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Using Raman spectroscopy to tackle polymorphism, an industry problem

Chemical sciences

This note looks at incidences of polymorphism in drug development including advantages and challenges. Ultimately this case study examines the trial of SmithKline Beecham (SKB) v Apotex, where Renishaw's Raman instruments were used by SKB in an attempt to prove infringement of its Paxil® patent by Apotex, a generic competitor.

Introduction

Differences between polymorphic forms is an area of great interest to the pharmaceutical industry for a number of reasons:

Dissolution, Solubility and Bioavailability

Different solid forms can have markedly different solubilities and dissolution rates – this can have a significant effect on bioavailability. Amorphous forms are generally regarded as offering the greatest increases in solubility, however, amorphous forms are thermodynamically unstable and, as such, crystalline polymorphs with improved solubility can be a preferred option.

Stability

Different solid forms offer different chemical and physical stability. Therefore choosing the solid form with the optimum stability for a particular drug product is often the best way of ensuring a longer product shelf life.

Processing and handling properties

Different polymorphs have different crystal lattice structures which can manifest as different particle morphologies with different flow, milling and compression properties.

- Particles approximating to a rounded/cubic shape tend to have good flow properties and are easier to process.
- Needle-like particles will have poor flow properties and will cause processing issues that will need to be managed.

Patent litigation

High-profile patent cases have, in recent years, thrown a spotlight on chemistry and the law.

- Fast-follower generic companies are keen to exploit drugs which have lost their market exclusivity by developing novel polymorphic forms of drugs which circumvent patent protection.
- Synthesising new or unpatented polymorphic forms of the same drug substance has been used successfully to circumvent patented molecules.

Spontaneous polymorphism

Controlled polymorphism is a powerful tool which allows scientists to create products with the optimal properties for a particular dosage form and indication.

Less beneficial is spontaneous polymorphism – when a different polymorph suddenly appears during a manufacturing run and, despite repeated attempts, it is not possible to return to the original polymorph.

Not all occurrences are necessarily bad, serendipity can yield new polymorphic forms with improved physicochemical properties.

However, even in these best-case scenarios, spontaneous polymorphism can lead to uncomfortable questions from regulatory authorities about lack of process control and knowledge of your design space. The obvious questions arise: "if it happened once, what is to stop it from happening again?" and "how will you seek to control this in future?".

It is therefore important to understand polymorph stability and the propensity for polymorphic conversion at every stage of the development process in order to mitigate these risks.

Ritonavir and the ‘seeding’ phenomenon

Probably the most infamous example of spontaneous polymorphism remains Abbot Laboratories’ anti-retroviral, drug ritonavir (Norvir™), for the treatment of HIV/AIDS.

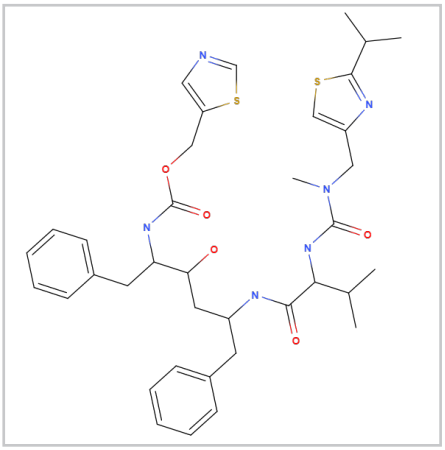

Figure 1- Molecular structure of ritonavir

Norvir was launched in 1996 and was marketed as a semi-solid gel capsule. The capsules were made using the only polymorphic form that had ever been synthesised – Polymorph A – and no other polymorphs were known to exist.

However, in 1998, scientists noticed a new polymorph – Polymorph B – had suddenly precipitated out of the gel capsules. Polymorph B was markedly less soluble than the original Polymorph A and, consequently, the dissolution tests failed and new batches could not be released. This eventually led to the whole product line being withdrawn.

Repeated attempts to re-manufacture Norvir failed to reproduce Polymorph A; from then on only Polymorph B could be produced. The theory of a phenomenon known as “seeding” rose to prominence; the idea that a polymorph, once synthesised, will form nanoscopic particles which will disperse throughout a facility on clothes and equipment and then seed all subsequent batches with which they come into contact. The seeding polymorph will always crystallise out eventually if it has preferable thermodynamics. The ubiquity and size of the tiny seed particles means they are virtually impossible to eliminate completely and makes this eventuality almost certain. In theory it only takes one seed to enter a batch and cause the seeded polymorph to precipitate out.

Eventually, after extensive research and experimentation, Abbott were able to develop a robust method that could consistently synthesise Polymorph A - even in facilities which had been seeded with Polymorph B - and Norvir was re-launched a year later. Abbott is estimated to have lost around $250m in sales revenues on top of the significant expense incurred in the time and resource it had to devote to finding out how to re-synthesise Polymorph A.

Patent case: SmithKline Beecham (SKB) v Apotex

Paroxetine hydrochloride is a selective serotonin reuptake inhibitor (SSRI) used to treat depression.

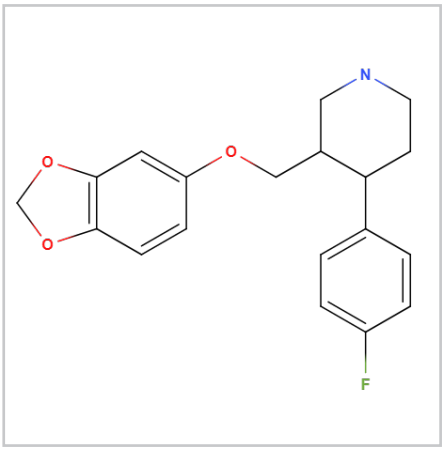

Figure 2 – Molecular structure of paroxetine

It was first synthesised by Ferrosan in the 1970s and was acquired by SmithKline Beecham (SKB) a decade later.

During the development of the hydrochloride salt SKB developed a method for synthesising an anhydrate form of paroxetine hydrochloride. However, in 1984 during the first pilot scale up, in another instance of spontaneous polymorphism, a hemihydrate emerged.

This instance of spontaneous polymorphism happened to be serendipitous – the hemihydrate was non-hygroscopic and had preferable handling properties. A patent application for the hemihydrate was submitted in 1986 and the hemihydrate form was launched in 1993 under the brand name Paxil®.

In 1998, once the market exclusivity awarded by the FDA of paroxetine had expired, Apotex, a Canadian generic drug company, filed an Abbreviated New Drug Application (ANDA) with the US FDA for the unpatented anhydrate form.

SKB opposed Apotex’s ANDA on the grounds that it would infringe its patent on the hemihydrate. SKB’s argument was based on its own findings that the anhydrate form would convert to the hemihydrate upon contact with water or humidity on storage.

SKB also argued that Apotex would have seeded their facility with the hemihydrate during their development work and this further increased the likelihood of the anhydrate form converting; in SKB’s own experience the anhydrate form would always convert when exposed to a facility seeded with hemihydrate.

Furthermore, Apotex’s anydrate batches were shown to convert almost entirely to the hemihydrate after 1 month of storage at 75% relative humidity.

Apotex countered that they were not infringing SKB’s patent as they were not manufacturing the hemihydrate from first principle and because they had improved their process and packaging to further minimise water ingress and therefore the risk of anhydrate conversion. Apotex also argued that the seeding phenomenon lacked any formal proof and was mere supposition.

Investigation using Renishaw's Raman systems

Renishaw's Raman microscopes were favoured by SKB for identification of the hemihydrate polymorph in Apotex's anhydrate product during the litigation proceedings.

Typically these types of tablets are effectively homogeneous on the length scale of larger than tens of microns, but exhibit local inhomogeneity on length scales of microns. At the time of the work, the 'gold standard' analysis technique was generally considered to be XRD, but this was not able to routinely sample on such a small length scale.

Similarly, IR could not sample on the micron lengths scale - indeed IR spectra were measured but these were often only distinguishable from reference spectra of the anhydrate form using numerical methods.

Raman microscopy, whereby many Raman spectra can be recorded from thousands of different spots within a sample, can overcome this issue. Each spectrum is recorded from a sample size of the order of low single digit microns, and hence can probe the local inhomogeneity. Indeed, with effectively random sampling, many of the spectra show nearly pure contributions from each of the various tablet components in turn.

Raman microscopy was the stand-out technique for both sensitivity and specificity for identifying the various components within tablet samples.

Other techniques were also investigated but none were found to have the sensitivity and specificity of Raman spectroscopy for identifying the different polymorphs. The hemihydrate and the anhydrate were easily differentiated by the Raman spectra generated by the Renishaw instrument.

Below are example spectra of paroxetine hydrochloride anhydrate and paroxetine hydrochloride hemihydrate both as references and as spectra collected from Apotex tablets. They confirm the presence of both the anhydrate and hemihydrate forms of paroxetine hydrochloride in the Apotex tablets.

The spectra also exhibit clear differences between the two forms – the anhydrate form produces discrete, sharp peaks whereas the hemihydrate produces doublet peaks at similar Raman shifts that are clearly - but not totally - resolved. These doublet peaks can be attributed to there being two paroxetine molecules plus a single water molecule in the unit cell of the hemihydrate but just a single paroxetine molecule in the unit cell of the anhydrate.

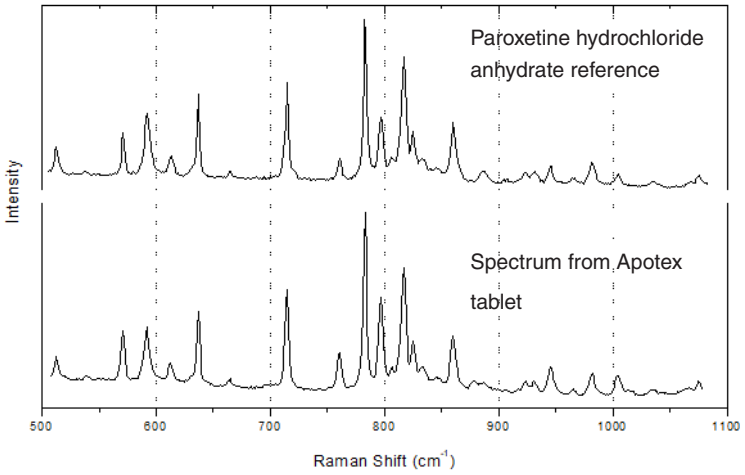

Figure 3 - Raman spectrum of anhyrdate reference vertically offset with Raman spectrum collected from a point on an Apotex tablet [1]

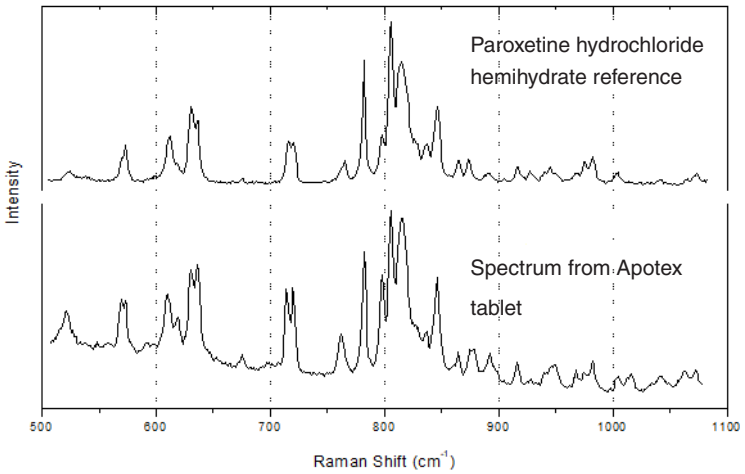

Figure 4 - Raman spectrum of hemihydrate reference vertically offset with Raman spectrum collected from a point on an Apotex tablet [1]

Renishaw plc

Spectroscopy Products Division
New Mills, Wotton-under-Edge,
Gloucestershire GL12 8JR
United Kingdom

T +44 (0) 1453 524524
F +44 (0) 1453 524901
E raman@renishaw.com

www.renishaw.com

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The lawyers insisted that each individual spectrum was analysed by an expert, rather than use software to analyse the acquired data. This led to an enormous task for the independent experts who had to individually examine 145,000 spectra collected from 150 samples of Apotex product.

53,000 of these spectra contained clear evidence of paroxetine hydrochloride and around 10% of these spectra showed clear evidence of the hemihydrate form.

The hemihydrate form was detected in 80% of the tablets analysed and at least one tablet from every pack of Apotex product tested positive for the hemihydrate form.

The verdict

Judge Posner, presiding, ultimately ruled in favour of Apotex, agreeing that Apotex was not infringing SKB's patent because it was not manufacturing the hemihydrate either intentionally or in commercially significant quantities.

This decision was later reversed on appeal in the US Federal Circuit Court; Apotex's product had infringed SKB's patent, however, the court of appeal also ultimately ruled in Apotex's favour in finding that SKB's patent was invalid for inherency.

SKB's patent covered "crystalline paroxetine hydrochloride hemihydrate". The court of appeal agreed with SKB that this meant and included all crystalline paroxetine hydrochloride hemihydrate, not just commercially significant quantities, meaning that by containing even a single crystal of hemihydrate, Apotex would be infringing SKB's patent.

However, for the same reason, the court of appeal found SKB's patent invalid. Because anhydrate crystals will inevitably convert either wholly or partially to the hemihydrate form due to favourable thermodynamics - accelerated by the presence of water and hemihydrate seeds - and with no human intervention, the court deemed this to be a natural process and therefore cannot be patented.

Patentable material excludes laws of nature, natural phenomena, and abstract ideas, which are deemed 'manifestations of laws of nature, free to all men and reserved exclusively to none.' Funk Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948).

Had SKB's patent been limited to "synthetic crystalline paroxetine hydrochloride hemihydrate", excluding naturally occurring hemihydrate, the patent would have remained valid, although, paradoxically, this would also have meant that Apotex would not have infringed.

Conclusion

Although the courts ruled in favour of Apotex, the court proceedings and appeals process delayed the launch of a generic competitor, effectively extending SKB's market exclusivity on Paxil for 5 years. The final decision came in 2006 when the US Supreme Court refused to hear SKB's second appeal.

Paxil was worth approximately $2.2bn per year to SKB. Despite an expensive and unsuccessful legal battle, the potential loss of Paxil sales revenues to a generic competitor - which would have forced down drug prices - far outweighed all the legal costs.

The use of Renishaw's Raman imaging system in this case is an excellent example of the power, specificity and sensitivity of the technique for identifying subtle chemical changes within complex mixtures containing multiple different ingredients, such as formulations and drug products.

It is almost certain that without Raman imaging - had scientists been forced to rely on other techniques such as XRD or IR-microscopy - SKB's case would have been much weaker. The Raman spectra generated by Renishaw's imaging systems were sufficiently clear to cast significant doubt as to whether or not Apotex had infringed SKB's patent and helped in delaying the release of the generic competitor, allowing SKB to extend the profitability of its Paxil product.

Acknowledgements

[1] Sourced from the retirement presentation of the late Emeritus Professor Dr David Batchelder of the University of Leeds, UK

Other information for this application note was sourced from:

Disappearing polymorphs revisited. Angew Chem Int Ed Engl. 2015 Jun 8;54(24) pp 6972-93. Bučar DK, Lancaster RW, Bernstein J.

Kind thanks also go to Dr Kurt Baldwin for his additional help and information.

Renishaw. The Raman innovators

Renishaw manufactures a wide range of high performance optical spectroscopy products, including confocal Raman microscopes with high speed chemical imaging technology, dedicated Raman analysers, interfaces for scanning electron and atomic force microscopes, solid state lasers for spectroscopy and state-of-the-art cooled CCD detectors.

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