timegate

ahead of time

Why solid state forms are so important in pharmaceutical industry?
Polymorphic identification
of pharmaceutical solids made easy

Many pharmaceutical solids can exist in different physical forms. Polymorphs are crystalline materials that have the same chemical composition but different molecular packing. Polymorphs are one type of solid form. Other solid form types include solvates, hydrates, and amorphous forms. Solvates are crystalline materials made of the same chemical substance, but with molecules of solvent regularly incorporated into a unique molecular packing. When water is the solvent, these are called hydrates. An amorphous form of a substance has the same chemical composition, but lacks the long-range molecular order of a crystalline form of the same substance. Many organic and inorganic compounds, including APIs, can exist in multiple solid forms.[1]
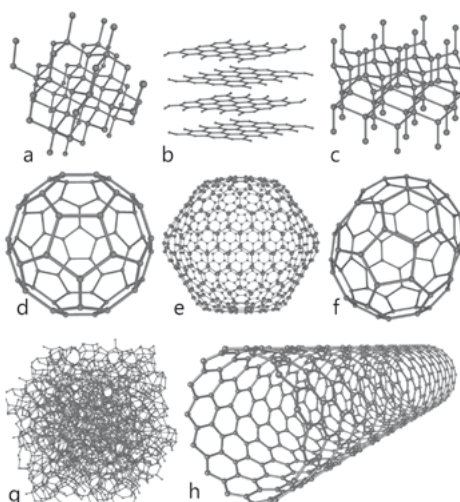

Figure 1:
The concept of polymorphism is well demonstrated by the different crystalline forms of carbon. Diamond, graphite, and fullerenes are all made of pure carbon, but their physical and chemical properties vary drastically.

AUTHORS:

Timegate Instruments Oy, Finland:
Lauri Kurki
Mari Tenhunen

University of Helsinki, Finland:
Tatu Rojalin
Clare Strachan
Tiina Lipiäinen

Different solid state forms of pharmaceuticals can have different chemical and physical properties such as color, solubility, crystal shape, water sorption and desorption properties, particle size, hardness, drying characteristics, flow and filterability, compressibility, and density. They can also have different melting points, spectral properties, and thermodynamic stability. In a drug substance, these variations in properties can lead to differences in critical quality attributes such as solubility, dissolution rate, stability, oral absorption and bioavailability more generally, gastric irritation, adverse effects, and clinical trial results. Ultimately both the safety and efficacy of drugs are impacted by properties that vary between different solid forms.

For these reasons, it is essential that this issue is carefully explored and understood during preformulation and, once the optimal solid state form has been selected, it should be controlled during API crystallisation. The potential for solid form variation does not end at API production. Solid form issues remain through formulation and manufacturing of pharmaceutical products as well as in the storage, and the use of drug products. This is why it is essential to have fast and easy-to-use methods to identify and monitor the changes in the polymorphic composition of pharmaceutical substances.
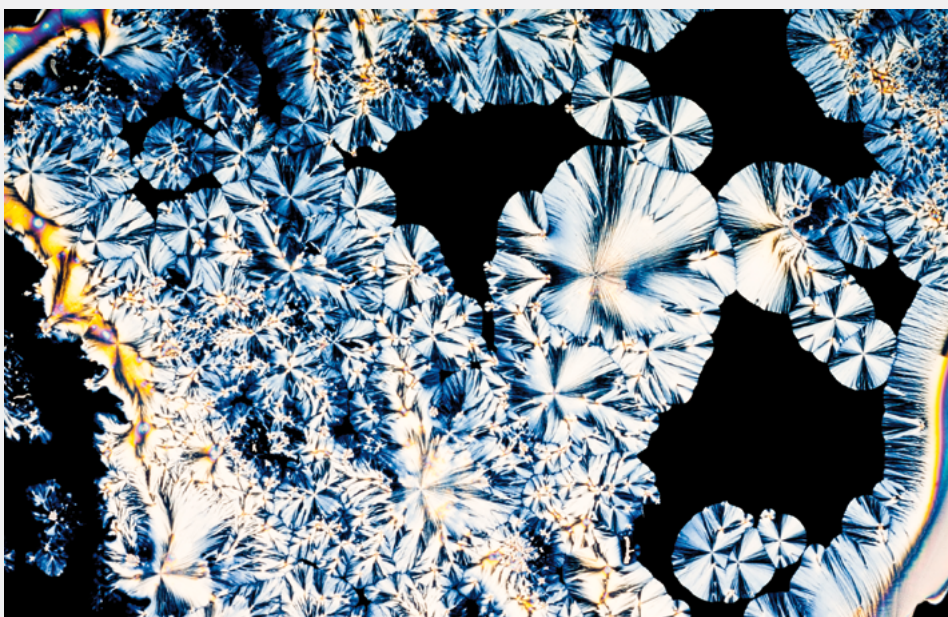

Figure 2:
Different solid forms of a single pharmaceutical substance.

## State of Art Methods to Characterize Polymorphic Composition

Among the most useful techniques for solid-state characterization are DSC, TGA, hot stage and optical microscopy, solid-state NMR, IR and Raman spectroscopy, and X-ray powder diffraction. There are numerous early publications demonstrating the methodology for using vibrational spectra to characterize polymorphs. Raman spectroscopy can be used to analyze chemical identity and confirm the solid form form as well as quantitatively predict the relative amounts of the various forms in a single formulation. However, one of the major hurdles to its use is fluorescence, which can partially or completely mask the weak Raman signal. Therefore, we demonstrate here the feasibility of Timegated® Raman spectroscopy to solve this fluorescence issue and to detect the variations in the polymorphic composition of various pharmaceutical substances.

Polymorphic Characterization Examples Using Raman Spectroscopy

In this application note, we briefly review some polymorphic studies of pharmaceutical substances performed at the University of Helsinki. In these studies, Raman spectra were recorded using both CW (Continuous Wave) and Timegated® setups. The conventional Raman spectrometer consisted of a CW laser excitation at 785 nm and Timegated® Raman spectrometer used pulsed, microchip laser at 532 nm. Furthermore, the reference analyses were done with the DSC and ATR IR analysis, see details in ref [2-5].

The polymorphic structure studies of two well-known and widely studied pharmaceutical substances – indomethacin and piroxicam – are presented here.

Indomethacin
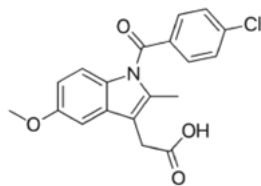
Indomethacin is a nonsteroidal anti-inflammatory drug commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation, and It is marketed under more than twelve different trade names. The old well-know polymorphic forms include α β γ and δ, however, *quite recently the new ε, ζ and η forms have been discovered [6].*

The time-resolved setup used in these studies has been a 532-nm pulsed laser, combined with the CMOS SPAD detector having relatively fast electronic gating possibility to temporally resolve the Raman spectrum from the fluorescence background. An example can be seen in Figure 3 with the amorphous form of indomethacin, which is yellow in color. With the non-time-resolved CW 785-nm setup, it was not possible to detect any Raman bands due to the fluorescence, whereas Timegated® Raman system was able to detect clear Raman bands.
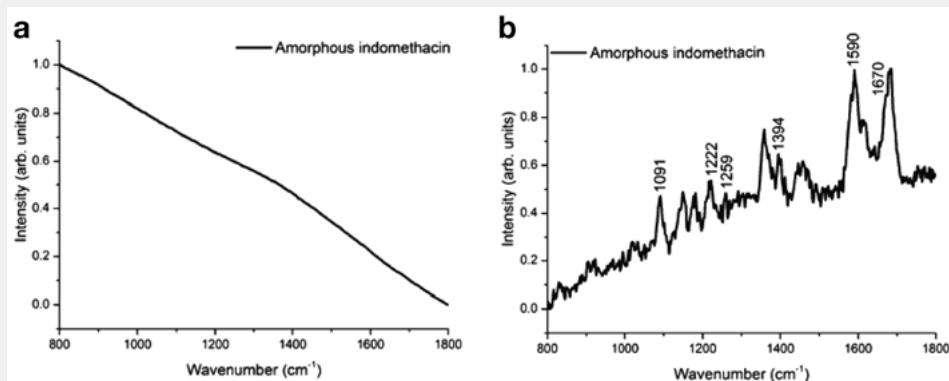

Figure 3:
Amorphous Indomethacin measured measured with (a) CW and (b)Timegated® Raman instruments [4].

The current Timegated® Raman instruments have two main capabilities: first, rejection of sufficiently long-lived fluorescence or other background radiation from a Raman signal, and on the other hand, measuring the spectrally resolved fluorescence decay shape, as shown in Figure 4. The capabilities of the system to analyse general fluorescence decay shapes in more detail (e.g., finding parameters of multi-exponential decays) will be expanded in the future.
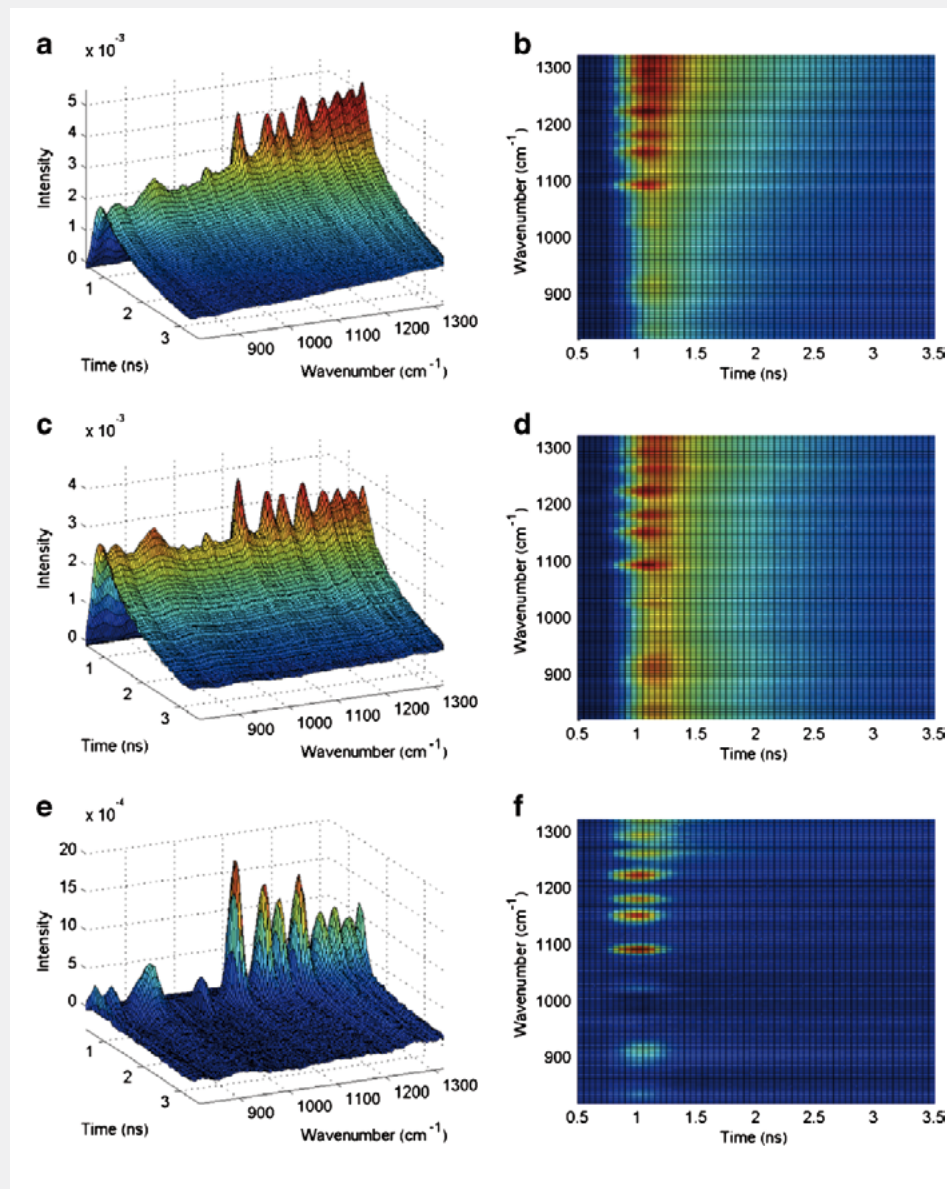

Figure 4:
Timegated® raw data from amorphous indomethacin (A, B); baseline-corrected data (C, D); and fluorescence subtracted data (E, F). Panels on the left illustrate the intensity vs. time measurements for each wavenumber shown as a 3D stack. Panels on the right are also the top views [4]

Piroxicam

Piroxicam is is a non-steroidal anti-inflammatory drug used to relieve the symptoms of painful, inflammatory conditions like arthritis. It was originally brought to market by Pfizer under the tradename Feldene in 1980, became generic in 1992 and nowadays it is marketed worldwide under many brandnames. Piroxicam can exist in at least four polymorphic crystalline anhydrate forms as well as a monohydrate and the amorphous form.

Figure 5 shows the Timegated® Raman spectra of piroxicam I, II and monohydrate forms. As can be seen form these spectra, different structural forms can be differentiated clearly based on their Timegated® Spectra.
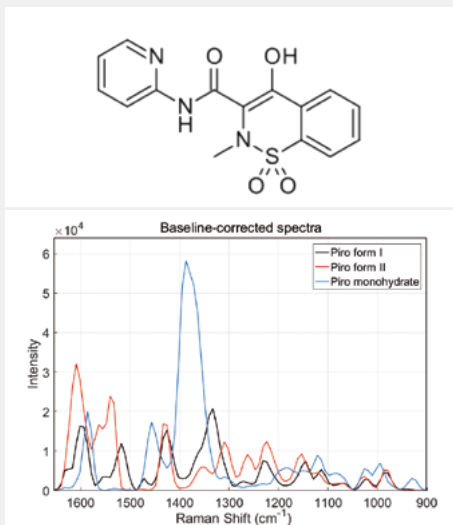

Figure 5:
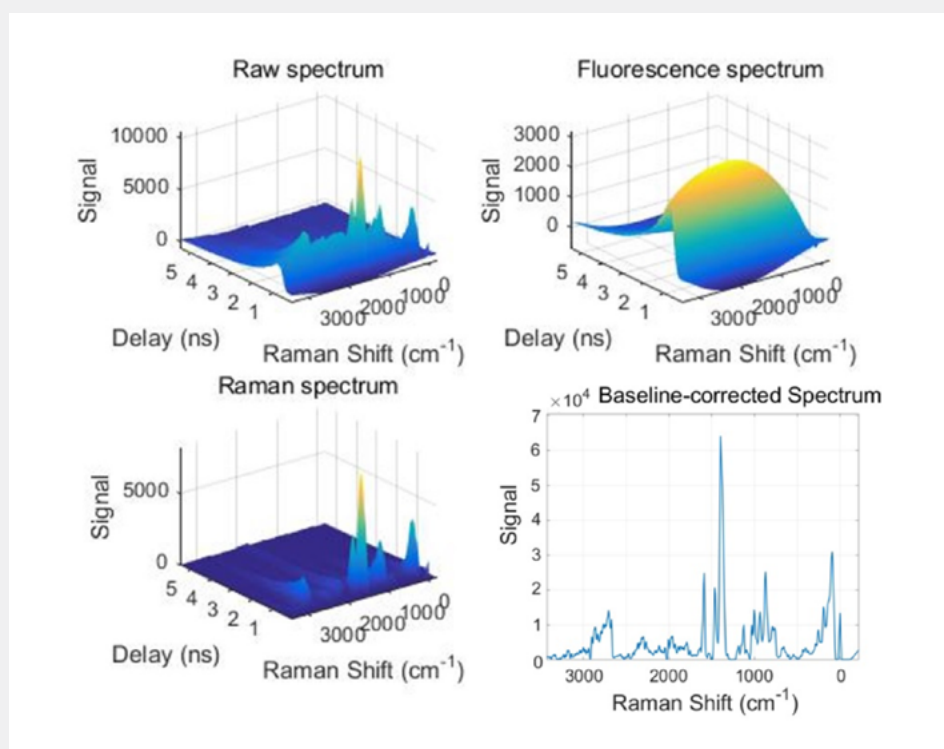Comparison of Timegated® Raman spectra of Piroxicam I, II and monohydrate forms.

Figure 6:
Timegated® data including 3D raw data, 3D time resolved fluorescence and Raman spectra and baseline corrected Raman spectrum of Piroxicam monohydrate.

Summary

Polymorphism and solid state variation more generally present opportunities as well as great challenges in the pharmaceutical industry. Investigation of the properties of different forms of a commercial drug can lead to new products with improved onset time, greater bioavailability, sustained release properties, or other therapeutic enhancements. However, this investigation needs efficient tools.

Timegated® Raman can provide several advantages for the studies of polymorphic forms of pharmaceutical substances and drugs, it

01

Gives information about polymorphic structures and chemical composition of pharmaceutical substances

02

Provides ease of use with efficient rejection fluorescence interference

03

Does not require any sample pretreatment

04

Can be easily adapted to various different measurement and monitoring needs, e.g. to drug development, API synthesis, formulation and manufacturing, dissolution and bioavailability studies and to validate the drug stability in storage

References

1. HIlfiker, R. (ed.), (2006), Polymorphism: In the Pharmaceutical Industry, Wiley VCH, Germany.

2. Rojalin, T., Konventionaalinen Raman-spektroskopia ja aika-erotteinen Raman-spektroskopia ei-fluoresoivien ja fluoresoivien lääkeaineiden tutkimuksessa, MSc. Thesis, 2014, Univ. Helsinki.

3. Rojalin, T. et al. Fluorescence Suppressed Time Resolved Raman Spectra of Drugs, Oral presentation in IFPAC 2015.

4. Rojalin et al., Fluorescence-suppressed time-resolved Raman spectroscopy of pharmaceuticals using complementary metal-oxide semiconductor (CMOS) single-photon avalanche diode SPAD) detector, Anal. Bioanal. Chem., 2015, Vol. 408, No. 3, p. 761-774.

5. Lipiäinen, T., Time-resolved Raman spectroscopy for fluorescence-suppressed qualitative and quantitative analysis of pharmaceutical solids, Poster presentation in AAPS2016, November, Denver, U.S.

6. Strachan et al., Indomethacin: New Polymorphs of an Old Drug, Mol. Pharmaceutics, 2013, 10 (12), pp 4472–4480.

timegate

ahead of time