

ABSTRACTS

Monday, June 15: Polymorphs and Solvates

From Solid Form Screen to Crystallization Development: Case Studies

Bing-Shiou Yang

Identification of a suitable solid form of an active pharmaceutical ingredient (API) for development is an essential and critical element in the pharmaceutical development. Very commonly, within a short timeline and sometimes with limited resources, crystallization development has to be conducted to support the delivery of kg quantity of the selected solid form to support the advancement of the development. This contributions use case studies to illustrate and discuss how the information obtained in the solid form screen is applied in the crystallization development and facilitate the overall API development.

API Process Development of a Polymorphic System

Authors: Chenchi Wang, Qi Gao, Beth Sarsfield, Yuping Qiu, Victor Rosso, Daniel Hsieh, Shih-Ying Chang, and Chiajen Lai.

Research and Development, Bristol-Myers Squibb Company, New Brunswick, New Jersey 08903.

Polymorphism of active pharmaceutical ingredients plays an important role in determining their physical and chemical properties, as well as their suitable use in drug substance application. The search for polymorphs requires thorough and systematic methodologies to gather sufficient understanding of crystal formation and stability in various solvent systems. A compound of interest undergoes multiple phase transformations during material preparations before leading to the desired crystal form. Polymorph control is made possible, from crystallization throughout drying, with knowledge collected in both polymorphism studies and process engineering to ensure consistent generation of the desired product. Our studies will be presented concerning the relation of different polymorphs, crystal form conversions, crystallization techniques and processing needed to tailor crystal morphology, crystallite size, and solid properties.

Concepts for successful co-crystal screening of pharmaceutical compounds

B. Baumgartner, Sanofi-Aventis

Co-crystals are becoming an important aspect of drug development. Mainly in cases where salt formation is not possible and the properties of the free base are not satisfying (usually in terms of bioavailability), the preparation of co-crystals can aid in the formulation of a drug. While the success of a screening is mostly governed by the molecule's properties, the efficiency of the screening can be enhanced by some beforehand considerations:

What tools are available for the selection of an efficient set of co-crystal formers ?

What techniques can be employed for the screening ?

Can the probability of success be estimated by the API's molecular structure ?

The identification of a possible co-crystal is however only the first step on its way into development. Scalability of the crystallization, stability and solubility of the co-crystal need to be assessed as well as the pharmaceutical acceptability of the co-crystal former and the in vivo bioavailability.

Validation of the quantification of polymorphism by spectroscopic methods combined with Partial Least Squares methods

Wilhelmina J. H. Janssen, Thanh N. Tran, [Marco Scarzello](#) and Peter J. C. M. van Hoof Schering-Plough, The Netherlands

Spectroscopic techniques, in combination with Partial Least Squares chemometrics methods, are powerful tools for the quantification of drug polymorphism, in particular in drug product formulations. General indications for the validation of these methods are presented, in particular concerning the determination of the optimal number of principal components, the specificity, accuracy, linearity, precision (*i.e.*, method repeatability, procedure repeatability and intermediate procedure precision), detection and quantitation limits. The validation of a FT-Raman spectroscopy method for the quantification of two crystalline forms and of the amorphous content in drug product tablets is discussed as an example.

Identification and Quantitation of Polymorphs and Amorphous Material Using Solid-State NMR Spectroscopy

Thomas Offerdahl, Boehringer Ingelheim

Solid-state NMR spectroscopy is a relatively new technique for the analysis of pharmaceutical solids. Due to its ability to detect small changes in the local chemical environment, this technique has great applications towards the analysis of polymorphic and amorphous components in either a drug substance or drug product. Since ^{13}C solid-state NMR spectra are usually acquired with the use of a cross-polarization pulse sequence, the dynamics involved must be evaluated and corrected for when making accurate quantitative determinations. Examples of quantitation of crystalline forms of anhydrous neotame polymorphs will be presented as well as quantitation of amorphous material.

Near Infrared Spectroscopy as a Tool to Guide Formulation Development for a Drug Molecules Prone to Polymorph and Solvate Conversion

Authors: Christopher T. John, Laura Sharon, Li Li, Russell Maus, Raija Suomela, Maria Cruanes, Yun Mao, and Mark Mowery

Near Infrared (NIR) spectroscopy has been a useful technique in characterizing the identity and polymorph composition of pharmaceutical ingredients because of the minimal sample preparation and fast acquisition time. In recent years, NIR has also been successfully used as a quick and non-destructive technique to measure content uniformity in formulated drug products and as an on-line PAT tool to measure content, particle size and moisture. This study will present several examples of how quantitative NIR methods were employed to monitor polymorph and solvate form changes of the active

pharmaceutical ingredient (API) in various formulations. These data were used to guide formulation composition and processing conditions to determine the most physically stable formulation. Additionally, the NIR method was used to quantify conversion of the polymorph during formulation processing and while on stability. A description of the method, and its validation, is also presented. NIR was chosen for this measurement because of complications with other solid state characterization techniques. Comparison to other techniques, Raman, will also be made.

QUANTITATIVE ANALYSIS OF PHASES WITH PARTIAL OR NO KNOWN CRYSTAL STRUCTURE

Arnt Kern, BRUKER AXS GmbH, Karlsruhe, Germany

The method of quantitative analysis of phases with Partial Or No Known Crystal Structure, PONKCS [1], allows the accurate quantification of compounds, where the classic Rietveld method or other classic quantification methods fail. Amorphous phases, disordered phases, or phases with unknown crystal structures (e.g. new polymorphs) can be quantified with the same or even higher accuracy as for well-defined crystalline phases.

With PONKCS, crystal structure information is replaced by measured intensities from a reference sample, requiring calibration using an internal standard. As a result, extremely accurate results can be also obtained in cases, where classic Rietveld analysis cannot be applied at all.

The methodology and examples will be discussed.

[1] Scarlett, N.V.Y. & Madsen, I.C. (2006): Quantification of phases with partial or no known crystal structure. - Powder Diffraction, 21(4), 278-284

The Importance of Diversity in Accomplishing Successful Comprehensive Solid State Screening Programs

Andrei Winkler, Avantium; The Netherlands

The presentation will address the scientific aspects of solid state screening & characterization and will present the practicality of executing large IP screens. We will review the main drivers for solid state space definition of drug substances in both early and late-stage development and identify the key tools scientists have available to successfully accomplish this task. We will discuss the impact on both intrinsic and bulk properties of drug substances and ways to differentiate between them.

The presentation will further highlight the underlying philosophy of solid state screening of drug substances and why innovator companies cannot afford to cut corners and in the process miss out on valuable life cycle management opportunities. The presentation will offer case studies and examples with timelines of industry cases.

Tuesday, June 16: Thermal Methods in Pharmaceutical Characterization

Characterization of Hydrates by Means of Thermal Analysis

Gabriele Kaiser, NETZSCH-Gerätebau GmbH, Selb, Germany

In many stages of the manufacturing process, drug substances are brought into contact with water or water vapor as commonly used solvents. This may take place during precipitation, crystallization or re-crystallization of the drug substance, or during composition of the drug product through excipients. Other solvent-based processes are wet-granulation, spray drying and lyophilization. On the other hand, dehydration steps may occur during drying, milling, mixing or tableting.

In addition, drug substances and drug products are exposed to various climatic conditions which may lead to unexpected hydration or dehydration phenomena. The investigation of hydrates is therefore an important aspect of the characterization of drug substances.

Water may be associated with a crystalline solid in different ways. It can be bound tightly in the crystal lattice, loosely in the bulk, can form both types of interaction or can show just physisorption on the surface.

A substance is usually called a hydrate if the solvent molecules – in this case, water – are a part of the crystal structure. This will affect the chemical and physical properties of the material, its stability and bioavailability.

The present paper discusses measurements by DSC (differential scanning calorimetry), TGA (thermogravimetry) and TGA/DSC-MS/FTIR (thermogravimetry coupled to gas analyzing systems), carried out mainly on sugar hydrates as model substances. The influence of such measurement parameters as sample mass, pressure and amount of humidity is taken into account. A combination of TGA or DSC and mass spectrometry (MS) or Fourier transform infrared spectroscopy can be used for quantification of the evolved water and thus for identification of the number of bound water molecules.

With thermokinetic evaluation it is possible to glean information about, for example, the stability (also long-term stability) of the drug substance, the excipient or the drug product during storage.

Introducing Large Sample Sized Scanning Calorimetry in Pharmaceutical Studies Peter Ralbovksy, Netzsch Instruments, USA

The characterization of pharmaceutical material is very often carried out with small sample sizes which is generally advantageous. Pharmaceutical materials in the discovery portion of development often times are expensive and time consuming to make.

Therefore any amount of destructive testing needs to be minimized when possible.

Larger sample sizes due offer advantages in certain applications. A pharmaceutical solid is only valuable in how it interacts with the desired targets in a multiphase and heterogeneous environment. The pharmaceutical must be able to be compatible with the

delivery system as well as being able to remain effective in a variety of storage and transport conditions as well as to be made safely in the large scale.

A new instrument has been designed with benefits to study pharmaceutical solids in isolation or as it relates to the broader range of commercial pharmacology. The instrument is called the Multi-Model Calorimeter (MMC) and provides data similar to a DSC but with increased versatility due to increased sample size. Typical sample size range between 100s of milligrams to gram-sized samples. The ability to inject material and stir the sample is also possible which is important in multiphase sample studies. Furthermore pressure is also as a function of time and temperature providing information not available in calorimeters typically used to study pharmaceutical solids. Pressure is important for both understanding physical properties but also provides more information on chemical reactions which may not be detected via heat signature. High pressure and pressure scanning studies can also be conducted which is crucial as pressure can stabilize enzyme and change their activity and specificity.

NEW SOLID STATE PROPERTIES OF DRUGS BY DIELECTRIC AND CALORIMETRIC ANALYSIS

Alan T. Riga ^(a,b) and Kenneth S. Alexander ^(b)

(a) Department of Chemistry, 2121 Euclid Avenue, SI 329,
Cleveland State University, Cleveland, Ohio, 44115-2406 USA a.riga@csuohio.edu

(b) College of Pharmacy Practice, University of Toledo, Toledo OH USA

Dielectric Analysis (DEA) by Electrical Conductivity and isothermal DEA differentiates drugs by melting, solid-solid transitions, solvent desorption, dehydration and amorphous/crystalline content well below the melt temperature for a number of drugs. New **isothermal DEA** tan delta properties are revealed by examining the same drugs in the solid state (20°C below the melt) and (at 5°C above the melt) in the amorphous state. In order to establish structure-property relationships the United States Pharmacopeia (USP) set of melting standard drugs were evaluated by Thermal Analytical techniques and Macro-photography. The USP standards evaluated in this study include Vanillin (melt temperature, T_m , 80.4°C), Acetanilide (T_m , 114°C), Acetophenetidin (T_m , 135°C), Sulfapyridine (T_m , 191°C) and Caffeine (T_m , 235°C). Other drugs evaluated by DEA/DSC are polymorphic Nifedipine and Tolbutamide

Examination of these drugs by scanning Dielectric Analysis (DEA) and isothermal DEA discovered a linear electrical conductivity in the pre-melt temperatures through to the melt. The activation energy (E_a) can be calculated from the slope of plots of log conductivity vs. the reciprocal temperature in Kelvin, which had a typical correlation coefficient of 0.999. The E_a for charge formation of the drugs below and above their melting temperature was frequency dependent and was typically 1100 ± 300 J/mole. The E_a for the pre-melt charge complex for Sulfapyridine was 990 J/mole, for Acetophenetidin 1300 J/mole and as outlier caffeine 320 J/mole. Other drugs and

excipients with known enhanced pre-melt conductivity behavior include Vanillin, Lidocaine, Acetanilide, Nifenipine and Tolbutamide. It is our observation that the chemicals studied form charged molecules as complexes or dimers just before melting. We have measured unique electrical properties of a number of drugs and chemicals e.g. amino acids, carbohydrates, heterocyclics (anthracene) which have thermally induced dielectric visco-elastic properties as charge transfer complexes in the solid state.

The amorphous content is also clearly and repeatably determined at temperatures below T_m by comparing the change in conductivity for the crystalline drug solid-liquid transition (typically 10^{-3} to 10^7 pS/cm), the semicrystalline drug (typically 10^{+2} to 10^7 pS/cm) and the amorphous drug with no definitive conductivity change but a conductivity of 10^7 pS/cm in the liquid amorphous-temperature range. The DEA method employed alternating current (a.c.) frequencies from 0.10 to 10,000 Hz which allowed evaluation of surface reactions at 0.10 to 1.0 Hz and bulk reactivity (loss of hydration) at $>5,000$ Hz. Residual moisture or solvent is detected at low frequencies and content estimated by comparing conductivity peak values. The combined Differential Scanning Calorimetry (DSC), Dielectric Analysis (DEA) Thermal Gravimetric Analysis (TGA) and Macro-photography techniques allow for a collection of a wide variety of physical and chemical properties.

Introduction

In preformulation studies determining the melt temperature and heat of fusion by DSC, a well established method, is relevant and significant (1-5). These melt properties define the drug and certainly in most cases the polymorphic form of a drug or its solvate. It is well known that the DSC melt properties are related to the structure of the drug which can be confirmed by various structural determining tools, for example, X-Ray Diffraction Analysis (6-8). Determining the glass transition of the amorphous portion of a drug can lead to the knowledge of the amorphous content (9). Additional thermal analysis testing on the same drugs by TGA reveals the stability of a drug and at what temperature the drug degrades (10). TGA can also relate the amount of residual solvent that is trapped in the drug or excipients.

Identifying the amorphous content in a drug is very important since crystalline drugs are more stable but amorphous drugs are more bioavailable (11). A new thermal analytical method utilizing DEA clearly and repeatably differentiates the crystalline and amorphous drug content at temperatures below the melting temperature has been developed (12-14). This method is accomplished by comparing the change in conductivity for the crystalline drug solid-liquid transition (typically 10^{-3} to 10^{+7} PS/cm), the semicrystalline drug (typically 10^{+2} to 10^{+7} PS/cm) and the amorphous drug with no definitive conductivity change but a conductivity of 10^{+7} PS/cm in the liquid-temperature range. The DEA method employed using a.c. frequencies from 0.10 to 10,000 Hz allowed evaluation of surface reactions at 0.10 to 1.0 Hz and bulk reactivity (loss of hydration) at $>5,000$ Hz. Residual moisture or solvent is detected at low frequencies and content estimated by comparing conductivity peak values. Previous studies, presentations and publications by Riga and Alexander employing DEA and DSC have characterized excipients, drugs,

transdermal patches, essential fatty acids, proteins, surfactants, dispersants, electro-rheological fluids and amino acids (15-19)

The combined Differential Scanning Calorimetry, Dielectric Analysis, Thermal Gravimetric Analysis and Macro-photography techniques allow for a collection of a wide variety of physical chemical properties that are related to the structure of a crystalline drug (12-14).

The focus of this paper is the use of DEA in Industrial Pharmacy. Therefore a review of the technique and the properties measured is in order. The DEA gives the pharmaceutical scientist new insights into the nature and behavior of drugs. DEA of the drugs studied has led to a better understanding of the chemistry and molecular mobility that relates to the structure of the drug. This information is of the utmost importance during pre-formulation development. DEA measures changes in phase (solid to liquid), transitions and loss of residual solvents as it is subjected to a periodic electric field. From DEA quantitative data one can determine the capacitive and conductive nature of solid drugs and excipients and characterize molecular relaxations or polarizations. DEA is ultra-sensitive making it possible to measure conductivity to 10^{-3} PS/cm and as high as 10^{+8} PS/cm and subsequently material transitions that other techniques can not define significantly to provide useful data. DEA compliments DSC by allowing a measurement of molecular motion through electrical properties. DEA measures two fundamental electrical characteristics of a crystalline or amorphous drug, capacitance and conductance as a function of time, temperature and frequency. *The capacitive nature of the crystalline solid is its ability to store electric charge and the conductive nature is its ability to transfer electric charge.* The four major properties reported during DEA are: $e' = \text{permittivity}$, $e'' = \text{loss factor}$, $\text{Tan } \delta = \text{dissipation factor or } e''/e'$ and $\sigma = \text{conductivity (PS/cm)}$. Ionic conductivity is proportional to $(2\pi) \times (f) \times (e'')$ where f is the applied frequency.

Experimental Procedures

A TAI 2920 DSC was used to profile the drug transitions and melting at $10^\circ\text{C}/\text{min}$ in nitrogen at a flow rate of 50 mL/min. Sample size was typically 3-5 mgs. Temperature range was typically about 40°C above the peak melting temperature for the drug under investigation.

A TAI 2970 DEA was used to determine the electrical conductivity curve for each drug studied. The heating rate was $5^\circ\text{C}/\text{min}$ in flowing nitrogen at 80 mL/min. Sample size was typically 20 mgs of solid powdered drug. The single surface gold ceramic interdigitated electrodes were used to evaluate the electrical properties of the drugs.

USP melting standards evaluated in this study include drugs and excipients with their DSC melt temperatures: Vanillin (*melt temperature, T_m , 80.4°C*), Acetanilide (T_m , 114°C), Acetophenetidin (T_m , 135°C), Sulfapyridine (T_m , 191°C) and Caffeine (T_m , 235°C and $T_{\text{sublimation}}$, $<220^\circ\text{C}$). Other drugs evaluated by DEA-ECA/DSC are polymorphic Nifedipine and Tolbutamide.

A Konica-Minolta DG 7D Digital Camera with a 28-80 mm macro lens was used to characterize the crystalline and amorphous materials on the single surface interdigitated array gold electrodes.

Results and Discussion

The DSC melting of Sulfapyridine was 190-192°C with a heat of fusion of 22 J/g. The accompanying DEA profile at multiple frequencies of 100 mHz to 5000 Hz indicated that the onset of the solid-liquid transition was 125-169°C, Figure 1. The onset temperature for the electrical conductivity variation was significantly and reproducibly lower than the peak melting at 192°C. In the melt temperature range the conductivity changed from 10^{-1} to 10^{+7} PS/cm. The second DEA curve for the cooled melt had conductivity values starting at 10^{+5} and in the amorphous liquid 10^{+7} PS/cm. Clearly the cooled sample, 2nd run, was semicrystalline with a high amorphous content. See also Figure 3 where the shiny glassy material after heating through the melt (left figure) is predominantly amorphous. Sulfapyridine did not appreciably re-crystallize on cooling in the DSC where the heat of crystallization was 2.2 J/g while fusion heat was 22 J/g, i.e. only 10% re-crystallized in the DSC.

DEA curves for the first and second heating of Vanillin, an excipient, also showed considerable differences in electrical conductivity values, see Figure 2. The electrical signature at multiple frequencies for the crystalline solid (1st run) could be easily differentiated from the 2nd run of the cooled melt with higher conductivity values (e.g. 3900 PS/cm vs. 0.11 PS/cm for the 1st run). The conductivity of the melt above the DSC melting temperatures of 81-83°C was $1.2 \times 10^{+5}$ PS/cm. The cooled Vanillin re-crystallized and was characterized by photomicrography which indicates an amorphous glassy structure along with definitive crystals (right of Figure 3). Vanillin typically and repeatably re-crystallizes at 30°C at a DSC cooling rate of 10°C/min. The cooled Vanillin melt cooled in the DEA was semicrystalline.

Caffeine characterized by DSC in an open and closed aluminum pan and DEA-electrical conductivity is summarized in Figure 4. The closed pan DSC test showed the melt to be 235-236°C with a heat of fusion of 105 J/g. The “open pan with no-lid“ DSC curve was broad and diffuse with an endothermic transition from 157-211°C and a transition heat of 543 J/g. The difference between the DSC curves indicates that caffeine sublimed with a heat of 438 J/g. The accompanying DEA curve as a function of frequency (0.1-1.0 Hz) had four repeatable electrical conductivity peaks at 34, 112, 191 and 226°C. The latter, 226°C, is associated with the melt and the 191°C peak indicative of sublimation. The % sublimation is estimated from the area under the DEA melt and sublimation peaks to be 15% sublimed. The other peaks are possibly associated with a solid-solid at 156°C (DSC) vs. 112°C (DEA) and solvent desorption.

Acetophenetidin examined by heat cool heat cycles DEA and DSC is recorded in Figure 5. The DSC has a melt at 135-136°C with a heat of fusion of 176 J/g and crystallization occurring at 123-120°C with a heat of 169 J/g. The DEA-Electrical Conductivity at 1000 Hz was recorded in three runs: first run as received sample, second run slow cooled in the

DEA to room temperature and reheated and the third run slow cooled in the DEA and reheated to above the melt. The onset of melting by DEA occurred at 131°C and 33 PS/cm-1st run, 124°C and 32 PS/cm-2nd run and 130°C and 226 PS/cm-3rd run. The amorphous liquid Acetophenetidin had an electrical conductivity at 1000 Hz of 817,000 PS/cm-1st run and 723,000 PS/cm for the 2nd run, see Figure 5. The onset of apparent melting by DEA was 6-12°C below the DSC peak melt temperature. Figure 6 is also the DEA of Acetophenetidin at 0.1 Hz (100 mHz) as a function of temperature. The onset of melting by DEA at 100 mHz occurred at 130°C and 0.076 PS/cm-1st run, 123°C and 5.3 PS/cm-2nd run and 129°C and 58 PS/cm-3rd run. The amorphous liquid Acetophenetidin had an electrical conductivity of 83,500 PS/cm-1st run, 68,400 PS/cm for the 2nd run and 85,800 PS/cm for the 3rd run. Recent calibration of the DEA with known aqueous standard conductivity solutions (1.2 to 20 micro-siemens/cm) indicated that the 1000 Hz values were in close agreement. The 2nd and 3rd DEA tests indicated that the Acetophenetidin was semi-crystalline while the 1st run was crystalline.

The DSC of Acetanilide melts at 114-116°C. The DEA-Electrical Conductivity of a heat cool heat sample of Acetanilide from 100 mHz to 5000 Hz is cited in Figure 7. The 1st run and 2nd run indicated that the onset of electrical conductivity and melting was at 95-96°C. The rapid rise in conductivity through the melt started at 0.68 PS/cm- 1st run and 624 PS/cm-2nd run. The liquid amorphous conductivity was >62,900 PS/cm to $1.0 \times 10^{+7}$ PS/cm. The DEA onset of Electrical Conductivity was approximately 20°C lower than the DSC peak melting at 116°C.

Included in this DSC-DEA study are two polymorphic drugs Nifedipine and Tolbutamide, Figures 8 and 9, respectively. Nifedipine was recrystallized from Dioxane and it is estimated that the DEA peak at 93°C is due to solvent desorption. The boiling temperature for Dioxane is 81-101°C at pressures of 400 to 760 mm Hg pressure (reference Merck Index). The estimated amount of solvent is based on a comparison of the peak conductivity at 93°C and the conductivity of the melt at 176°C. Therefore, there is 2 ppm Dioxane present on the sample. The onset of DEA melting was 164°C and 8°C lower than the DSC peak value of 172°C.

Tolbutamide had a DEA onset of 118°C and a DSC peak value of 128°C, 10°C lower for the DEA measurement, see Figure 9. Based on a comparison of electrical conductivity at 84°C and 32 PS/cm and the conductivity of the melt at 133°C of 444,000 PS/cm there is relatively 70 ppm of a solvent desorbed from the drug. The solid-solid transition at 38-39°C (DSC) was observed in an expanded DEA-Conductivity curve with a peak at 45°C.

Conclusions

A comparison of the DEA-Electrical Conductivity Analysis (ECA) and the DSC for a number of USP melting standards and several polymorphic drugs revealed new and significant drug physical properties. The DEA-ECA curves for each drug or excipient studied occurred 8-20°C below the DSC peak temperature. It is well known that the electrical properties will lead the calorimetric properties (20). The lower temperature response by DEA-ECA prior to melting by DSC can be attributed to several physical chemical explanations. First, the electrical properties are detecting the effects of

structural defects (melting point depression due to impurities or defects (20) on the surface of the drug crystals and probably at ppm concentrations which are not detectable by DSC. Secondly, cooperative thermal motion of the molecules in an oscillating electric field in the solid drug just prior to melting can also contribute to enhanced electrical conductivity (21). Finally, if a low molecular weight dipolar or ionic solvent is incorporated into the drug crystals (for example water) then increased conductivity could be observed as the solvent is released prior to the drug crystals melting.

To further understand the DEA-ECA rapid increase from 10^{-2} to 10^{+7} PS/cm over a fairly narrow temperature range as the solid approaches and transitions into melting (as determined by DSC) one must investigate the charge or dipole distribution within the drug molecule and the mechanism of DEA polarization or relaxation (22). These observations are the course for a future study.

The 2nd DEA heat of all the crystalline drugs studied had a significant and repeatable greater conductivity than the 1st DEA heat. The 2nd and 3rd DEA run on the same sample represented a loss of crystallinity and an increase in amorphous character. This observation was validated by photomicrography. It appears that the percent crystallinity can be determined well below the melt by comparing the conductivity values at a given temperature and fixed frequency. If the DEA-ECA of crystalline and amorphous drug were known then one could easily determine the percent crystallinity or percent purity as frequently determined by DSC (23).

It appears that residual solvent absorbed on a drug can be determined by examining the DEA-ECA. Heating through the solvent volatilization and comparing it to the liquid amorphous drug conductivity after melting may be a way of evaluating ppm solvent on the drug crystals. An alternate is to heat the sample and volatilize the solvent and then reheat the sample to see the amount of loss by DEA and compare that loss to a TGA loss of mass.

References

1. D. Giron, "Applications of Thermal Analysis in the Pharmaceutical Industry", *Journal of Pharm and Biomedical Analysis*, 4, 6, 755-770 (1986).
2. D. Giron, C. Goldbronn and P. Riechon, "Thermal Analysis Methods for Pharmacopoeial Materials", *Journ. Pharm. And BioChemical Anal.* 7, 12, 1421-1433 (1989)
3. B. Perrenot and G. Widmann, "Polymorphism by DSC", *Thermochimica Acta*, 234, 31-39 (1994)
4. S. Roy, K. Alexander and A. Riga "A statistical approach for the evaluation of parameters affecting preformulation studies of pharmaceuticals by DSC, ", *Proceedings of the North American Thermal Analysis Society*, 30, 675 (2002)
5. J.L. Ford, "Pharmaceutical and Thermal Analysis", Special Edition, *Thermochimica Acta*, 248, 1-360 (1995)
6. H.G. Brittain, "**Polymorphism in Pharmaceutical Solids**", Marcel Dekker, New York, NY (1999)
7. A. Riga and R. Collins, "Differential Scanning Calorimetry and Differential Thermal Analysis", in the **Encyclopedia of Analytical Chemistry**, R.A. Meyers, Ed, J.Wiley and Sons Ltd, Chichester, England, 13147-13179, (2000)
8. A. Riga, J. Cahoon and W.P. Pan "Characterization of Polymers: Thermal Analysis", R. F. Brady, Ed., in "**Comprehensive Desk Reference of Polymer Characterization and Analysis**", Oxford Publishing, an American Chemical Society publication, Washington DC, Chapter 13, 307-340, (2003)

9. S. Roy, K.S. Alexander, A. Riga, and K. Chatterjee "Characterization of Physical Mixtures and Directly Compressed Tablets of Sulfamerazine Polymorphs: Implications on In Vitro Release Characteristics", **Journal Pharmaceutical Sciences**, 92, no.4, 747-759 (2003).
10. H.G. Brittain, "**Physical Characterization of Pharmaceutical Solids**", Dekker, N.Y. (1995)
11. R. Suryanarayanan "X-Ray Powder Diffractometry" in **Physical Characterization of Pharmaceutical Solids**" ed H. Brittain, Dekker NY 187-222 (1995)
12. A. Riga, Invited lecturer, Thermal Analysis Forum of Delaware Valley, U of PA March 10, 2005," "Characterization of Polymorphic Drugs by Thermal Analytical Methods: Dielectric Analysis and Differential Scanning Calorimetry".
13. A. Riga, Plenary Lecturer, "Physical Analytical Characterization of Polymorphic Drugs", Canadian Thermal Analysis Society, Montreal, Canada, May 17-18, 2005
14. A. Riga, Invited Lecturer, "Advanced Thermal Analytical Characterization of Drugs and Biological Active Chemicals", Canadian Thermal Analysis Society, Montreal, Canada, May 17-18, 2005
15. A. Riga, J. Cahoon, and J. Pilaet "Characterization of Electrorheological Processes by Dielectric Thermal Analysis", in "**Materials Characterization by Dynamic and Modulated Thermal Analytical Techniques**, ASTM STP 1402, 139-156 (2001)
16. A. Riga, J. Cahoon and V. Lvovich, "Characterization of Organic Surfactants and Dispersants by Frequency –Dependent Electrochemical and Dielectric Thermal Analysis Techniques", in "**Materials Characterization by Dynamic and Modulated Thermal Analytical Techniques**, ASTM STP 1402, 157-173 (2001)
17. A. Riga, K. Alexander, R. Macedo and G. Pan Characterization and Analysis of Pharmaceuticals Part One. Multiple and In-Tandem Thermal Analytical Techniques, **American Pharmaceutical Review**, 6, Issue 1, 110-114 (2003)
18. A. Riga, K. Alexander, R. Macedo and G. Pan "Characterization and Analysis of Pharmaceuticals Part Two. Multiple and In-Tandem Thermal Analytical Techniques", **American Pharmaceutical Review**, 6, Issue 2, 64-70 (2003)
19. Riga, A.T., Smiechowski, M., Lvovich, V., Alexander, K. "Dielectric Analysis of Transdermal Patches". Proceedings of the North American Thermal Analysis Society 30, 102-105.(2002)
20. R.J. Sime, "**Physical Chemistry**", Saunders, Philadelphia, 462 (1990)
21. S. Glasstone, K. Laider and H. Eyring "**Theory of Rate Processes**", McGraw Hill, NY, (1941)
22. N.G. McCrum, B.E. Read, and G. Williams, "**Anelastic and Dielectric Effects in Polymeric Solids**" Wiley, NY (1967)
23. R. L. Blaine and C. Schoff, Eds, "**Purity Determination by Thermal Methods**, ASTM Special Technical Publication 838, West Conshohocken Pa., (1984)

Spontaneous Salt Dissociation & Effect of Crystallinity on Form Conversion

Robert J. Behme, Sr. Research Scientist
Eli Lilly & Company

Salts of some pharmaceutical compounds may incongruently melt, that is, melt and dissociate while some spontaneously dissociate even below their melting point. Characterization of an example by thermal methods will be described. Because chemical reactions are time, temperature and pressure dependent, variable heating rate thermal analysis is useful to measure decomposition kinetics. The rate of dissociation from a crystalline drug is significantly lower from an amorphous counterpart of the same compound. Consequently, less than optimal crystallinity of API from crystallization process or a phase process induced phase transition producing amorphous material dramatically increases the susceptibility of the API to dissociate. Physical properties of amorphous phases may further impact salt dissociation, play a role in interactions between components in the formulation and alter the physical or chemical attributes of the drug product.

Thermodynamic stability relationship of polymorphs and hydrates of an investigational drug

Yuan-Hon Kiang

Department of Pharmaceutics, Amgen Inc., Thousand Oaks, CA 91320, U.S.A.

Polymorph screening of AMG-XXX, an investigational drug, revealed two anhydrous polymorphs (Forms I and II) and two monohydrates (Forms III and IV) of this pharmaceutical solid. The aim of this study was to compare the thermodynamic stability of the four forms. Thermodynamic stability relationship was inferred from melting data for Form I and Form II and evaluated by van't Hoff plot for Form III and Form IV. Form I and Form III were found to be the more stable anhydrous and hydrate form respectively.

Tuesday, June 16: Solid-State Characterization of Lyophiles and the Lyophilization Process

Physical Characterization of Formulations in Frozen and Freeze-dried Solid States: An Overview

Jinsong Liu

Product Development, Abraxis BioScience, Melrose Park, IL 60061

Lyophilization process (freeze-drying cycle) and formulation are two major elements, which determine the quality of a lyophilized product. Physical characterization of formulations in frozen and freeze-dried solid states not only provides information indispensable to both formulation and process development, but also give a deep understanding of how formulation and process interact to influence critical quality

attributes for lyophilized products, which is the basis for Quality by Design (QbD) in development and manufacture of lyophilized pharmaceutical products. This presentation provides an overview of the physical characteristics of pharmaceutical formulations in frozen and freeze-dried solid states, as well as the techniques often used in physical characterization for freeze-drying development. Applications of and recent improvements to these techniques will be discussed, with special attention to (1) techniques designed or modified specifically for *in-situ* characterization (or Process Analytical Technology) of the physical properties of the formulation under conditions similar to the real pharmaceutical lyophilization process, (2) novel applications of some conventional techniques, such as microcalorimetry, which facilitated freeze-drying development. As a closing remark of this presentation, research and developmental needs in the area of physical characterization for freeze-drying will be addressed.

Relaxation Dynamics in Amorphous Pharmaceuticals and Applications to Stability Prediction.

M.J. Pikal, School of Pharmacy, University of Connecticut, Storrs, CT, 06269

The qualitative relationship between dynamics in glassy systems and pharmaceutical stability is well understood. Degradation of any type, from aggregation in proteins to re-crystallization of amorphous small molecule systems, requires some level of molecular mobility to occur on a time scale of relevance. We traditionally have characterized molecular mobility in amorphous pharmaceuticals by evaluating the dynamics of structural relaxation, typically using calorimetric techniques. This presentation will outline the limitations of the experimental methods, both DSC and Isothermal Microcalorimetry, and will review the correlations between relaxation dynamics and degradation rate constants for a variety of small molecule and protein systems.

We find that one cannot determine separately the relaxation time, τ , and the stretched time constant, τ^* , from a Kohlrausch-Williams-Watts (KWW) analysis of enthalpy relaxation due to changes in relaxation time during the measurement, but one can evaluate the time constant, τ^* . Further, we find that this time constant is often well correlated with degradation of both small molecules and proteins in the amorphous solid state, and frequently does correlate with re-crystallization times. However, DSC and Isothermal Microcalorimetry do not necessarily measure the same average mobility. Furthermore, factors other than mobility as measured by $1/\tau^*$ may well dominate tendency to re-crystallize in a series of samples, and it is clear that well below T_g , measures of mobility other than the “global mobility” measured by relaxation dynamics may be critical in determining stability differences in both small molecule and protein systems. In particular, we find good correlations between degradation rates and “fast

dynamics” as measured by amplitude of motion on a nano-second time scale via neutron scattering.

Usefulness and Limitation of NMR relaxation time as an indicator of stability-related molecular mobility in freeze-dried formulations

Sumie Yoshioka

University of Connecticut, School of Pharmacy

Fast dynamics, which has shorter length- and time-scales than structural relaxation, has recently attracted attention as molecular motion relevant to the instability of freeze-dried formulations. NMR relaxation measurement is one of the most useful methods for determining fast dynamics. NMR has the advantage that it allows us to determine the mobility of a specific site in the molecule and to identify the origin of molecular motion, unlike dielectric relaxation spectroscopy and calorimetry. This advantage of NMR can be enhanced by using not only ^1H - and ^{13}C -NMR but also ^{15}N -, ^{17}O - and ^{19}F -NMR.

It has been demonstrated that spin-lattice relaxation time (T_1 and $T_{1\rho}$), which sensitively reflect molecular motions on the order of MHz and kHz, respectively, show correlations with the instability of freeze-dried formulations for peptides and proteins. Spin-spin relaxation time (T_2) also reveals correlations with the instability. These findings suggest that NMR relaxation time can be used as an indicator of stability-related molecular mobility.

On the other hand, NMR relaxation times have several intrinsic characters that need to be considered in data analysis; the measured value of relaxation time represents the average mobility of multiple sites in the molecule, if their peaks in the spectrum are overlapped. Furthermore, the measured value of relaxation time represents the average mobility of multiple motions with different time scales, if the site of interest shows multiple scales of motions.

Here, usefulness and limitation of NMR relaxation time as an indicator for evaluating the instability of freeze-dried formulations are discussed, focusing on the time scale of molecular motions reflected on NMR relaxation times.

Calorimetric assessment of enthalpy relaxation in lyophilized glasses

| Suman Luthra, Pfizer; USA

The purpose of this presentation is to review the methodology by which dynamics in amorphous pharmaceutical solids may be characterized by calorimetry and to specifically review the determination of the optimum annealing conditions to obtain maximum structural relaxation in pharmaceutically relevant lyophilized glasses both by experimental studies (Differential Scanning Calorimetry-DSC) and theoretical analysis (Tool-Narayanaswamy-Moynihan phenomenology-TNM). Structural relaxation in amorphous systems was described in terms of the change in the fictive temperature (T_f) and was measured using the enthalpy relaxation endotherm in DSC. A second objective that emerged was a systematic study of the unusual pre- T_g thermal events that were initially observed during DSC heating scans after annealing the lyophilized glasses.

Structural relaxation during storage at a temperature between room temperature and T_g yielded either pre- T_g enthalpy recovery endotherms or overshoots at T_g , suggesting a wide distribution of structural relaxation times in lyophilized glasses. The presence of a minimum in the fictive temperature vs. annealing temperature data demonstrated the existence of an optimum annealing temperature for maximum structural relaxation during a fixed time period. Freeze drying process involves temperature and composition changes throughout the freezing and drying below T_g , which has no simple counterpart in a simple temperature history used in the TNM model. However, the modeling approach used was sufficiently accurate to predict the optimum annealing with reasonable accuracy. The results showed that the systems annealed at $T_g -15$ to $T_g -20^\circ\text{C}$ had the lowest molecular mobility.

Characterization of Mannitol Polymorphic Forms in Lyophilized Protein Formulations Using a Multivariate Curve Resolution (MCR)-based Raman Spectroscopic Method

Yong Xie, Amgen

We developed a novel multivariate curve resolution (MCR)-based Raman spectroscopic method for the characterization and quantitation of five known mannitol solid-state forms in lyophilized protein formulations. The multivariate quantitation method was based on second derivative Raman spectra of three anhydrous crystalline forms (α -, β -, and δ -mannitol), a hemihydrate and an amorphous mannitol form. The method showed a 5% quantitation limit of mannitol forms in lyophilized model protein formulations. X-ray powder diffraction data confirm the Raman results. This Raman method has been demonstrated for the application of monitoring and controlling of mannitol polymorphic forms in the lyophilized drug products during formulation and process development.

Potential Application of Pair Distribution Function Analysis to Measurement of Phase Separation in Freeze-Dried Solids

David A. Engers, Ph.D., SSCI Inc, An Aptuit Company

Recognizing limitations with the standard method of determining whether an amorphous API-polymer mixture is miscible based on the number of glass transition temperatures (T_g) using differential scanning calorimetry (DSC) measurements, x-ray powder diffractometry (XRPD) coupled with two computational methods have recently been reported to more fully assess miscibility in such systems (Newman *et al. J Pharm Sci* (2008), I. Ivanisevic, *et al. J Pharm Sci* (accepted)). In this presentation, mixtures of dextran-poly(vinylpyrrolidone) (PVP) at different molecular weights of the pure components and trehalose-dextran, prepared by lyophilization are examined. By the pair distribution function (PDF) method, phase separation is determined when the PDFs of the pure components taken in proportion to their compositions in the mixture are able to describe the PDF of the mixture. A lack of agreement between the PDFs for the prepared mixture and that calculated from the PDFs for the pure components indicates that the mixture with a unique PDF is miscible. For mixtures of dextran-PVP, the conclusions drawn from the PDF analysis were found to match well with the conclusions drawn from other techniques being used to assess the physical state of the mixture. From the PDF

analysis, indomethacin-PVP as an example of a miscible dispersion with a single T_g value measured for the mixture. In the case of the trehalose-dextran mixture, where only one T_g value was detected, however, PDF analysis clearly revealed phase separation. Since it has been suggested that DSC can not detect two T_g values when phase separation produces amorphous domains with sizes less than approximately 30 nm, this analysis indicates that the trehalose-dextran system is a phase separated mixture with a structure equivalent to a solid nanosuspension having nanosize domains.

Wednesday, June 17: Patent and Litigation Support for Pharmaceutical Solids

Pharmaceutical Patents – from invention to invalidation

This presentation will explore how pharmaceutical drugs are protected by patents and their underlying inventions within the UK and EU. Particular attention will be placed on:

- Identifying the invention(s) that resulted in a new pharmaceutical drug.
- Obtaining and maintaining adequate patent protection.
- Assessment of patent infringement.
- Counter arguments concerning patent invalidation.

Robert Whittock, PhD
Freshfields Bruckhaus Deringer LLP
robert.whittock@freshfields.com

Invention Strategies from the Laboratory to Litigation

Mark J. Feldstein, Ph.D.; Finnegan, Henderson, Farabow, Garrett & Dunner, LLP,
Washington, D.C.

The importance of pharmaceutical inventions is typically interdisciplinary. A new synthetic route, for example, is one piece of the complex therapeutic treatment puzzle, not an end of its own. Understanding the story of a pharmaceutical invention based on its context and practical significance can be critical to establishing patentability before the patent office, and defending validity during litigation. Together with an understanding of the requirements for patentability and the legal burden to prove patent infringement, taking a broader view of research objectives and developments can shape later patent claiming and enforcement strategies.

To this end, identifying the “inventive concept” of and problems solved by pharmaceutical research will be addressed. By focusing on the abstract inventive concept, patent claims can be directed more broadly than when focusing on the specific embodiments of the invention. A stronger case for patentability also results from understanding the invention in the context of the problems it solves. It will be shown how these considerations, taken together, can better protect the invention by eliminating avenues for others to design around.

Novelty and Inherent Anticipation as Criteria for the Patentability of Crystalline Forms

Aaron M. Raphael
O'BRIEN JONES PLLC
8200 Greensboro Drive, Suite 1020A
McLean, VA 22102

Obtaining patent protection on a newly-discovered solid form of a compound can be critical. One significant hurdle that patent applicants often have to deal with, particularly in the field of solid forms, is inherent anticipation. The discussion will examine several U.S. court decisions where inherent anticipation of a solid form was an issue, and will also consider ways to avoid a finding of inherent anticipation.

Lessons from U.S. Case Law to Guide Preparation, Prosecution, and Enforcement of Patents Covering Pharmaceutical Solid Forms

Lin J. Hymel, J.D., Ph.D.
Weingarten Schurgin Gagnebin & Lebovici, LLP
Ten Post Office Square
Boston, MA 02019

In addition to improving bioavailability and stability, novel solid forms of pharmaceuticals can be integrated into an appropriate patenting strategy to improve competitive position and extend market exclusivity. Patents directed to new solid forms, such as salts, solvates, or crystal forms, or to methods of making them, can be obtained as part of the IP portfolio surrounding an active pharmaceutical ingredient. Several U.S. court cases in recent years have pointed to pitfalls with this approach. Issues of inherent anticipation by earlier forms, obviousness, and patent claim scope and clarity have arisen. The outcomes of these cases will be discussed with a view to extracting lessons that can be utilized to improve successful outcomes in preparing and obtaining patents to new solid forms, such as which data to include, prior art to be aware of, and claiming strategy.

Impact of the European Commission Pharmaceutical Sector Inquiry

Mark Engelman (Barrister, BSc (Pharmacology))
Hardwicke Building
mark.engelman@hardwicke.co.uk

On 15 January 2008 the European Commission launched an inquiry into competition in the pharmaceuticals sector, in response to indications that there is delayed entry of generics and a reduction in the number of new medicines being brought to the European market. This presentation will focus on the preliminary report that was issued on 28 November 2008. Particular attention will be placed on:

- The remit of the European Commission Pharmaceutical Sector Inquiry.
- Whether generics have been delayed in entering the market.
- Sanctions and their impact on anti-competitive practices.

Wednesday, June 17: Solid-State Characterization Methods and Physical Stability of API Dispersions

Solid-State NMR Spectroscopy for the Examination of Drug Substance and Drug Product

Thomas Offerdahl, Boehringer Ingelheim

Solid-state NMR spectroscopy is a powerful method for evaluating both drug substance and drug product. Due to differences in the chemical shifts of the active ingredient and the excipients, the resulting NMR spectrum achieves excellent spectral resolution and detection limits of the active component when compared to other spectroscopic or thermal techniques. During the formulation process some highly energetic species can be formed which in turn could affect the overall stability of the formulation. Solid-state NMR spectroscopy was used to evaluate such a species using ^{13}C labeled aspirin. This processed material was added to bulk aspirin at a 2% (w/w) level and evaluated by solid-state NMR spectroscopy after being stored under highly stressed stability conditions. Spectral subtraction was used to isolate the labeled portion and thus characterize the processed material only.

Terahertz pulsed imaging as an analytical tool for tablet film coating

Thomas Rades, Louise Ho

School of Pharmacy, University of Otago, Dunedin, New Zealand

As a process analytical technique, terahertz pulsed imaging (TPI) exploits radiation that resides in the far-infrared region of the electromagnetic spectrum ($2\text{ cm}^{-1} - 120\text{ cm}^{-1}$). This radiation is able to penetrate through most pharmaceutical excipients allowing the non-destructive analysis of tablet coating quality [1]. TPI can detect tablet coating defects, coating thickness, uniformity and batch-reproducibility [2]. This technique has been validated with microscopy imaging with respect to measuring precision.

Moreover, terahertz parameters (coating layer thickness and terahertz electric field peak strength/TEFPS) have been successfully extracted from the terahertz images and applied to monitor a tablet film coating process during process scale-up [3]. We found that TPI offers means of fast measurement of coating density and thickness which are both important coating quality parameters in reflecting water permeability during the dissolution test [4].

In this talk, applications of TPI as a process analytical technique will be discussed with illustrations on how early abnormalities in coating layer thickness and coating density can be detected (during a coating process or process scale-up) and used to predict subsequent drug dissolution behaviour.

References

[1] Zeitler JA, Taday PF, Newnham DA, Pepper M, Gordon KC, Rades T, Terahertz pulsed spectroscopy and imaging in the pharmaceutical setting. *Journal of Pharmacy and Pharmacology* 59: 209 – 223 (2007).

- [2] L. Ho, R. Müller, M. Römer, K.C. Gordon, J. Heinämäki, P. Kleinebudde, M. Pepper, T. Rades, Y.-C. Shen, C.J. Strachan, P.F. Taday, J.A. Zeitler, Analysis of Sustained-Release Tablet Film Coats using Terahertz Pulsed Imaging. *Journal of Controlled Release* 119(3) (2007) 253-261.
- [3] Ho L, Müller R, Gordon KC, Kleinebudde P, Pepper M, Rades T, Shen YC, Taday PF, Zeitler J, Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance. *Journal of Controlled Release* 129: 78 – 87 (2008).
- [4] Ho L, Müller R, Gordon KC, Kleinebudde P, Pepper M, Rades T, Shen Y, Taday PF, Zeitler JA, Monitoring the film coating unit operation and predicting drug dissolution using terahertz pulsed imaging. *Journal of Pharmaceutical Sciences* (2009), IN PRESS.

Experiences Utilizing a Wide-Area Illumination (WAI) Raman Probe in Form Selection and Quantitation Studies

Paul K. Isbester, Ph.D.

Senior Research Scientist, Pharmaceutical Development

AMRI

- Review typical solid form screening workflow, analytical techniques, and requirements for substrates to be used for both solid generation and sample analysis.
- Introduce WAI Raman macroscopy and advantages for quantitative analysis.
- Describe opportunities available from utilizing the WAI Raman probe to minimize sample manipulation through a unique substrate design.
- Provide examples and some experiences utilizing WAI Raman macroscopy to identify or quantitate salts, polymorphs, and hydrates in drug substances and drug products.

Characterizing Phase Separation by SSNMR

Ales Medek, Vertex Pharmaceuticals

Phase (im)purity of API affects a range of physical and chemical properties such as dissolution rate or stability. However, phase purity is often difficult to assess, especially in cases where single crystal structure and reference pure phase standards are not available. The method of choice is differential scanning calorimetry (DSC). In many cases, DSC may not be sensitive enough due to either similar thermal properties of the different phases or due to the masking effects of other components in formulations. In contrast, SSNMR is a well suited technique to determine phase purity even in formulations. Examples of a range of SSNMR experiments from very routine to slightly more complex will be presented. The common feature of these experiments is the utilization of dipolar coupling to characterize spatial relations between the components of the different phases. It will be shown that the presence of fluorine atoms in API greatly facilitates such an analysis due to the fluorine high sensitivity and selectivity (no common excipients contain fluorine atoms).

Thursday, June 18: Amorphous Pharmaceutical Materials: Where Are We and What's Next?

Kinetics and Thermodynamics of Amorphous Pharmaceutical Solids

Lian Yu

University of Wisconsin – Madison

School of Pharmacy and Department of Chemistry

If a liquid is cooled without crystallization, it eventually becomes an amorphous solid (glass). Amorphous solids are a promising alternative to crystalline solids for delivering poorly soluble drugs. Besides cooling liquids, amorphous solids can be produced in other ways, including grinding, drying crystalline hydrates, and vapor deposition. Stability against crystallization is essential for amorphous drugs because crystallization negates their advantages. In this talk I will discuss a few issues concerning the structure, thermodynamics, dynamics, and crystallization of amorphous solids, with attention to their relevance to the stability of amorphous solids. I will discuss two mechanisms of fast crystal growth in amorphous solids (surface-enhanced and diffusionless crystal growth).

Chemical Reaction Kinetics & Mechanisms in Amorphous Solids

Bradley D. Anderson, H.B. Kostenbauder Professor, Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY

Despite the fact that most commercial drug products are solid dosage forms few formal methodologies are available to reliably predict drug degradation kinetics in solid formulations. In contrast, a comprehensive mathematical and conceptual kinetic framework does exist for solution formulations, from which it is possible to determine reaction order, characterize reactive intermediates, determine rate constants for various reaction steps and their pH and temperature dependence, and identify the contributions of various ionizable species to the overall reaction rate. Models that have been widely adopted for extrapolating data generated at early stages in the development of solution formulations such as simple zero- or first-order models or the Arrhenius equation are less useful for designing quality into solid-state formulations because the reaction kinetics are often non-linear both as a function of time and temperature. This presentation will focus on chemical reactions in amorphous glasses. Bearing in mind Angell's characterization of an amorphous glass as a liquid that has lost its ability to flow, one might reasonably expect that certain aspects of the solution reaction of a given drug molecule may carry over to reactions of the same compound in amorphous matrices. While diffusion-controlled decomposition reactions are seldom rate-determining in solution, molecular mobility plays a critical role in amorphous solid-state reaction kinetics. Spatial heterogeneity in dynamic relaxation processes and their time dependence, as well as possible heterogeneity in the distribution of drug molecules, water, and other formulation components may also be important. Finally, the multi-step nature of most chemical reactions relevant to pharmaceutical stability requires that one identify the rate-determining step and the reactive intermediates generated in order to predict both the rate of degradation but also the products formed. While the same reaction pathways may be available in both solution and the amorphous state, the pathways that dominate may shift

in response to differences in water content, reactant mobility, and proximity of reactant molecules.

Can milling really amorphize a compound? Can it also induce recrystallization?

Marc DESCAMPS, Jean-François WILLART

“Therapeutic Materials Group”, Bat P5, University LILLE1, 59655 Villeneuve d’Ascq Cedex, France. Mail: marc.descamps@univ-lille1.fr

The pharmaceutical industry has frequently recourse to milling operations in order to reduce the size of the particles. Milling is also used for more specific applications such as preparation of co-crystals or to produce enhanced surface properties by co-milling API with silicates for examples. These millings can however induce changes of the physical state of the product which may have harmful consequences for their stability

We will address questions such as these:

- Is it really possible to amorphize a crystal by milling? And the connected question: Does the amorphous-like compound obtained that way undergoes a calorimetric glass transition upon heating?

- Is the apparent amorphization simply the results of a local heating and quenching (hot point interpretation)?

- What is the possible role of amorphous intermediates in solid – solid conversions induced mechanically (also questionable for co-crystals formation)?

- What about the chemical stability in the course of solid state amorphization for a compound which undergoes chemical degradation at high temperature?

- What about modifying a glassy compound by milling it?

- How can a heuristic rationalization of the observed transformations be given?

Ref: Solid State Amorphization of Pharmaceuticals.

Mol. Pharmaceutics, 2008, 5(6), 905,920

Terahertz pulsed spectroscopy and other spectroscopic techniques to investigate amorphous pharmaceutical solids

Thomas Rades¹, Clare Strachan¹, Axel Zeitler²

¹*School of Pharmacy, University of Otago, New Zealand*

²*Department of Chemical Engineering, University of Cambridge, UK*

In this presentation I will initially give an overview of the various techniques to improve poor dissolution and solubility of drugs, including the formulation of glass solutions and amorphous suspensions by solvent methods, melt methods, mechanical activation, and melt-extrusion.

In the main part of the presentation I will focus on the various physico-chemical techniques to determine crystallinity / amorphousness classified according to the level at which they are probing the solid state, i.e. at the intramolecular level (e.g. spectroscopic techniques), the intermolecular level (e.g. thermal analysis and X-ray powder diffraction) or the bulk level (e.g. flow properties, solubility, dissolution rate). Besides vibrational spectroscopy (FTIR and Raman spectroscopy, especially in combination with multivariate analytical techniques) particular emphasis will be placed on modern

techniques such as terahertz pulsed spectroscopy (TPS) [1-5]. Examples for the identification and quantification of polymorphic mixtures, amorphous / crystalline mixtures and crystalline / liquid crystalline mixtures will be given.

References

- [1] Zeitler JA, Taday PF, Pepper M, Rades T, Crystallisation of amorphous carbamazepine studied by terahertz pulsed spectroscopy. *Journal of Pharmaceutical Sciences* 96: 2703 – 2709 (2007).
- [2] Zeitler JA, Taday PF, Gordon KC, Pepper M, Rades T, New insights into the solid state transition mechanism of carbamazepine polymorphs by time resolved terahertz pulsed spectroscopy. *ChemPhysChem* 8: 1924 – 1927 (2007).
- [3] Zeitler JA, Newnham DA, Taday PF, Threlfall TL, Lancaster RW, Berg RW, Strachan CJ, Gordon KC, Pepper M, Rades T, Characterisation of temperature induced phase transitions in the five polymorphic forms of sulfathiazole by terahertz pulsed spectroscopy and differential scanning calorimetry. *Journal of Pharmaceutical Sciences* 95: 2486 - 2498 (2006).
- [4] Strachan CJ, Taday PF, Newnham DA, Zeitler JA, Gordon KC, Pepper M, Rades T, Using terahertz pulsed spectroscopy to quantify pharmaceutical polymorphism and crystallinity. *Journal of Pharmaceutical Sciences* 94: 837-846 (2005).
- [5] Zeitler JA, Newnham DA, Taday PF, Strachan CJ, Pepper M, Gordon KC, Rades T, Temperature Dependent Terahertz Pulsed Spectroscopy of Carbamazepine. *Thermochimica Acta* 436: 70-76 (2005).

X-RAY SCATTERING STUDIES ON NANO CRYSTALLINE AND AMORPHOUS MATERIALS USING HIGH-ENERGY X-RAYS ON A LABORATORY SYSTEM ***D. Beckers, M. Gateshki and J. te Nijenhuis, PANalytical B.V., Almelo, The Netherlands***

Recent interest in nano materials has increased the need to analyze structures on a local (nano) scale. However, the atomic structures of nano structured and amorphous materials are not accessible by conventional methods used to study crystalline materials, because of the short ordering range in these materials. One of the most promising techniques to study nano structures using X-ray scattering is by using the total scattering (Bragg peaks and diffuse scattering) from the samples and the pair distribution function (PDF) analysis. The pair distribution function provides information of finding atoms separated by a certain distance. This function is not direction dependent; it only looks at the absolute value of the distance between the nearest neighbors, the next nearest neighbors and so on. The method can therefore also be used to analyze non-crystalline materials.

We have developed the application of PDF analysis on a standard laboratory system employing an X-ray tube with a silver anode as X-ray source. Previous measurements have shown that meaningful results have been achieved on various samples of different nature –crystalline, nano crystalline, amorphous solid and liquid.

In this study we compare PDF calculations on different amorphous materials. As an organic model substance we used lactose. We present results on the monitoring of crystallization processes of freeze- and spray-dried lactose as well as the analysis of lactose of different constitution (alpha-lactose monohydrate / beta-lactose mixtures). After crystallization the quantitative results from the PDF refinement are in good agreement with the results from Rietveld refinement of the XRPD data.

Thursday, June 18: Detecting Process-Induced Transformations in Solid-State Formulations

Detecting Process Induced Transformations in Crystallisation

Thomas Rades, FangTian

School of Pharmacy, University of Otago, New Zealand

In an aqueous environment, polymorphic forms I, II and III of carbamazepine all convert to the dihydrate. This study investigated the conversion of each polymorphic form individually and of a mixture of forms III and I to the dihydrate [1, 2]. Two batches of form I with different crystal morphology were used. Samples were dispersed independently in water at 23 ± 1 °C and recovered at various time points varying from 10 to 210 min.

Scanning electron microscopy, X-ray powder diffraction and Raman spectroscopy were used to characterize the initial polymorphic forms and the recovered samples after 210 min. Raman spectroscopy combined with partial least squares analysis was used to generate quantitative models of binary and ternary mixtures of the different polymorphic forms with the dihydrate.

On the basis of these models the conversion kinetics of the polymorphic forms I, II and III were characterized. First order kinetics with an unconverted portion were used to model the data ($R^2 \geq 0.95$). The unconverted portions ranged from 16 % to 51 % after dispersion for 210 min.

The conversion kinetics were similar between polymorphic forms with comparable crystal morphology, but differed significantly between batches of the same polymorph (form I) with different crystal morphology. Furthermore, the conversion of forms III and I in the aqueous suspension was not influenced by the presence of the other polymorph when dispersed together.

References

- [1] Tian F, Sandler N, Aaltonen J, Lang C, Saville DJ, Gordon KC, Strachan JC, Rantanen J, Rades T, Influence of polymorphic form, morphology and excipient interactions on the dissolution of carbamazepine compacts. *Journal of Pharmaceutical Sciences* 96: 584 – 594 (2007).
- [2] Tian F, Zeitler JA, Strachan CJ, Saville DJ, Gordon KC, Rades T, Characterizing the conversion kinetics of carbamazepine polymorphs to the dihydrate in aqueous suspension using Raman spectroscopy. *Journal of Pharmaceutical and Biomedical Analysis* 40: 271-280 (2006).

Detecting Process Induced Transformations in Drying

Clare Strachan, University of Otago, New Zealand

Drying is a pharmaceutical unit operation in which a pharmaceutical material in the presence of a solvent is subjected to changing temperatures and humidities. The loss of solvent, together with changing environmental conditions, make the operation ripe for inducing solid-state transformations (commonly termed process induced transformations (PITs)). PITs that may occur include polymorphic transformations, desolvation (including dehydration), and changes in degree of crystallinity. Such changes have caused drug product failures during dissolution testing. Traditional monitoring methods offer very limited insight into the existence and degree of transformations, let alone any insight into their mechanisms. In the last few years, methods that probe the molecular level, such as vibrational spectroscopy have been introduced to detect, quantify and understand PITs during drying. This talk will cover recent work by the presenter and other researchers on PITs during drying, with a focus on recently introduced analytical methods to investigate PITs during drying and methods that may be used to control the transformations.

Detecting Process Induced Transformations in Milling

Thomas Rades, Norman Chieng

School of Pharmacy, University of Otago, New Zealand

Pharmaceutical solids often exhibit polymorphism, which leads to different physicochemical properties. Therefore the understanding, manipulation and control of polymorphic forms are essential aspects for product development in the pharmaceutical industry. Ranitidine HCl has been reported to exist in two forms, termed forms 1 and 2. This study reports the effect of milling time and temperature on the polymorphic stability of ranitidine hydrochloride using an oscillatory ball mill [1,2]. The samples were characterized using XRPD and DSC. Transformation of form 1 (XRPD peaks at 17.0, 21.8 and 24.9 °2θ) to form 2 (XRPD peaks at 20.2 and 23.5 °2θ) via amorphous drug was consistently found at ambient temperature. However repeated experiments showed variability in both the solid temperature and the extent of polymorphic transformation even though a halo (XRPD) was consistently observed. In warm room milling, the transformation rate was faster. Milled form 1 samples (120 minutes) yielded a majority of form 2 and some form 1 (XRPD; 21.8 and 24.9 °2θ) peaks. This finding could be attributed to recrystallization of nuclei of both forms at high solid temperature. When samples were milled in the cold room, XRPD showed both form 1 and 2 became amorphous. A glass transition (T_g) was clearly observed between 12 to 30°C, and recrystallization temperature (T_c) was usually between 40 to 60°C. The recrystallization enthalpies recorded in the cold and warm room samples were between 60 to 80 J/g and 30 to 55 J/g respectively. Interestingly, both T_g and T_c peaks show a shift to a lower temperature as milling time increases. In all conditions of milling, one-way transformation of ranitidine HCl form 1 to 2 is observed. Form 2 did not transform to form 1. The transformation process was thought to be initiated when the order of form 1 crystals was disrupted by the energy impact from the balls, followed by the production of amorphous drug combined with formation of form 2 nuclei. With continued milling, the

heat generated provides the propagation factor for crystallization. From our observations, sample temperatures below T_c favoured the amorphous form; temperatures close to T_c led to complete transformation while a solid temperature higher than T_c resulted in significant conversion to form 2 combined with slight recrystallization of form 1.

References

- [1] Chieng N, Rades T, Saville D, Formation and physical stability of the amorphous phase of ranitidine hydrochloride polymorphs prepared by cryo-milling. *European Journal of Pharmaceutics and Biopharmaceutics* 68: 771 – 780 (2008).
- [2] Chieng N, Zujovic Z, Rades T, Saville D, Effect of milling conditions on the solid-state conversion of ranitidine hydrochloride form 1. *International Journal of Pharmaceutics* 327: 36 - 44 (2006).

Detecting Process Induced Transformations During Dissolution

M. Savolainen

Department of Pharmaceutics and Analytical Chemistry, Faculty of Pharmaceutical Sciences, University of Copenhagen, Denmark

In order for an orally administered drug to be absorbed and effective, the drug has to first dissolve in the gastrointestinal tract. Thus, changes in the dissolution behaviour of a drug can affect the performance of an oral solid dosage form. The dissolution rate depends on the properties of the solid dosage form as well as the dissolution medium. Any changes in the formulation during the manufacturing or storage such as changes in the physical properties of the drug or the excipients can alter the dissolution performance. The dissolution behaviour can also be affected by changes occurring in the dosage form during dissolution. The dissolution rate can for example decrease if a drug that is administered in a metastable form transforms to a more stable form when in contact with the dissolution medium.

Dissolution testing is a commonly used method in both product development and quality assurance. The dissolution behaviour of a solid dosage form is studied by immersing the dosage form into liquid and analyzing dissolved drug concentration as a function of time. Nowadays, UV imaging can be used to visualize the changes happening in the solution during dissolution. However, analysis of the dissolution medium gives no direct information about the changes occurring in the solid dosage form. To understand the phenomena happening during dissolution, the dissolution testing has to be combined with additional approaches such as *ex situ* x-ray diffraction or spectroscopic analysis. Raman spectroscopy can be used *in situ* to analyze the changes in the solid-state of the sample during dissolution. By combining the analysis of both the solution and the solid state, a deeper insight into the dissolution process can be obtained.

Imaging of solid dosage forms during dissolution using coherent anti-Stokes Raman scattering (CARS) microscopy

Clare Strachan, University of Otago, New Zealand

Coherent anti-Stokes Raman scattering (CARS) microscopy is a relatively new analytical technique that shares many similarities with Raman microscopy. However, CARS microscopy is much more rapid allowing real time imaging, it is not susceptible to interference from single photon fluorescence, and a slightly higher spatial resolution is possible. In this talk, CARS microscopy will be introduced as a tool for the chemical imaging of oral solid dosage forms during dissolution testing. An example will be presented where CARS microscopy was used to visualize the changes in lipid-based oral dosage forms containing theophylline anhydrate during dissolution in real time. The drug release from the dosage form matrix was imaged with a spatial resolution of about 1.5 μm . In addition, a solid-state transformation of the drug during dissolution was observed. The potential of CARS microscopy in solid-dosage form development will be discussed.

Characterization and stabilization of amorphous pharmaceutical solids

Fang Zhang, Fang Tian, Marja Savolainen, Dorothy Saville, Jukka Rantanen, Thomas Rades

Amorphous solids show enhanced solubility and dissolution rate but lower physical and chemical stability than those of the corresponding crystalline form. The amorphous form tends to transform to the more stable crystalline form during processing and storage. The formation of a solid dispersion using a carrier is one of the methods to improve the stability of amorphous solids. An example of stabilization of amorphous simvastatin will be given in this talk.

Quench cooled amorphous simvastatin (QC) and cryomilled amorphous simvastatin (CM) were prepared. Both amorphous forms showed improved solubility compared to the crystalline drug. Moreover, a lower solubility was observed for CM than QC indicating a difference in the internal structure. XRPD measurements of recovered samples from buffer confirmed that CM recrystallized faster than QC which explained the difference on solubility. The two amorphous simvastatin forms tended to convert back to the crystalline form during storage with different recrystallization rates. It was found that QC was more physically stable than CM.

An amorphous copolymer, polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA64) was chosen to stabilize amorphous simvastatin by forming a solid dispersion. Quench cooling the melt of physical mixture of crystalline drug and copolymer (SD_{qc}) resulted in an amorphous solid dispersion which showed improved stability compared to the neat amorphous drug. Another preparative method was cryomilling the physical mixture of QC and copolymer (SD_{cm}). With increased milling time (30 min), the physical mixture transformed from a two phase to one phase solid dispersion. The sample after short time milling (10min), which was still a two phase mixture, showed dramatic enhanced

stability.

This study showed that preparation methods influence the physical stability of amorphous simvastatin. Adding a carrier to form solid dispersions by different methods proved to be effective in stabilizing the amorphous drug.