POLYMORPHISM

Draft chapter for The International Pharmacopoeia

(May 2018)

DRAFT FOR COMMENT

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.716:

Draft chapter for *The International Pharmacopoeia*

Polymorphism

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<td>Drafting of the text by a WHO Expert</td>
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[Note from the Secretariat. It is proposed to publish the following chapter on Polymorphism in the Supplementary Information section under “Notes for guidance”.]
Polymorphism

Introduction and terminology

The aim of this chapter is to provide a brief overview of

- the terminology associated with crystal polymorphism;
- some analytical techniques commonly used to characterise polymorphs;
- the relevance of polymorphism for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs);
- the control strategies for polymorphism employed by *The International Pharmacopoeia*.

APIs and excipients, in the solid phase, can be classified as either crystalline or non-crystalline solids or a mixture thereof. A crystalline structure implies that the structural units (i.e. the unit cells) are repeated in a long range order. The atoms and/or molecules of an amorphous solid, however, are arranged in a non-ordered, random system, such as in the liquid state, and do not possess a distinguishable crystal lattice. Amorphous solids are classified as non-crystalline solids.

Variation in the crystallization conditions (temperature, pressure, solvent, concentration, rate of crystallization, seeding of the crystallization medium, presence and concentration of impurities, etc.) may cause the formation of different forms.

When the crystalline structure of the same chemical compound (and atomic formula) exhibit two or more patterns of the repeated unit cells, these crystalline structures are called *polymorphs* and the phenomena is referred to as *polymorphism*. The difference in internal crystal structure could be attributed to differences in molecule packing arrangements and/or different molecular conformations. When a chemical element (e.g. sulfur) exists in different crystalline forms, it is referred to as *allotropy*, not polymorphism (*I*). Due to the identical
chemical composition of the polymorphic substance it will have the same chemical behaviour in solution, irrespective in the form in which it is presented.

Crystals of the same chemical compound with the same internal structure may exhibit different external shapes or crystal habits.

Solvates are crystal forms containing stoichiometric or non-stoichiometric quantities of a solvent. When the solvent incorporated into the crystal structure of the compound is water, the molecular adduct formed is referred to as a hydrate. Solvation and hydration products are also sometimes referred to as pseudopolymorphs (2, 3, 4). However, the term “pseudopolymorphism” is ambiguous because of its use in different circumstances. It is therefore preferable to use only the terms “solvates” and “hydrates”.

Occasionally a compound of a given hydration/solvation state may crystallize into more than one crystalline form; an example of such a compound is nitrofurantoin (5). Nitrofurantoin can be crystallized as two monohydrate forms (Forms I and II) and two anhydrous forms (designated polymorphs α and β) (5).

Crystal forms are said to be isostructural when they have the same overall crystal packing. Solvates, which have the same overall crystal packing, but differ only in the solvents included in their crystal structures, are termed isostructural solvates, e.g. hydrate and isopropanolate of hexakis(2,3,6-tri-O-acetyl)-α-cyclodextrin (6).

The term desolvated solvate (which includes hydrates) has been used to classify a compound that was originally crystallized as a solvate but when the incorporated solvent is removed the crystal lattice of the solvated and desolvated crystal lattices show no or only relatively small differences (4), for example, desolvated monohydrate of terazosin HCl (7).

Amorphous forms of APIs and excipients are of substantial interest because they are usually more soluble than their crystalline counterparts but are usually considered to be
thermodynamically less stable. Solid-state properties of amorphous forms of the same chemical compound (i.e. thermal behaviour, solubility profile, etc.) may differ; this phenomenon is referred to as polyamorphism (6).

Traditionally polymorphic forms of an API are classified as either crystalline, amorphous or solvate and hydrate forms. Co-crystals are crystalline materials composed of two or more different molecules, typically an API and co-crystal formers (“conformers”) within the same crystal lattice that are associated by nonionic and noncovalent bonds. An example of a co-crystal is fluoxetine HCl/succinic acid co-crystal (8). Co-crystals are thus more similar to solvates, in that both contain more than one component in the lattice. However, for co-crystals the conformer is non-volatile (3).

Pharmaceutical co-crystals have gained considerable attention as alternative forms in an attempt to enhance the bioavailability, stability and processability of the API in the manufacturing process. Another advantage of co-crystals is that they generate a diverse array of solid state forms for APIs that lack ionisable functional groups, which is a prerequisite for salt formation (3). Guidance and reflection papers on the use and classification of pharmaceutical co-crystals have been published (3, 9).

Characterization and thermodynamic stability of solid forms

Crystalline forms are characterized based on the differences of their physical properties. Table 1 lists some examples of the properties that may differ among different forms (9).

**Table 1.** Examples of physical properties that may differ among different forms

1. **Packing properties**
   a. Molar volume and density
   b. Refractive index
   c. Conductivity (electrical and thermal)
   d. Hygroscopicity

2. **Thermodynamic properties**
Table 2 summarizes some of the most commonly used techniques to study and/or classify different forms. These techniques are often complementary and it is indispensable to use several of them. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can also be used to provide unequivocal proof of polymorphism (10).
Any technique(s) chosen to confirm the identity of the specific form(s) must be proven to be suitably specific for the identification of the desired form(s). Care must be taken in choosing the appropriate sample preparation technique, as heat generation or exposure to elevated pressure may trigger conversion between different forms.

**Table 2.** Examples of some techniques that may be used to study and/or classify different crystalline forms

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<td>1.</td>
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<td>2.</td>
<td>Single crystal X-ray diffraction</td>
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<td>3.</td>
<td>Microcalorimetry</td>
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<td>Moisture sorption analysis</td>
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<td>8.</td>
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<td>9.</td>
<td>Spectrophometry: <em>Spectrophotometry in the infrared region (1.7)</em> and Raman spectrophotometry</td>
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<td>10.</td>
<td>Intrinsic dissolution rate</td>
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<td>Density measurement</td>
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* Methods currently employed by *The International Pharmacopoeia*

Using suitable analytical techniques, the thermodynamic stability of the forms should be investigated. The form with the lowest free energy is the most thermodynamically stable at a given temperature and pressure. The other forms are said to be in a metastable state. At normal temperature and pressure, a metastable form may remain unchanged or may change to a thermodynamically more stable form. In general the more stable the form the less soluble it
is. Conversion to a thermodynamically more stable form, may cause changes in some of the
physical properties (see Table 1) of the compound that may result in changes to other critical
properties such as bioavailability, manufacturability (also referred to as processability), etc.

If there are several crystalline forms one form is thermodynamically more stable at a given
temperature and pressure. A given crystalline form may constitute a phase that can reach
equilibrium with other solid phases and with the liquid and gas phases.

If each crystalline form is the more stable within a given temperature range the change from
one form to another is reversible and is said to be enantiotropic. The change from one phase
to another is a univariate equilibrium so that at a given pressure this state is characterized by
a transition temperature. However, if only one of the forms is stable over the entire
temperature range, the change is irreversible or monotropic (11).

Relevance of polymorphism for APIs and FPPs

Polymorphism of APIs and excipients are of interest as they may affect bioavailability,
toxicity and processability. Also the thermodynamic stability of the form included in the FPP
is considered important as environmental conditions may compromise the stability thereof.
For formulations where the API is dissolved, attention has to be paid to supersaturation with
regards to different forms. A formulation might not be supersaturated regarding a metastable
polymorph but supersaturated with regards to the thermodynamically stable polymorph.
Control of the form by the manufacturer may be required during the processing of APIs and
excipients and during the manufacturing of a dosage form to ensure the correct physical
characteristics thereof. The control of a specific form is especially critical in the areas where
the bioavailability, stability or processability are directly impacted (4).

The form of a readily soluble API that is incorporated into a solution, for example, an
injection, an oral solution or eye drops, is normally non-critical (an exception to this
statement might be if the concentration of the solution is such that it is close to the limit of
solubility of one of the possible polymorphs – as mentioned above). Similarly, if an API is processed during the manufacturing process to obtain an amorphous form (e.g. hot melt extrusion, spray-dried dispersion, etc.), the original form is considered non-critical, as long as the processability is not influenced.

The form may be critical when the material is included in a solid dosage form or as a suspension in a liquid dosage form. In such cases the characteristics of the different polymorphs may affect the bioavailability or dissolution of the material. The polymorphic form of a biopharmaceutical classification system (BCS) class I or III API in a solid oral dosage form is normally non-critical in terms of dissolution rate or bioavailability as by definition it would be readily soluble, but confirmation thereof by the manufacturer, is recommended. The ICH Harmonised Tripartite Guideline on Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances Q6A, provides guidance on when and how polymorphic forms should be monitored (4).

The inclusion of potentially harmful solvents in the crystal lattice, which may render APIs or excipients to be toxic or harmful to patients (i.e. solvates), should also be suitably regulated and monitored by the manufacturer.

**Polymorphism in The International Pharmacopoeia**

Where a monograph indicates that a compound shows polymorphism this may be true crystal polymorphism, occurrence of solvates or occurrence of the amorphous form.

*The International Pharmacopoeia* controls the forms of a limited number of substances by restricting it to either:

- a single form, for example, carbamazepine API (Anhydrous Form III), mebendazole API (Form C); or
by limiting the presence of unwanted forms, for example, chloramphenicol palmitate API (should contain at least 90% of polymorph B).

The control of forms specified in *The International Pharmacopoeia* may be achieved by:

- permitting no deviation from the infrared absorption spectrum of the reference substance prescribed (or reference spectrum supplied) – when the infrared absorption spectrum has been proven to be specific to the preferred form and able to distinguish the undesired form(s), for example, indomethacin API;
- restricting the melting point range, for example, phenobarbital API;
- recommending the use of any other suitable methods such as X-ray powder diffractometry, for example, carbamazepine tablets;
- limiting the incorporated solvent (in the case of solvates/hydrates) with a specific limit test, for example, nevirapine hemihydrate API.

When the infrared identification test is able to detect differences in forms for a specific compound (i.e. polymorphism may be present for this compound), but the control of a specific form is not required by the monograph, the user may be instructed to:

- recrystallize both the test substance and the specified reference substance, in the event where the infrared spectra are found to be not concordant, for example, fluconazole API; and/or
- dry the API and/or specified reference substance to ensure that both forms are in the anhydrous or dehydrated state, for example, nevirapine hemihydrate API.

Whenever the choice of a specific form is critical with regard to bioavailability and/or stability, the method of the manufacturer of the product must be validated to consistently yield the desired polymorph in the final product at release and over its shelf life. The monograph will include a statement under the heading “Manufacturing” to draw attention to
the control of a specified form during manufacturing where control is known to be critical, for example, carbamazepine oral suspension.

It is the intention of The International Pharmacopoeia to extend the inclusion of explicit statements in monographs, where appropriate, as information on the occurrence of polymorphism becomes available. The Secretariat thus cordially invites the users of The International Pharmacopoeia and manufacturers to share any relevant information that could be included in the monographs.

REFERENCES


