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Patentability of polymorphic crystalline forms of pharmaceutically active compounds

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05 November 2014

Polymorphism

Definition:

-a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state (*W.C. McCrone, 1965*)

or

-when a substance can exist in more than one crystalline state it is said to exhibit polymorphism (*Rosenstein and Lamy, 1969*)

Occurence of polymorphs

The existence of more than one crystal form (polymorphs and/or solvates) is not predictable. However, it is not surprising when new crystal forms are discovered, either by systematic searching, or by serendipity.

Polymorphism

The oft-quoted statement…

„..every compound has different polymorphic forms and…the number of forms known for a given compound is proportional to the time and energy spent in research on that compound.”

W. C. McCrone (1965)

The less quoted…

„With the accumulation of data there is developing a gradual realization of the generality of polymorphic behavior, but to many chemists polymorphism is still a strange and unusual phenomenon.”

M.J. Buerger és M.C. Bloom (1937)

Polymorphism

Ostwald's law of stages:

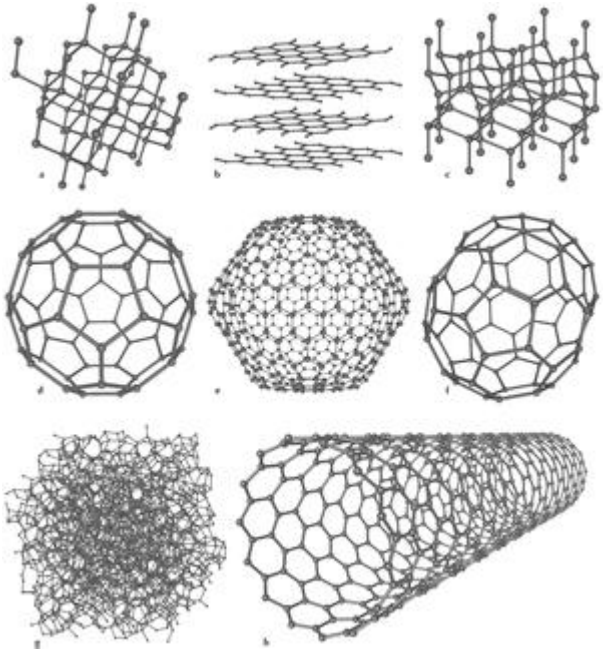
- at high supersaturation, the first form which crystallizes is the thermodinamically least stable (more soluble) form
- this form subsequently dissolves and transforms into a more stable one
- this cycle continues until the thermodinamically stable (less soluble) polymorph remains.

Practical implication:

should be possible to isolate the different polymorphs of a given compound at different levels of solution supersaturatiion and exercise (some) control over the crystallization process

Polymorphism

- Complex molecules may crystallize in many different forms
- At a certain temperature only one crystalline form can be stable
- In some cases the metastable forms can be stored for a long period
- The crystalline forms can be thermodinamically or kinetaically favoured



Even the good old aspirin…

Acetylsalicilyc acid

- first prepared in 1897
- determination of its crystalline structure in 1964
- second polymorphic form discovered in 2004 (co-crystallization of ASA and levetiracetam form hot acetonitrile)
- stable only at 100 K
- at ambient temperature recrystallization into form I

Polymorphism

Pharmaceutical excipients

- may be present either in amorphous or polymorphic form or as solvates
- eg. lactose, sorbitol, glucose, sucrose, magnesium stearate, mannitol etc.
- strongly influence the formulation of medicaments, hence the final physical properties of the tablet
- may induce the polimorphic transformation of the active compound

Polymorphism in the practice

The most common technological factors inducing polymorphism:

- scale-up and/or optimization of crystalization
- change of solvent
- drying
- warming
- compression (eg. pressing tablets)
- grinding/milling

Relevance of the crystalline polymorphism in the industry

New polymorphic forms may

- have better stability;
- have longer shelf-life;
- be produced in an easyier way;
- be better handled;
- possess better formulation properties
- have better bioavailability.

Most relevant polymorphic drugs

Steroids
Barbiturates
Sulfonamides

Ribavirin (antiviral)
Ritonavir (antiviral)
Ranitidin (H2 receptor antagonist)
Famotidin (H2 receptor antagonist)
Acetaminophen (analgesic)
Loperamide (inhibits GI motility)
Risperidone (atypical antipsychotic)
Atorvastatin Ca-salt (cholesterole lowering agent)
Clopidogrel bisulphate (platelet aggregation inhibitor)

Drugs having polymorphic forms

- **Acetaminophen:** two polymorphic forms, the marketed one is the stable Form I having monoclinic crystals
- **Famotidin:** two polymorphic forms, stable polymorph A and metastable polymorph B
- **Piroxicam:** non-steroidal anti-inflammatory having three polymorphic forms (I, II and III)
- **Norfloxacin:** synthetic antibiotics having two anhydrous polymorphic forms (A and B), at ambient temperature form B is the most stable, but the less stable metastable form has been marketed

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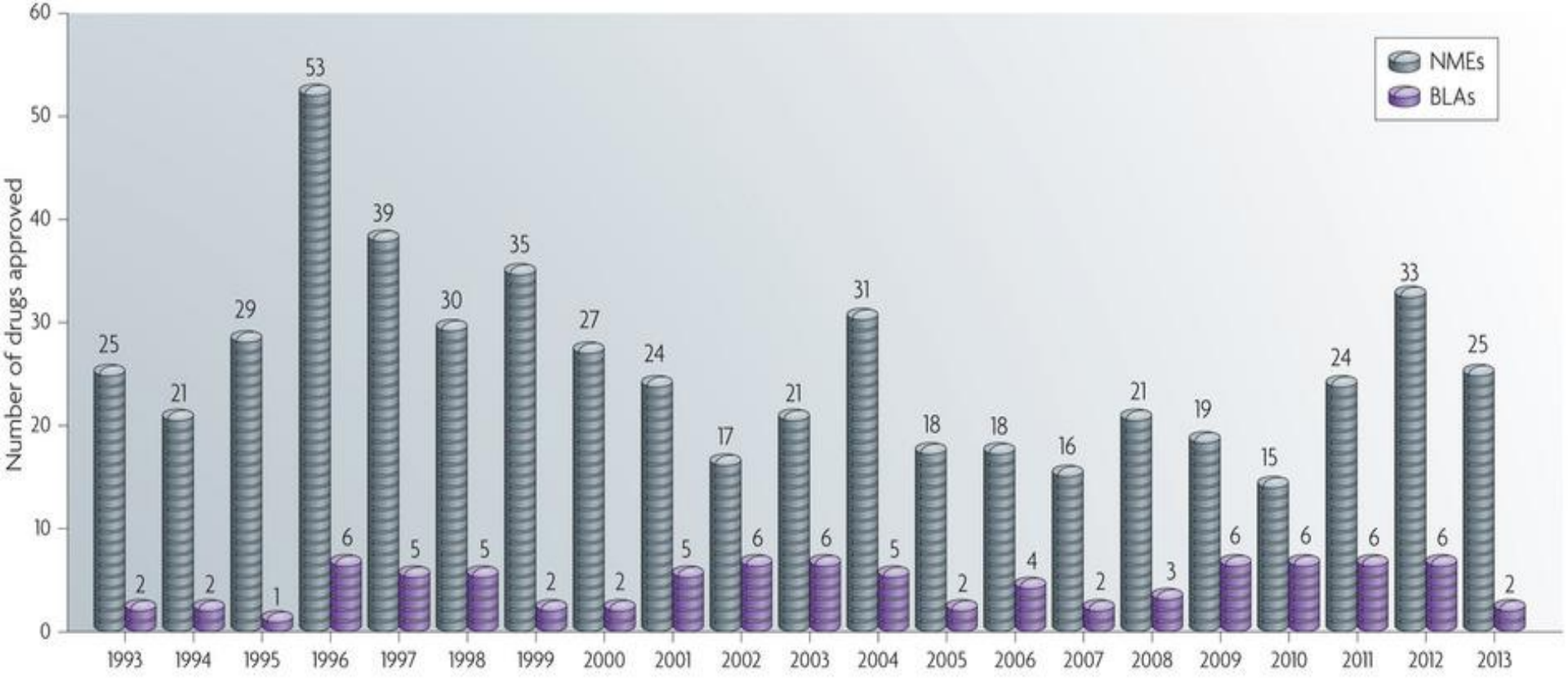
Approved drugs (FDA)



Nature Reviews | Drug Discovery

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Patents in the pharmaceutical industry

Patent lifecycle management = patent strategy

First generation patents: development and marketing (early stage)

Typical claims for first generation patents:

- product
  - Markush-formula
  - certain compounds by name
  - pharmaceutical preparations
- production process
- use (first medical use)

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Patents in the pharmaceutical industry

Second generation patents: on the market and when the protection approaches or exceeds the 20 years (late stage)

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Patents in the pharmaceutical industry

Typical claim formats for second generation patents (when the compound is known):

- second medical use (eg. new therapeutical effect)
- new dosage or dosage regimen
- new medicine form (eg. controlled release) or combinations
- prodrugs or metabolites
- new patients
- selection of certain salts (and their preparation)
- enantiomerically pure compounds (and their preparation)
- **crystalline polymorphs**

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Why are polymorphic forms important?

- Polymorphism is playing an increasingly important role in establishing and protecting intellectual property rights in the pharmaceutical industry

- As in the analysis and characterization of polymorphs a variety of analytical methods may be used in patent specifications

- The preparation, prosecution and protection of a patent involving polymorphs is a challenging scientific and legal activity

The most famous polymorphic patents

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Drug name	Active compound	Patentee	Drug patent	Polymorph
ALLEGRA	Fexofenadin	Sanofi	1979	1984
COZAAR	Losartan	Merck	1986	1993
CLARINEX	Desloratadin	Schering-Plough	1984	1997
DURICEF	Cefadroxil	Warner Chilcott	1967	1977
EPIVIR	Lamivudin	GlaxoSmithKline	1989	1992
GEODON	Ziprasidon	Pfizer	1988	1992
OMNICEF	Cefdinir	Abbott	1980	1988
PAXIL	Paroxetin	GlaxoSmithKline	1974	1986, 1995
PEPCID	Famotidin	Merck	1979	1987
VALTREX	Valacyclovir	GlaxoSmithKline	1988	1996
ZANTAC	Ranitidin	GlaxoSmithKline	1977	1981
ZOLOFT	Sertralin	Pfizer	1979	1992

Polymorphism: Three Key Issues

•What is the frequency of occurrence of polymorphism and/or different crystal forms?

• How do we prepare different crystal forms in a controlled and reproducible manner?

• What are the similarities and differences of properties of the different crystal forms?

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Polymorphism and patents

Questions arising:

- patentability
- validity of the patent
- harmonization of jurisdiction
- patent enforcement

Patentability criteria

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Basic requirements:

- Novelty
- Inventive step (= non-obviousness)
- Industrial applicability

+1

- Clarity, disclosure and support

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Polymorphism: Issue with patentability

- Cannot predict the existence of new crystal forms - polymorphs and solvates

NOVELTY

- Cannot predict in advance how to make as yet undiscovered crystal forms

NON-OBVIOUSNESS

- They can be used as medicines

INDUSTRIAL APPLICABILITY

Patentability criteria - claims

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A compound can be identified by its

- structure,
- production process (if there is no other data) or
- physical/chemical properties.

In case of polymorphs

- their structure is given (the same),
- their preparation process is irrelevant,
- **definition of their physical/chemical properties** is inevitable (eg. by their X-ray or infrared absorption data).

Crystalline polymorphs Issue with validity

- How different should X ray spectra be?
- Should peaks be of different heights, different positions, or…?
- Lord Justice Jacob in Servier *v* Apotex 2008 CA (paroxetine):

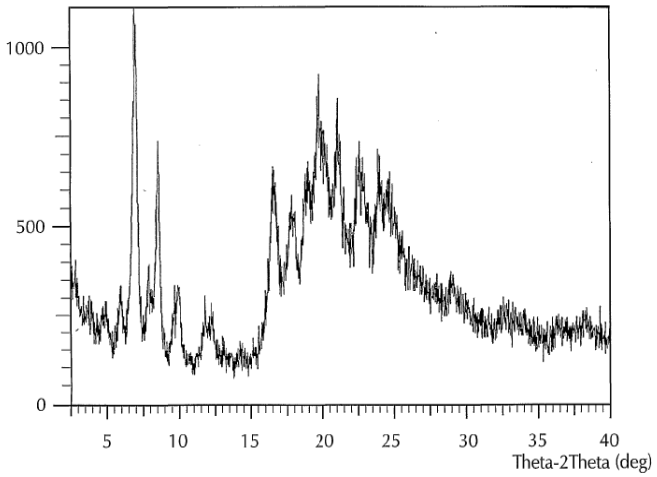
> "The individual peaks of the table should not have too much significance attached to them – it is the overall set that matters"

Patentability criteria - claims

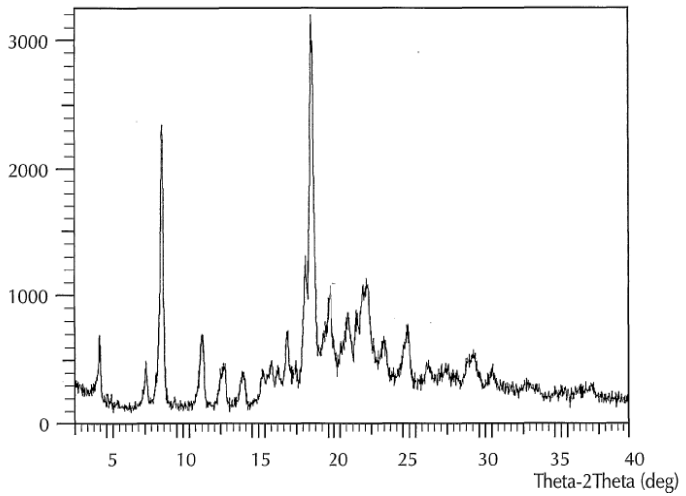
Crystalline polymorphs – Xray data

- Atorvastatin:

form V



form VI



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Crystalline polymorphs Issue with validity

- Was the “new” polymorph already manufactured in the past?
- Polymorphs are known to interconvert or revert spontaneously to other forms.
- *Servier v Apotex*
  - Patented form α was the inevitable product of the prior art protocols (see later).

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Crystalline polymorphs
Issue with validity

- Often polymorph patents claim several new forms at once but do not state what the new polymorph is for
- Often polymorph patent make vague claims about improved stability with no data
- Problems with inventive step under the EPO (problem-solution approach)
- Is there really an invention or a crystalline oddity?

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Crystalline polymorphs Issue with infringement

- What if some peaks are different?
- What if the X ray spectra of the alleged infringement is more similar to the prior art X ray spectra?
- The novelty/infringement squeeze
- Evidential problems may arise as excipient peaks (such as lactose) easily mask the relevant peaks.

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Perindopril
Novelty issue

- crystallization process and circumstances
- what is disclosed in the basic patent
- basic patent relates to the α form?

- Independent laboratories
- Analysis of XRPD data

Consequences:

- α form was the inevitable product covered by the basic patent
- patent revoked - lack of novelty

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Atorvastatin Ca salt
Inventive step issue

- polymorphism is usual in the pharmaceutical industry
- testing for polymorphism is strongly advisable at the very early stage of drug development
- changing parameters of crystallization is a routine work in the field of polymorphic forms (optimization)
- technical effects of crystalline polymorphs are well known
- the person skilled in the art would have aimed at producing a polymorph instead of the amorphous form

Consequence:

without a non-obvious beneficial property and/or effect bound to the novel polymorph an ***inventive step cannot be recognized.***

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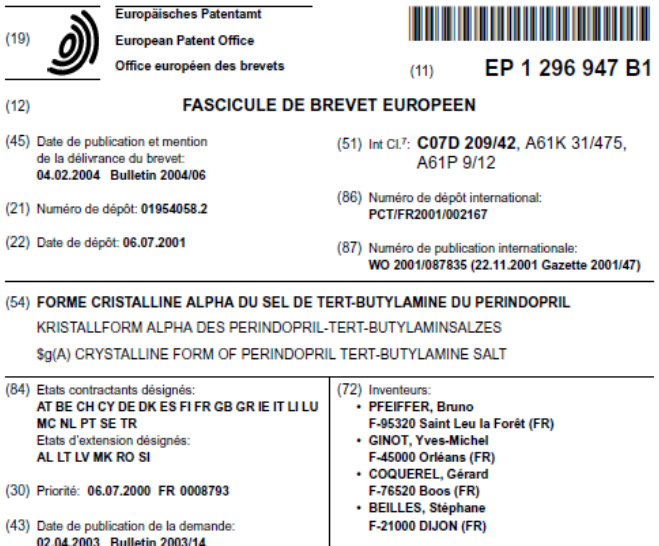
How to draft a good patent application on polymorphs?

This secret will be revealed by the speakers from the EPO in a couple of minutes…



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 296 947 B1

(12) FASCICULE DE BREVET EUROPEEN

(45) Date de publication et mention de la délivrance du brevet:
04.02.2004 Bulletin 2004/06

(21) Numéro de dépôt: **01954058.2**

(22) Date de dépôt: **06.07.2001**

(51) Int Cl.[7]: **C07D 209/42**, A61K 31/475, A61P 9/12

(86) Numéro de dépôt international:
PCT/FR2001/002167

(87) Numéro de publication internationale:
WO 2001/087835 (22.11.2001 Gazette 2001/47)

(54) **FORME CRISTALLINE ALPHA DU SEL DE TERT-BUTYLAMINE DU PERINDOPRIL**
KRISTALLFORM ALPHA DES PERINDOPRIL-TERT-BUTYLAMINSALZES
$g(A) CRYSTALLINE FORM OF PERINDOPRIL TERT-BUTYLAMINE SALT

(84) Etats contractants désignés:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Etats d'extension désignés:
AL LT LV MK RO SI

(30) Priorité: **06.07.2000 FR 0008793**

(43) Date de publication de la demande:
02.04.2003 Bulletin 2003/14

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Thank you for your attention!

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