NMR researchers unlock hydrogen's secrets to spot polymorphism in pharmaceuticals

October 16 2007

Researchers at the University of Warwick and Astra Zeneca have found a new way to use solid-state NMR equipment to crack the secrets of hydrogen atoms and thus spot unwanted polymorphs in pharmaceuticals.

Pharmaceuticals companies are constantly battling the problem of polymorphism in which an active drug can actually exist in more than one form or crystal structure which can cause the drug to act in very different ways. Now researchers at the University of Warwick and Astra Zeneca have devised a new method of using solid-state NMR (nuclear magnetic resonance) equipment to spot unwanted polymorphs that should be adopted as a routine tool by pharmaceutical companies.

NMR equipment is already used to detect polymorphism in pharmaceuticals. However the standard technique looks at the carbon 13C nuclei in the drugs by a method called cross-polarisation magic-angle spinning (CP MAS). This is a very insensitive technique as only 1 in 100 carbon nuclei are the 13C isotope. This means that 99 out of 100 carbon nuclei are a NMR-invisible form of carbon. Only one-dimensional spectra are routinely possible from such an experiment.

Researchers have long wished to be able to couple this carbon based solid–state NMR technique with one that looks at hydrogen nuclei. It has been possible to look at hydrogen when the sample is a solution (solution-state NMR) but this is not as easy in solid-state NMR as the extensive network of coupled together 1H nuclei leads to broad lines in the spectrum that are hard to tell apart. This makes it almost useless when

you are examining a tablet. Tablets are also particularly difficult to examine as the active drug within the tablet is combined with a mixture of other filler compounds (excipients).
This breakthrough by the Warwick team opens up hydrogen nuclei to useful study by solid-state NMR which will bring immense benefits to the study of polymorphism in drugs and organic molecules in general. This is because hydrogen atoms are central to hydrogen bonding (as opposed to carbon atoms which "observe" from afar). Hydrogen bonding is often the driving force in determining how organic molecules do differ in their methods of "3D packing" forming polymorphs or pseudo-polymorphs (pseudo-polymorphism referring to crystal structures that differ through the inclusion or non inclusion of small molecules, eg with or without water). This new NMR technique can identify which pseudo polymorph of an active pharmaceutical is present in a complete tablet.

The research team led by Dr Steven Brown from the University of Warwick's Department of Physics have exploited recent developments in NMR hardware and pulse sequence design allowing them to gain high-resolution 1H solid-state NMR spectra by a method called CRAMPS (combined rotation and multiple-pulse spectroscopy). By using this high-resolution two-dimensional 1H CRAMPS solid-state NMR they obtained a spectrum for a tablet formulation in less than 2 hours, which is equivalent to the time required for a good 13C CP MAS one dimensional spectrum.

Dr Steven Brown said: "This Hydrogen 1H solid-state NMR method gives powerful new insight that complements established Carbon 13C based techniques - this new approach should be adopted as a routine tool in pharmaceutical characterisation"

The research paper entitled "Distinguishing Anhydrous and Hydrous Forms of an Active Pharmaceutical Ingredient in a Tablet Formulation Using Solid-State NMR Spectroscopy" by John M. Griffin, Dave R.

Martin, and Steven P. Brown has just been published in *Angewandte Chemie* Volume 119, Issue 42 , Pages 8182-8184

Source: University of Warwick