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Probing the Solid-State Chemistry of Molecular Crystals

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The ability to identify polymorphic and other solid-state forms of molecular crystals is of great value to the pharmaceutical industry in discovery research and development of drug products. Historically, the need to evaluate solid-state chemistry was of practical concern. Did the solid-state form of the drug developed meet the metabolic requirements for its indication; and did it provide adequate stability to meet manufacturing, shipping and shelf-life requirements? In 1984, however, the law governing the pharmaceutical industry changed with the enactment of The Drug Price Competition and Patent Term Restoration Act of 1984 and made the solid-state form of a drug product's active pharmaceutical ingredient (API) legally significant. Since then, drug developers have scrambled to understand the solid-state properties of their patentable compounds at the earliest stages of the drug-development process.

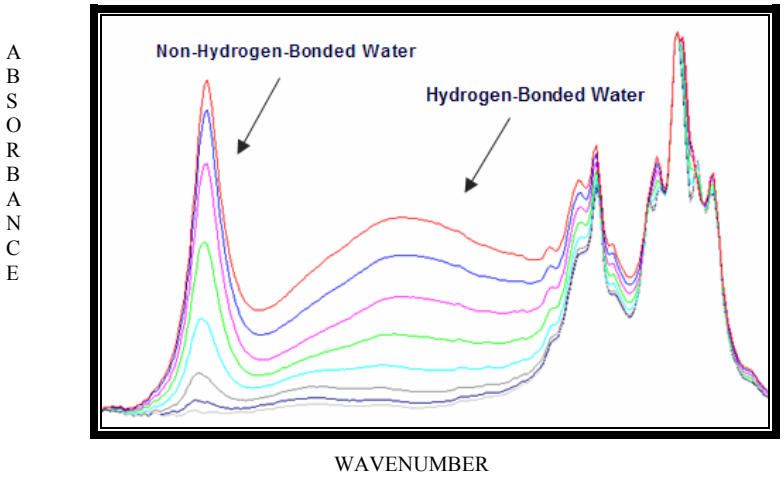
Recent civil litigation within the pharmaceutical industry surrounding this type of patent are forcing these companies to address the way solid-state forms are identified at the time patents are granted. Methods for identification must be able to meet the stringent requirements for admissibility of scientific evidence to Court. Precedent has been set for the use of infrared spectroscopy for the identification of polymorphic form when defending solid-state-form patents in Court.(1) Developments in infrared microprobe technology have married infrared spectroscopy with the use of the light microscope and its accessories (variable-temperature and variable-humidity stages) making the ability to perform this type of analysis a critical necessity for any drug-development laboratory.

Aside from the legal precedent which was set for admissibility in Court, there are other reasons to use infrared microprobe technology for the evaluation of solid-state chemistry. Traditional infrared methods, as well as other analytical techniques, require samples be "prepared" for analysis, potentially altering the exact property intended to be measured. Use of carbon (diamond) attenuated total reflection microscope objectives eliminates this preparation process. Samples are directly analyzed without any preparatory treatment. The sample is observed, the area for analysis is visualized and photographically documented, and infrared spectral data is collected from that precise location. What you see is what you measure.

The question then becomes why use infrared spectroscopy? Infrared analysis measures vibrational and rotational energy changes occurring in a sample when exposed to infrared radiation. These changes arise as a result of the molecular composition and arrangement of the sample. These changes are directly related to the functional group's present within the molecule. They are also directly related to the arrangement of these functional groups within the molecule, and within the molecular complex. This makes it possible to evaluate the infrared spectra of different solid-state forms to determine which functional groups are affected by differences in solid-state form. This very powerful proposition provides insight about molecular crystals unattainable using other techniques.

Infrared microprobe technology also enables analysis of solid-state chemistry earlier in the drug development process. Microscopic samples are easily evaluated. Alone, this ability enables the evaluation of samples that would otherwise be too small for analytical testing. When linked with microscope-scale environmental chambers enabling variable humidity and temperature conditions (under ambient pressure), the potential applications are limitless. These systems make it a trivial matter to detect the changes of molecular bonding as water is added to an anhydrate form by increasing the relative humidity; or how crystallization from an amorphous to crystalline form occurs as a sample is heated.

Figure 1. Ratio of Hydrogen-Bonded to Non-Hydrogen-Bonded Water Changes as Water is Removed from the Hydrated Form



The power of the infrared microprobe is its ability to resolve molecular chemistry, not in its spatial resolution. Chemistry can be summarized as the study of bonds breaking and bonds forming; the infrared microprobe let you record molecular chemistry. Because no vacuum is needed, it operates like a conventional light microscope and extensive data bases assist spectral analysis, infrared microprobes are simplifying analytical science.

1 Glaxo, Inc., v. Novopharm Ltd., 931 F. Supp. 1280 (E.D.N.C. 1996)

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