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 properties such as unit packing, thermodynamic, spectroscopic, 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
- Vibrational 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

Clathrates and hydrates can exist in polymorphic forms.

An amorphous form is not a polymorph

Amorphous Forms

Many pharmaceutical solids exist in amorphous forms and because of their distinctive properties are sometimes regarded as polymorphs.

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 in the crystal lattice.

Molecules of one substance are completely enclosed within the crystal structure of another.

Useful References for Examination of Polymorphs

H. Brittain, ed. Polymorphism in Pharmaceutical Solids 1999

Yu et al. Physical Characterization of Polymorphic Drugs PSST vo1. 1(3) 1998

H. Brittain, ed. Physical Characterization of Pharmaceutical Solids 1995

Useful References, Continued

Morissette et al. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Advanced Drug Delivery Reviews 56 (2004) 275-300.

Rodriguez et al., General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Advanced Drug Delivery Reviews 56 (2004) 241-274.

Case Law Relevant to Novel Crystalline Forms

In re Cofer, 354 F2d 664, 148 USPQ 268 (C.C.P.A. 1966)

SmithKline Beecham v Apotex, 403 F.3d 1331, 74 USPQ2d 1398 (Fed. Cir. 2005)

What is required to show possession of the claimed invention?

Polymorphic forms are often identified by XRPD. Claims should contain sufficient identification to distinguish forms. Peak location must be provided and relative intensity may also be provided. Peak heights can vary depending on conditions.

Details such as instrument settings and types should be included in the specification. Art recognized variation (scattering angles $\pm 0.2°$, relative intensity varying by no more than 20%) is expected.

Melting point alone is not sufficient to identify any particular form. Melting points can be very close.

If, for example, "Form I" is defined in the specification in such a way as to sufficiently describe the invention claims drawn to "Form I" are acceptable. If the definition is ambiguous or the claim is not limited to that particular form more is required in the claim.

Enablement

If the crystallization process has been described in detail and the claims are limited to the form produced by this detailed method, the invention is probably enabled.

A generic claim to a “polymorph,” “hydrate,” etc. would generally raise issues of enablement since the generation of these forms is not predictable. Such claims may also lack written description.

Art rejections

If the art teaches a crystalline form with no characterization, or with characteristics similar to what is instantly claimed, a rejection under 102 should be considered.

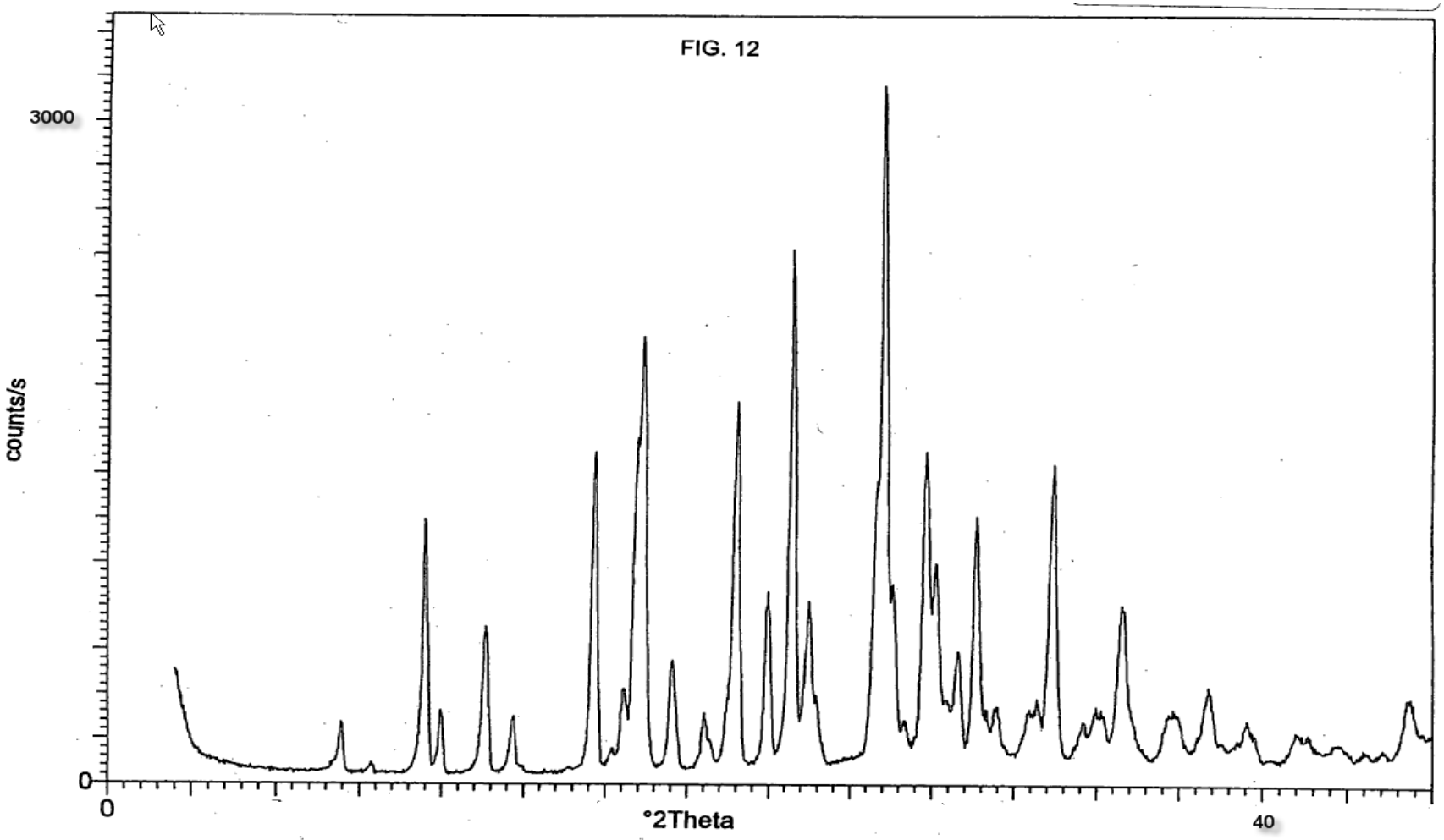
In most cases, if the melting point or XRPD is significantly different, no rejection can be made. A prima facie case that the two crystals are the same must be presented to make an art rejection.

Since the final form of a polymorph is unpredictable, 103 rejections of the novel form cannot generally be made.

The Specification

- Compound X is a calcium channel antagonist used as an antihypertensive agent. The commercial form is a crystalline hydrochloride salt.
- The specification discloses a crystalline form of Compound X hydrochloride, form I, identified in the specification by XRPD and melting point determined by DSC.
- IR, Raman, and solid phase NMR spectra are provided in the drawings. Instrumentation and conditions used are described.
- The method of crystallization is also described in detail.
- Pharmaceutical compositions which include the crystalline forms with standard additives are disclosed.

X-Ray Powder Diffraction



Claims

1. Isolated Compound X hydrochloride crystalline form I, which has an X-ray diffraction pattern at wavelength Kα as shown in Figure 12.

Claim 2

2. Isolated Compound X hydrochloride crystalline form I, wherein distances, (I/Io) ratios, and 2Θ angles of significant peaks as determined by XRPD are:

D(Å)	I/Io	2Θ angle
9.3	35	9.5
3.77	100	23.6

Claim 3

3. Isolated compound X hydrochloride crystalline polymorphic Form I having a melting point of 207 - 211 °C.

Claim 4

4. Isolated crystalline Compound X hydrochloride, wherein distances, (I/Io) ratios, and 2Θ angles of significant peaks as determined by XRPD are:

D(Å)	I/Io	2Θ angle
9.3	35	9.5
3.77	100	23.6

Claim 5

5. Isolated crystalline Compound X hydrochloride, wherein distances, (I/Io) ratios, and 2Θ angles of significant peaks as determined by XRPD are:

D(Å)	I/Io	2Θ angle
9.3	35	9.5
6.0	45	14.7
5.67	48	15.9
5.49	65	16.7
4.65	52	16.1
4.27	74	20.8
3.81	41	23.4
3.77	100	23.6
3.58	44	24.8
3.54	29	25.2

Claim 6

6. Compound X hydrochloride crystalline form produced by a method comprising:

   a) adding ethanol with a water content below 10% by weight to Compound X hydrochloride and refluxing to produce a solution;

   b) cooling the solution and stirring until the concentration of Compound X hydrochloride dissolved in the crystallization solvent is less than 2%; and

   c) recovering the solid produced in step b) to produce crystalline Compound X hydrochloride.

Claim 7

7. A method of making a crystalline form of Compound X hydrochloride comprising:

   a) adding ethanol with a water content below 10% by weight to Compound X hydrochloride and refluxing to produce a solution;

   b) cooling the solution and stirring until the concentration of Compound X hydrochloride dissolved in the crystallization solvent is less than 2%; and

   c) recovering the solid produced in step b) to produce crystalline Compound X hydrochloride.

Claim 8

8. A method of making Compound X hydrochloride form I comprising

   a) adding ethanol with a water content below 10% by weight to Compound X hydrochloride and refluxing to produce a solution;

   b) cooling the solution and stirring until the concentration of Compound X hydrochloride dissolved in the crystallization solvent is less than 2%; and

   c) recovering the solid produced in step b) to produce crystalline Compound X hydrochloride form I.

Claim 9

9. A pharmaceutical composition comprising Compound X hydrochloride crystalline Form I.

Analysis, written description: claims 1-3

Claims 1 -3 meet the written description requirement.

Applicant has described the characteristics of Form I in the specification. Thus claims drawn to Form I meet the written description requirement.

Analysis, continued: claim 4

Claim 4 may not comply with the written description requirement. The claim does not require that the crystalline form be Form I. While the listed peaks may differ from a crystal known in the art, the listed peaks are not generally sufficient to describe this one. See Brittain, 1999, indicating that 10 peaks are sufficient to describe a crystalline form.

Analysis continued: claim 5

Claim 5 meets the written description requirement because the XRPD data presented are sufficient to describe the claimed crystalline form. See Brittain, 1999.

Analysis continued: claims 6-9

Claims 6 -8 meet the written description requirement since the method is detailed enough to produce form I.

Claim 9 may meet the written description requirement; the specification discloses pharmaceutical compositions. However, if the examiner can cite a reference indicating that the formulation process is likely to damage the crystal, more than a statement of ingredients may be required.

Enablement

Claims 1-3 and 5-8 meet the enablement requirement since the specification provides sufficient guidance as to how to make Form I.

Claim 4 may raise scope issues as it is not limited to Form I and the specification does not teach how to make other forms with these characteristics.

Claim 9 may raise issues of enablement since the crystalline structure must be maintained in the composition.

Art Rejections

The specification teaches that Compound X hydrochloride was crystallized from ethanol and has a melting point of 207-211°C.

The art teaches that Compound X hydrochloride has been crystallized from ethyl acetate and has a melting point of 200 ◦C. No other data are provided.

Would a Rejection Under 102 or 103 be appropriate?

A rejection of claims 1- 3 and 5-9 under 102 would not be appropriate. The method of crystallization is different and the melting point is different. Thus there is no prima facie case that the crystals are the same. As to claim 9, the pharmaceutical composition must maintain crystalline form I and thus is not anticipated. A rejection of claim 4 under 102 should be considered.

A rejection of claims 1-5, 8, and 9 under 103(a) would also not be appropriate. While the artisan would consider it obvious to purify the compound by crystallization that would not necessarily lead to the instant form. Further, the reference would not lead the artisan to the crystallization conditions that produce instant form I.

However, claims 6 and 7 may be obvious over the prior art as they are not limited to form I.

Art Rejections: a Different Fact Pattern

The art teaches a crystalline form of Compound X hydrochloride crystallized from isopropanol. A melting point of 205°C is given. Pharmaceutical compositions are taught. No other information as to the characteristics of the crystalline form is provided.

Would a rejection under 102 or 103 be appropriate?

A rejection of claims 1-6 and 9 under 102 would be appropriate as there is sufficient evidence for a prima facie case that the crystals are the same based on the similar melting point. Applicant could rebut this evidence by comparing the two crystals. The method claims, which require a different solvent, are not anticipated.

A rejection of these claims under 103(a) would not be appropriate. As in the previous fact pattern, while the artisan would consider it obvious to purify the compound by crystallization that would not necessarily lead to the instant form.

Claims 7 and 8 are potentially obvious over the prior art; a prima facie case must be made that the method steps are obvious over the art.

Another Fact Pattern

The prior art teaches crystallization of Compound X hydrochloride from hexane but provides no analysis of the product crystals. Pharmaceutical compositions are also taught. The post-filing art teaches that Compound X hydrochloride crystallized from hexane exhibits a melting point within the range of 207 - 211 ◦C.

A rejection of claims 1-6 and 9 under 102 would be appropriate. The post filing evidence demonstrating that the melting point of crystals obtained from hexane provides sufficient grounds for asserting that the structure of the prior art crystal is the same as the claimed polymorph. Recall that the methods require different steps.

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THANKS!