Patenting of polymorphs

Runjhun Tandon¹, Nitin Tandon^{*,1} & Rajesh Kumar Thapar²

¹Department of Chemistry, Lovely Professional University, Jalandhar - Delhi G.T. Road, Phagwara, Punjab 144411, India

²Brawn Labs Ltd, Plot no 30, Sector 33, Near Hero Honda Factory, Gurgaon 121001, Haryana, India

* Author for correspondence: tandonnitin12004@gmail.com

“polymorphism plays an important role in the areas of chemical research where full characterization of materials has an important role in determining their ultimate use, which can be in pharmaceutical, pigment, agrochemical, explosive or fine chemical industry.”

First draft submitted: 23 November 2017; Accepted for publication: 2 February 2018; Published online: 19 March 2018

Keywords: amorphous • crystalline • efficacy • evergreening of patents • Indian Patent Act • lumacaftor • polymorph patents • polymorphs • section 3d • strategy of patents

Polymorphism comes from the Greek word 'polus' meaning many and morph meaning different shapes. It can also be taken as an ability of any molecule to rearrange itself into different shapes [1]. If the difference is because of packing of the molecules, it is termed as "*packing polymorphism*" and if it is due to difference in conformation, then it is called "*conformational polymorphism*" [2]. This different arrangement of atoms in a molecule can have profound effect on its physical properties like solubility, dissolution, among others [3]. Awareness of polymorphism dates back to the year 1812, when Napoleon Bonaparte and his soldiers in the army wore highly decorated and shiny buttons on the uniform. The β -form of tin is white and stable at 18°C while the α -form is gray and stable below this temperature. Shining buttons of tin made in summers changed to dirty gray in winters. This change at that time was considered as God's wrath. However today, the scientific reason for crumbling of buttons can be attributed to polymorphic transition [4]. The change in crystal structures of the same chemical compound is called polymorphic transformation and is exhibited by a number of inorganic, biological and pharmaceutical compounds [5,6]. In fact, polymorphism plays an important role in the areas of chemical research where full characterization of materials has an important role in determining their ultimate use, which can be in pharmaceutical, pigment, agrochemical, explosive or fine chemical industry. Therefore, it is important to discuss the difference between true and pseudopolymorphs and how the patent laws should be redefined in order to produce the intended polymorph with increased bioavailability, safety and efficacy. Section 3d of the Indian Patent Act 1970 clearly draws a thin line between polymorphic patents with technological advancements and the patents filed just to be a part of the number game for the companies. This article has taken polymorph as an example to discuss Section 3d in detail.

The impact of polymorphism

The Q3 guidelines of US FDA highlight the importance of organic volatile impurities in the final compound or drug. Polymorphs can trap crystallizing solvent, effecting the solubility, stability and dissolution pattern of the final drug molecule [7]. Thus, the study of polymorphism in pharmaceutical compounds has become a very tedious and arduous task in drug development. A detailed polymorphic drug study helps to resolve the problems of drug solubility, drug formulation, among others throughout the drug-manufacturing process. Polymorph stability also plays an important role in the expiry of the drug. Aguiar and colleagues illustrated the effect of polymorphism on drug bioavailability and dissolution rate in the case of chloramphenicol palmitate [8,9]. The requirements of regulatory filing for new drug application (NDA) or abbreviated new drug application (ANDA) are stringent, with pharmaceutical companies required to carry out extensive polymorphic studies before a product can be brought to market.

The search for new polymorphs with novel properties is a fascinating but arduous task. New research and insights support the view of Walter McCrone, who said *"every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and energy spent in research on that*

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compound" [10]. Different polymorphs can require different methods of formulation during drug development. For example, where a polymorph has poor solubility, self-emulsifying drug delivery systems or lipid formulations can be used to increase the solubility of the final drug product [11]. On the other hand, if a metastable or amorphous form is used, a suitable excipient can be chosen to improve the drug's chemical stability [12].

Case study: ritonavir

The ability of drug molecule to exist in different polymorphic forms was first observed in ritonavir, an antiretroviral drug used to treat HIV infections and AIDS, marketed under the brand name of Norvir® by Abbott Laboratories. The drug was initially introduced to the market in 1995, as semisolid capsules of polymorph, melting at 122°C. The drug was withdrawn in the summers of 1998, on account of changes observed in the dissolution profile. Upon detailed investigation, it was found that a polymorphic transformation had occurred, probably due to high temperature, resulting in a different polymorph with a higher melting point of 125°C. Further work identified three additional polymorphs with melting points of 80, 97 and 116°C, respectively. The temperature had caused a polymorphic transformation, with the new polymorph, changing the bioavailability of the drug. To overcome this, the drug capsules were replaced by refrigerated gelcaps. More recently, ritonavir has been reformulated into a white oblong solid tablet that no longer requires refrigeration [13].

The case opened the eyes of chemists to the possibility of polymorphism affecting the solubility and bioavailability of a final drug.

Case study: atorvastatin

Patents on polymorphs have more recently started to Channel Orange Book Data, as in the example of atorvastatin, a blockbuster drug marketed by Pfizer Inc., under the brand name of Lipitor®. The first generic patent for this drug molecule was filed in 1986 for the class of HMG-CoA inhibitors, expiring in 2010 [14]. The company also filed a specific patent for atorvastatin calcium in 1991 that expired in 2011 giving an additional year of exclusive rights to market the drug [15]. To further extend market rights, another patent was filed, disclosing the drug's novel polymorphs (form-I, -II, -IV, out of which form-I was the most stable and marketed form) in 1996 which expired recently in 2017 [16]. Through this strategy of polymorphic patenting, the company was able to extend market exclusivity by six additional years.

The strategy set a precedent, with many pharmaceutical companies now choosing to file the polymorph patent as a separate patent. As in the case of rifaximin and sitagliptin, new polymorphic patents are now commonly used to stop the generic companies from entering the market. To bring generic drugs to market, generic companies must now either look for a new and stable polymorph, or wait for the polymorph patent to expire [17,18]. The alternate way of entering the market is invalidation of patents which costs money and time, and not all generic companies can afford to do so.

Indian patent act 1970

In India, patent laws exist to prevent this 'ever greening of patents' in this manner, as Section 3(d) of Indian Patent Act of 1970 highlights:

"the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant. Explanation. – For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy" [19].

The section clearly states that patents on polymorphs, salts and esters with same bioavailability and efficacy will not be considered by the Indian patent office.

The case of lumacaftor is a good example of this [20]. Lumacaftor is given in combination with ivacaftor to treat cystic fibrosis. In the USA, Vertex Pharmaceuticals holds 14 patents with a polymorph patent extending the market lifetime from 2026 to 2030 (Table 1). In India, a patent equivalent for the form-I polymorph has been refused by Indian patent office on the grounds of section 3d, as increased bioavailability was included in the patent specifications, which does not necessarily lead to better efficacy [21]. Other than those listed in Orange Book,

Table 1. Orange book data.

Product no	Patent expiration	Drug substance claim	Ref.
N206038	20 May 2027	Specific product patent	[20]
N206038	8 November 2026	Method of treatment with compound generic structure	[24]
N206038	5 August 2027	Method of treatment for cystic fibrosis with specific compound structure	[25]
N206038	28 December 2026	Polymorph with amorphous form	[26]
N206038	20 September 2030	Form I	[27]
N206038	4 December 2028	Composition using form I	[28]
N206038	20 September 2030	Dosage unit	[29]
N206038	8 November 2026	Method of treatment	[30]
N206038	28 December 2026	Solid dispersion using amorphous form	[31]
N206038	4 December 2028	Method of treatment using form I	[32]
N206038	11 December 2030	Composition with structure	[33]
N206038	4 December 2028	Method of treatment	[34]
N206038	29 September 2029	Dosage unit with polymorph	[35]
N206038	8 November 2026	Composition with structure	[36]

there are only two more patent applications for lumacaftor. The first, filed by Vertex pharmaceuticals, identifies form A, which is the solvate form of its hydrochloric salt. Recently, Dr. Reddy's Laboratories has filed for a World Intellectual Property Organization (WIPO) application for lumacaftor for an amorphous form, which is also not a true polymorph [22,23].

Increased bioavailability does not equal increased efficacy

Efficacy of any drug can be defined as a relation between receptor occupancy and the ability of the molecule to initiate a response at the molecular, cellular, tissue or system level in the body. While a polymorph may lead to increased bioavailability, it does not necessarily mean that it will increase the efficacy, which may depend on the salt formation, the formulation technique, the binder used or many more factors [37]. Polymorphs are not the only factor for increasing the efficacy of the drug.

The arrangement of molecules in space to create different crystal structures depends on a large number of factors. Polymorph screening is an integral part of drug synthesis and should be done with great care. It should not be done purely to increase the life of drug in the market, but so as to actually make the drug more potent.

Future perspective

Whether a patent application on a new polymorph of an active pharmaceutical ingredient should be allowed or not, is a matter for a nation's intellectual property laws. But patent laws may be modified so as to promote the patenting of true polymorphs, or new polymorph with genuine technological advancements over the prior art, rather than to support pseudopolymorphs that serve purely to extend a company's portfolio. In the forthcoming era, the organizations should focus their research on finding a stable polymorph of better quality and efficacy, which is the most important part of the drug development process.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

- Purohit R, Venugopalan P. Polymorphism an overview. *Resonance* 14, 882–893 (2009).
- **An article on polymorphism that clearly states the theory behind monotropes and enantiotropes formed. Also explains how polymorphic transformation takes place.**
- Bernstein J. *Organic Solid State Chemistry*. Elsevier, Amsterdam, The Netherlands, 471–518 (1987).

3. Bernstein J, Davey RJ, Henck JO. Concomitant polymorphs. *Angew. Chem.* 38(23), 3440–3461 (1999).
4. Weintraub B. Tin disease and Ernst Julius Cohen (1869–1944), chemistry in Israel. *Bull. Isr. Sche. Soc.* 9, 31–32 (2002).
5. Brog JP, Chanez CL, Aurelian *et al.* Polymorphism, what is it and how to identify it: a systematic review. *RSC Advances* 3(38), 16905–16931 (2013).
6. Lee EH. A practical guide to pharmaceutical polymorph screening and selection. *Asian J. Pharm. Sci.* 9(4), 163–175 (2014).
7. ICH. www.ich.org/products/guidelines/quality/quality-single/article/impurities-guideline-for-residual-solvents.html
8. Aguiar AJ, Kinkel AW, Samyn JC. Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate. *J. Pharm. Sci.* 56, 847–853 (1967).
9. Aguiar AJ, Zelmer JE. Dissolution behavior of polymorphs of chloramphenicol palmitate and mefenamic acid. *J. Pharm. Sci.* 58, 983–987 (1969).
10. Halebian J, McCrone W. Pharmaceutical applications of polymorphism. *J. Pharm. Sci.* 58, 911–929 (1969).
11. Gupta S, Kesarla R, Omri A. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. *ISRN Pharm.* 2013, 1–16 (2013).
12. Telford R, Seaton CC, Clout A. Stabilisation of metastable polymorphs: the case of paracetamol form III. *Chem. Commun.* 52(81), 12028–12031 (2016).
13. Chemburkar SR, Bauer J, Deming K *et al.* Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. *Org. Proc. Res. Dev.* 4(5), 413–417, (2000).
14. Warner–Lambert Company. US4681893A (1986).
- **The product patent of atorvastatin.**
15. Warner Lambert Company. US 5273995A (1991).
- **Specific product patent of atorvastatin calcium.**
16. Warner–Lambert and Company. US 5969156A (1996).
- **Patent of atorvastatin calcium-claiming form I.**
17. Alfa Wassermann S.P.A. US7902206B2 (2008).
- **The patent for different polymorphs of rifaximin, along with their reaction conditions and powder x-ray diffractogram.**
18. Merck and Co Inc. US 6699871B2 (2004).
- **Patent for polymorph of sitagliptin and conditions in which it is formed. The examples are also given in its product patent.**
19. Kant A. Section 3(d): ‘New’ Indian perspective. *J. Intellect. Prop. Rights* 14, 385–396 (2009).
20. Vertex Pharmaceuticals Incorporated. US7495103B2 (2005).
21. Mondaq. India: analysis of the rejection of lumacaftor (polymorph) patent application in India. www.mondaq.com/india/x/560502/Patent/Analysis+of+the+rejection+of+Lumacaftor+Polymorph+patent+application+in+India
22. Vertex Pharmaceuticals Incorporated. US8507687B2 (2013).
23. Dr. Reddy’s Laboratories Limited. WO2017118915A1 (2017).
24. VertexPharmaceuticals Incorporated. US7973038B2 (2010).
25. VertexPharmaceuticals Incorporated. US8324242B2 (2009).
26. VertexPharmaceuticals Incorporated. US8410274B2 (2009).
27. VertexPharmaceuticals Incorporated. US8507534B2 (2008).
- **Patent Form I of Lumacaftor whose Indian equivalent is not granted sue to section3d of Indian Patent Act.**
28. VertexPharmaceuticals Incorporated. US8653103B2 (2012).
29. VertexPharmaceuticals Incorporated. US8716338B2 (2009).
30. VertexPharmaceuticals Incorporated. US8741933B2 (2013).
31. VertexPharmaceuticals Incorporated. US8754224B2 (2013).
32. VertexPharmaceuticals Incorporated. US8846718B2 (2013).
33. VertexPharmaceuticals Incorporated. US8993600B2 (2008).
34. VertexPharmaceuticals Incorporated. US9150552B2 (2014).
35. VertexPharmaceuticals Incorporated. US9192606B2 (2014).
36. VertexPharmaceuticals Incorporated. US9216969B2 (2013).
37. Aitipamula S, Bannerjee R, Bansal AK *et al.* Polymorphs, salts, and cocrystals: what’s in a name? *Cryst. Growth Des.* 12(5), 2147–2152 (2012).

- It clearly states the differentiation between polymorphs and their salts. And also tells about cocrystals and how cocrystals differ from polymorphs.