceutical materials, either the active pharmaceutical ingredients (APIs) or the excipients, are produced and stored as solids. Additionally, most common drug products are manufactured and formulated as solid-dosage forms, such as tablets and capsules. Drugs for parenteral application are formulated as lyophilized products and dry powder inhalers are becoming popular for delivery of respiratory products. Based on the order of molecular packing, solids are classified into two major classes of crystalline forms and amorphous forms. In the crystalline state, molecules arrange into a highly regular fashion [2, 3].

![Figure: 1.1. Broad classification of polymorphism as per ICH guidelines.](image-url)
Polymorphism is a fairly common phenomenon, though highly polymorphic systems (containing more than three polymorphs) are rare. A famous example of a highly polymorphic compound is 5-methyl-2-[(2-nitrophenyl) amino]-3-thiophene-carbonitrile [4-6] (figure: 1.2) known more commonly as ROY (named for the varying red, orange and yellow colours of the different polymorphs). ROY has ten known polymorphs, though only seven of the polymorphs have known crystal structures.

![Image: Polymorphs of ROY](image)

**Figure: 1.2.** The polymorphs of 5-methyl-2-[(2-nitrophenyl) amino]-3-thiophene-carbonitrile (ROY).

Yang and Guillory [7] noticed correlation between the regularity of polymorphism incidence in sulfonamides with different these stronger hydrogen bonds are not readily stretched or broken to form crystalline structures.

Polymorphs of a drug are usually prepared by crystallization of the drug from different solvents under diverse conditions. The metastable polymorphic form
crystallized from the mother liquid follows Ostwald’s step law; subsequently these crystals are transformed into the stable polymorphic form. The phase-transformation pathway (phase diagram of crystals) is determined by the thermodynamic parameters (chemical potentials) of the mother liquid and the crystallized solid phase, based on the interaction between the chemical structure of the drug and the solvent.

Since polymorphs differ from one another in their crystal energies, the more energetic ones seek to revert to the most stable (and the least energetic) crystal form. In the presence of a number of polymorphs and solvates (drug plus molecules of solvent), the conditions under which they may interconvert are complex. Therefore, preformulation studies are of prime importance for the development of dosage forms. In order to design a dosage form, the inherent stability of the drug against heat, humidity, light and mechanical stress must be understood. Therefore, many preformulation studies have been published concerning the solid-state stability of organic compounds under various conditions of temperature, humidity and grinding [8].

1.1. Phase transformation

The physical stability of crystalline solid forms depends on environmental conditions (e.g. temperature, pressure, and relative humidity). During product development, crystalline solids may be exposed to solvents, mechanical stress, or physical characteristics of the crystal examples are crystal habit, size, and the presence of impurities each of which can induce phase transformations. If crystals grow from and remain in contact with solution, a phase transformation likely takes place via solution by dissolution and recrystallization [9-11]. When a transformation is interfered by solution, it is most a common and successful approach to transform high-energy forms to more constant polymorphs [12].

The exchange is motivated by the variations in energy between the metastable and stable polymorphic form, so which reflect as in solubility difference between the two forms [13]. Finally the metastable form converts into the stable polymorph by way of growth of crystals followed by suspension processes [14].
The condition of polymorphism and/or amorphism affects the solid-state stability of the preparation against environmental factors, because the metastable crystalline solids have a higher chemical potential and are less stable. The physicochemical properties of bulk powders affect the bioavailability of a drug by altering the dissolution rate, especially those of polymorphic forms of drugs that are practically insoluble in water [15-17].

1.2. Methods employed for preparation of polymorphs.

The methods employed for the preparation of polymorphs are as follows

1.2.1. Sublimation

During heat around every part of organic substances are renewed from state of solid to the vapors state and reverse to again solid phase is called sublime. Although this process refers phase change from solid to gaseous devoid of liquid phase. Habitually which are found that crystals were formed only on cooler surface in close nearness to the melting point of organic compounds and below the melting point there were no crystals were formed.

1.2.2. Crystallization from a single solvent

In this method the solution should evaporate slowly to produce crystals and then filter the solution, keep a side. It should cover with an aluminum foil to adjust the rate of evaporation containing a few small holes. The process of solution mediated transformation can be considered the result of two separate events

(a) Dissolution solute

(b) Nucleation

If crystals do not grow as expected from a saturated solution, the interior of the vessel can be scratched with a glass rod to induce crystallization by distributing nuclei throughout the solution. Alternatively, crystallization may be promoted by adding nuclei, such as seed crystals of the same material. If two polymorphs differ in their melting point by 25–50°C, monotropic polymorphs the lower melting, more soluble, form will be difficult to crystallize. The smaller the difference between the two melting points, the more easily unstable or metastable forms can be obtained.
1.2.3. Evaporation from a binary mixture of solvents

When the single solvent solutions are not giving the preferred phase, binary mixture of solvents can be selected. This type evaporation of solvent method depends on the solubility proportions of the solute in a choice of solvents. In this a solute which is sparingly soluble in second solvent and this was added to a saturated solution of the compound in a primary solvent. The regularly a system of solvent selected in which the active substance is more soluble with the elevated vapor pressure. As the solution starts evaporation, the solution volume is lowered.

1.2.4. Vapour diffusion

This method involves, select a suitable solvent for a solute placed in a small, open container then it was stored in a better vessel containing a trace amount of a volatile, miscible non-solvent and then the vessel was closed tightly. When solvent reached equilibrium state, the non solvent gets diffuses throughout the vapor phase into the beaker containing solution, and became saturation or super saturation.

Figure: 1.3. Crystallization by vapor diffusion.
1.2.5. Thermal treatment

Frequently when using differential scanning calorimetry as an analysis technique, one can observe an endothermic peak corresponding to a phase transition, followed by a second endothermic peak corresponding to melting. Sometimes there is an exothermic peak between the two endotherms, representing a crystallization step. In these cases it is often possible to prepare the higher melting polymorph by thermal treatment.

1.2.6. Crystallization from the melt

In which the Ostwald’s principles, stating that a cooling of polymorphic melt compounds produces the metastable forms and these are latterly rearranges into the stable compounds. Generally these high energy forms has lower melting point, and it followed that super cooling is essential to crystallize it solute from the melt.

1.2.7. Precipitation of basic or acidic substance by changing solution pH

Many drug substances fall in the category of slightly soluble weak acids, or slightly soluble weak bases, whose salt forms are much more soluble in water. Upon addition of acid to an aqueous solution of a soluble salt of a weak acid, or upon addition of alkali to an aqueous solution of a soluble salt of weak base, crystals often result. These crystals may be different from those obtained by solvent crystallization of the weak acid or weak base. Nucleation does not necessarily commence as soon as the reactants are mixed, unless the level of super saturation is high, and the mixing stage may be followed by an appreciable time lag before the first crystals can be detected. Well-formed crystals are more likely to result in these instances than when rapid precipitation occurs.

1.2.8. Thermal desolvation of crystalline solvates

The term “desolvated solvates” has been applied to compounds that were originally crystallized as solvates but from which the solvent has been removed (generally by vaporization induced by heat and vacuum). Frequently, these “desolvated solvates” retain the crystal structure of the original solvate form and exhibit relatively small changes in lattice parameters. For this reason, these types have been
referred to as pseudo polymorphic solvates. However, in instances where the solvent serves to stabilize the lattice, the process of desolvation may produce a change in lattice parameters, resulting in the formation of either a new crystal form or an amorphous form. These solvates have been referred to as polymorphic solvates. Which has characterized the desolvation of polymorphic solvates as occurring in four steps, (a) molecular loosening, (b) breaking of the host-solvent hydrogen bonds (or other associations), (c) solid solution formation, and (d) separation of the product phase.

1.2.9. Growth in the presence of additives

In the crystallographic studies, the presence of fewer impurities can effect on the crystals growth. Sometimes they may completely inhibit growth, or initiate growth. Some others may begin to act on only crystal faces and consequently modifying the crystal habit. Some impurities can an influence at very low concentrations which is > 1 part per million, while others in large amounts to be present and showed their effect. Hence these types of additives can be prepared to attach in particular to the surfaces of polymorphs and to inhibit the critical size for nucleation and allowing without competition to grow a desired phase of new polymorphic form.

1.2.10. Grinding

Above the method is play major role in the conversion of crystal solid surface to polymorphic amorphous form. This type transformation has been experimentally to occur on materials grinding, when the crystals undergoes in to mechanical stress the transformation takes place by followed steps, crystal molecular loosening, formation of new solid solutions and product which leads to formation new surface. Examples are sulfa derivatives, few cephalosporin and anti depressants such as barbitals.