

Polymorphs in Pharmaceutical Products

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Definition Of Polymorphs

- Polymorphs are different crystalline forms of the same pure substance in which molecules have different arrangements and/or different molecular conformation.

Definition Of Polymorphs (contd)

- Polymorphic solids have different unit cells.
- Display different physical properties such as unit packing, thermodynamic, spectroscopic, interfacial, and mechanical properties.

Physical Properties Differ Among Various Polymorphs

- Molar volume and density
- Refractive index
- Melting and sublimation temperatures
- Enthalpy (i.e., heat content)
- Solubility
- Vibration transitions (i.e., infrared absorption spectra and Raman spectra)

Physical Properties Differ Among Various Polymorphs (contd)

- Dissolution rate
- Stability
- Hardness
- Compatibility
- Handling, flow, and blending

Polymorphs

- An amorphous form is not a polymorph
- A clathrate or a hydrate can be a polymorph

Amorphous Forms

- Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as a polymorph.
- Unlike true polymorphs, an amorphous form is not a single type of crystal and not considered a polymorph.

Clathrate/Inclusion Compounds

- A chemical substance consisting of a lattice of one type of crystal structure trapping and containing a second type of molecule. Therefore, a clathrate is a material which is a weak composite, in which molecules of suitable size are captured in spaces which are left by the other compounds.
- Molecules of one substance are completely enclosed within the crystal structure of another.

Channel Hydrates

Compound. $x\text{H}_2\text{O}$

- Hydrates in this class contain water in lattice channels, where the water molecules included lie next to other water molecules of adjoining unit cells along an axis of the lattice forming “channels” through the crystal.

Claiming A Polymorph

- Include name or structure of the chemical compound.
- Apply a “standard” convention to designate and name the polymorphic form and distinguish it from other polymorphic and pseudomorphic forms already in the art.
- Incorporate comparison and characterization data.

Structure of three compounds

- Cpd.HCl
- Cpd.H₂O
- Cpd.HCl.H₂O, a new compound

Polymorphs May Be Unobvious Over Prior Art Forms

- The specific crystal lattice(s) and number of lattices of a polymorph are not predictable.
- Even if one could predict that polymorphs exist, there is no general teaching or suggestion in the art that allows one to predict how to make a particular polymorph.
- No teaching or suggestion exists in the art to identify and to appreciate the properties and characteristics of a particular polymorph prior to it being identified.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- A method of making the new polymorph was not known until its identification.
- The new crystalline form has different properties over the prior art compound.

Polymorphs May Be Unobvious Over Prior Art Forms (contd)

- It may not be obvious, and not possible to predict
 - How many different crystal forms can be prepared
 - How to prepare any, as yet unknown, crystal forms
 - The properties of any, as yet unknown, crystal forms

Therefore, new crystal forms are potentially patentable entities

Include Available Polymorph Comparison and Characterization Data Such As:

XRPD

Single crystal x-ray

Infrared absorption

Raman spectroscopy

Solid state NMR

Morphology determination

Include All Available Polymorph Characterization Data Such As: (contd)

- Beyond having a diverse collection of characterization data, the data for a novel polymorph should be analyzed to demonstrate how it distinguishes over other disclosures including the compound per se, and more particularly, over other polymorphic forms.

Include all available polymorph characterization data such as (contd)

- Furthermore, characterization data that evidences unexpected or superior properties over properties of the compound per se, and other polymorphic forms, could make the prosecution easier.

QUESTIONS