



Crystal Pharmatech

Suite 427, Bldg A2, Biobay
218 Xinghu Street, Suzhou Industrial Park
Suzhou, China, 215123
Phone: 86-512-69561921
Toll-Free: 1-855-546-4986
Fax: 86-512-69561922
Email: contact@crystalpharmatech.com
www.crystalpharmatech.com

Characterization of Amorphous Solid Dispersions: One of Many Integrated Solid State Solutions Provided by Crystal Pharmatech

*By Dr. Alex M. Chen, CEO, Crystal Pharmatech
Dr. Yanfeng Zhang, CSO, Crystal Pharmatech
Dr. Hailu Zhang, Associate Professor, Suzhou Institute of Nano-tech and Nano-bionics, Chinese Academy of Sciences
Dr. Zongwu Deng, Professor, Suzhou Institute of Nano-tech and Nano-bionics, Chinese Academy of Sciences*



Contents

Company Introduction	2
An Interesting Solid State Problem	2
Crystal Pharmatech Solution	3
Implementation	4
Why Choose Crystal Pharmatech?	4
References	6

Company Introduction

Pharmaceutical outsourcing is a multi-billion dollar business with China being a leading outsourcing partner. Even though API and formulation processes are being readily outsourced to China, there are no companies focusing on solid state characterization. Crystal Pharmatech is the first China based company to offer integrated solid state solutions to both API and formulation development projects. Our labs are fully cGMP compliant and our researchers have years of experience with solid state issues at major innovator companies. Our experience ranges from pre-clinical development all the way to supply. Our services support all aspects of organic process development, formulation development, regulatory support, and intellectual property protection. Specifically, our expertise encompasses:

- Polymorph/salt/co-crystal screening
- Single crystal growth
- Crystallization optimization
- Phase mapping
- Phase detection and quantitation
- Solid-dispersion and other pre-form screens
- Excipient compatibility testing
- Clinical release testing
- Regulatory dossier support

Our state of the art characterization tools include ssNMR, transmission XRPD, and modulated DSC in addition to the standard equipment. With these tools and our experience, Crystal Pharmatech offers innovative solutions to solid state issues. One powerful example of this relates to amorphous solid dispersions.

An Interesting Solid State Problem

A common way of increasing solubility, dissolution rate, and/or absorption for poorly



soluble API is by forming an amorphous solid dispersion into a hydrophilic matrix. The API is usually dispersed on a molecular level as amorphous particles. There are a variety of methods for forming solid dispersions including fusion, hot melt extrusion (HME) and spray drying (SD) onto sugar beads. A significant challenge in solid dispersions is keeping the API amorphous during preparation and storage.

Since all components in solid dispersions are amorphous, typical characterization techniques (XRPD, IR, RAMAN, etc.) are of limited utility in fully understanding the molecular level interactions in these samples.

Crystal Pharmatech Solution

ssNMR offers a great advantage in characterizing amorphous mixtures since it probes atomic level connectivity thru distance interactions [1-4]. Crystal Pharmatech utilizes novel ssNMR methods [5-11] to both detect small amounts of API crystallization and gain a true molecular level understanding of solid dispersions. This understanding of how the components are mixed on a molecular level is correlated to crystallization propensity of the API. Specific techniques that are utilized include 1D cross-polarization magic-angle spinning (CPMAS), relaxation methods, and either hetero- or homo-nuclear correlation. Hetero- and homo-nuclear correlation methods (HETCOR and HOMOCOR respectively) offer a great opportunity to study spatial proximities of nuclear environments based on the dipole-

dipole interaction. The combined use of CRAMPS (Combined Rotation And Multiple Pulse Spectroscopy) methods (i.e. w PMLG, FSLG, and DUMBO) with MAS in HETCOR or an additional CRAMPS in HOMOCOR can yield high-resolution two dimensional spectra. HOMOCOR experiments yield correlated high resolution proton spectra in both spectral dimensions, while HETCOR yields correlated high resolution spectra for proton in one dimension and a second nuclei in the other dimension. This second nuclei is typically spin-1/2 nuclei such as ^{19}F , ^{13}C or ^{15}N . These HETCOR and HOMOCOR experiments allow us to probe distances in the solid state that can yield a plethora of structural information for solid dispersions. Crystal Pharmatech combines data from ssNMR with DSC and other characterization tools, when applicable, to provide the most comprehensive understanding of amorphous dispersions available.

Benefit 1

CPMAS can detect very low levels of API crystallization since spectral regions of the API are resolved from matrix components and relaxation methodologies can be incorporated to provide spectra editing. An example of this technique's power is displayed in Figure 1.

Benefit 2

HETCOR and HOMOCOR techniques have extensive application in the polymer and mesoporous silica industry, [9] and have been applied recently to pharmaceutical materials.[12-13] Crystal Pharmatech uses this technology to gain a molecular level understanding and identify phase separation – a major contributor to crystallization. An example of the two-dimensional data obtained from this technique is displayed in Figure 2. This powerful two-dimensional method can yield atomic level correlations



between specific components of API or API mixtures.

Benefit 3

ssNMR data is combined with a deep understanding from DSC/modulated DSC (mDSC) data. The DSC/mDSC efforts include glass transition (T_g) analysis, enthalpy relaxation study (Figure 3) that can reveal important information on the relaxation of amorphous phase. Such knowledge is vital to understanding and predicting the physical and chemical stability of amorphous phase

Implementation

Crystal Pharmatech offers an amorphous solid dispersion screen that is designed to evaluate the feasibility and risk of using an amorphous formulation. We implement this screen combined with the characterization tools provided above to help clients make informed decisions in formulation development. We can also focus on specific dispersions that are chosen by the client.

Why Choose Crystal Pharmatech?

Crystal Pharmatech is currently the only high-quality, dedicated solid state characterization company based in China. Our researchers have extensive experience with dispersions used for pharmaceutical development. We incorporate the most advanced characterization tools (including ssNMR and DSC/mDSC) to provide our customers with a complete understanding of their solid dispersion system including:
Detection of API crystallization;
identification of phase separation;

complete understanding of $T_{g(s)}$ associated with the dispersion. This complete characterization work can guide customers in choosing the most appropriate matrices and storage conditions for their dispersions.

Solid Dispersion characterization is only one of the many innovative solid state solutions that Crystal Pharmatech can provide. We will be your ideal partner and tailor our business to your specific needs.

Whether you are a top-tier innovator company or a pre-emerging biotech, Crystal Pharmatech can handle all of your solid-state property needs. We offer a full range of services from being the solid state characterization arm of your company to consultation on a specific issue. For smaller companies, there is no need to purchase and maintain expensive characterization equipment, let alone the expertise to operate and utilize the instruments. Instead, partner with Crystal Pharmatech for all your solid state characterization needs.

Having worked in "Big Pharma" for many years, we know your issues first hand. We know what is critical and how to efficiently solve your problems. We have the appropriate workflows in place to provide optimal solutions using the most advanced technology. And, last but not least, this can all be done at *very* competitive prices.

Crystal Pharmatech is currently accepting partnerships and/or collaborations with all pharmaceutical companies, either directly or through partner sites located in China. We are eagerly waiting to be your preferred solid state vendor.

FIGURES

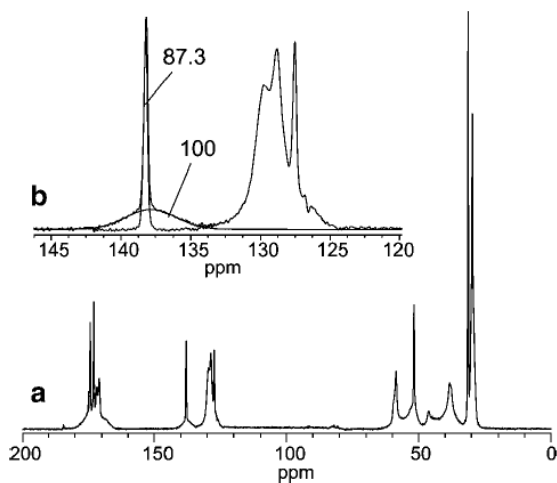


Figure 1. (a) ^{13}C CPMAS NMR spectra of a mixture of 50/50 (w/w) neotame Form G and amorphous neotame, and (b) the resulting carbon peak areas from deconvolution of the two peaks. [5]

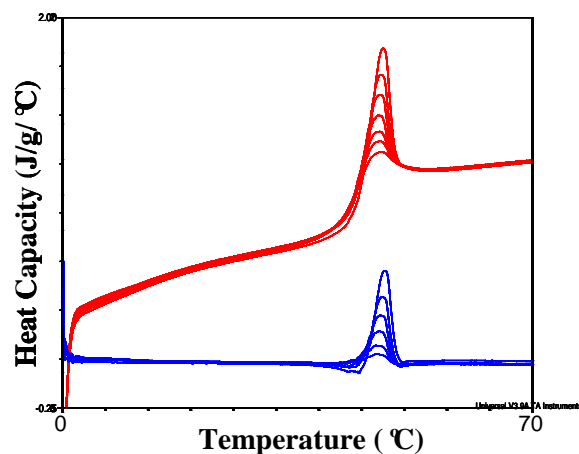


Figure 3. DSC curves of amorphous phase prepared by different quenching rates in a typical enthalpy relaxation study. Red: unsubtracted, blue: subtracted by reference.

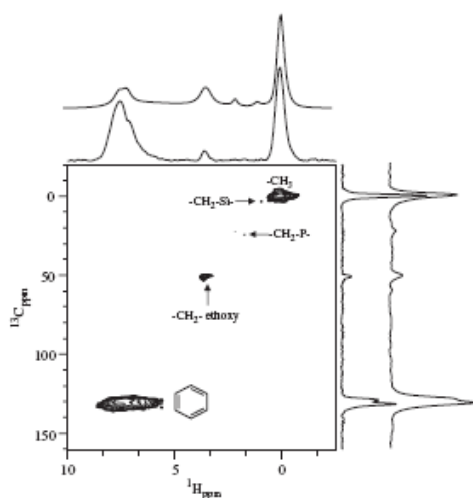


Figure 2. 2D HETCOR spectra displaying the spectral editing capabilities of the technique. Direct correlation for specific ^1H and ^{13}C components are available. [9]



References

- [1] Bugay, D. E. "Characterization of the Solid-State Spectroscopic Techniques" *Adv. Drug Deliv. Rev.* **2001**, *48*, 43.
- [2] Tishmack, P. A.; Bugay, D. E.; Byrn, S. R. "Solid-State Nuclear Magnetic Resonance Spectroscopy-Pharmaceutical Applications" *J. Pharm. Sci.* **2003**, *92*, 441.
- [3] Harris, R. K. "NMR Study or Organic Polymorphs and Solvates" *The Analyst* **2006**, *131*, 351.
- [4] Offerdahl, T. J. and Munson, E. J. "Solid-State NMR Spectroscopy of Pharmaceutical Materials" *Amr. Pharm. Rev.* **2004**, *7 (1)*, 109.
- [5] Offerdahl, T. J.; Salsbury, J. S.; Dong, Z.; Grant, D. J. W.; Schroeder, S. A.; Prakash, I.; Gorman, E. M.; Barich, D. H.; Munson, E. J. "Quantitation of Crystalline and Amorphous Forms of Anhydrous Neotame Using ^{13}C CPMAS NMR Spectroscopy" *J. Pharm. Sci.* **2005**, *94*, 2591.
- [6] Saindon, P. J.; Cauchon, N. S.; Sutton, P. A.; Chang, C. – J.; Peck, G. E.; Byrn, S. R. "Solid-State Nuclear Magnetic Resonance (NMR) Spectra of Pharmaceutical Dosage Forms" *Pharm. Res.* **1993**, *10*, 197.
- [7] Suihko, E. J.; Forbes, R. T.; Apperley, D. C. "A Solid-State NMR Study of Molecular Mobility and Phase Separation in Co-Spray-Dried Protein–Sugar Particles" *Eur. J. Pharm. Sci.* **2005**, *25*, 105.
- [8] Koga, A.; Yonemochi, E.; Machida, M.; Aso, Y.; Ushio, H.; Terada, K. "Microscopic Molecular Mobility of Amorphous AG-041R Measured by Solid-State ^{13}C NMR" *Int. J. Pharm.* **2004**, *275*, 73.
- [9] Rapp, J. L.; Huang, Y.; Natella, M.; Cai, Y.; Lin, V. S.-Y.; Pruski, M. "A Solid-State NMR Investigation of the Structure of Mesoporous Silica Nanoparticle Supported Rhodium Catalysts" *Solid State NMR.* **2009**, *35*, 82.
- [10] Geppi, M.; Mollica, G.; Borsacchi, S.; Veracini, C. A.; "Solid-State NMR Studies of Pharmaceutical Systems" *Appl. Spectros. Rev.* 2008, *43*, 202.
- [11] Vogt, F. G. "Evolution of Solid-State NMR in Pharmaceutical Analysis" *Future Med. Chem.* 2010, *2*, 915.
- [12] Pham, T. N.; Watson, S. A.; Edwards, A. J.; Chavda, M.; Clawson, J. S.; Strohmeier, M.; Vogt, F. G. "Analysis of Amorphous Solid Dispersion Using 2D Solid-State NMR and ^1H T_1 Relaxation Measurements" *Mole. Pharm.* **2010**, *7*, 1667.
- [13] Griffin, J. M.; Martin, D. R.; Brown, S. P. "Distinguishing Anhydrous and Hydrus Forms of an Active Pharmaceutical Ingredient in a Tablet Formulation Using Solid-State NMR Spectroscopy" *Angew. Chem.-Int. Edit.* **2007**, *46*, 8036.