

Simultaneous detection of dissolution and solid-state properties of solid dosage forms

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A solid phase transformation from a metastable to a stable form can take place when a solid is in contact with a solvent, for example during pharmaceutical manufacturing processes and also dissolution testing. Such transformations can cause changes in the physicochemical properties of the drug. These changes can have an effect on the dissolution behaviour, and traditionally, a change in the intrinsic dissolution rate has been used as an indication of a solid-state change during dissolution. However, such solid phase information is indirect and can be due to other phenomena e.g. a change in the surface area. In this talk, examples of solid phase transformations during dissolution testing and analysis thereof will be given.

To better understand the dissolution process, dissolution rate (concentration of the dissolution medium) and solid phase composition of the dissolving solid were measured simultaneously. The concentration of the dissolution medium was measured with UV-vis spectrophotometry, and in-situ Raman spectroscopy was used to detect solid-state changes in the solid sample during dissolution testing. Different calibration methods were used to extract qualitative and quantitative information, namely univariate and multivariate methods, and the changes in the dissolution rate were attributed to the occurring solid-state phenomena.

By measuring the solid state of the dissolving sample in situ during dissolution testing, direct molecular level information from possible changes can be obtained and used to explain anomalous dissolution behaviour. As a result, a deeper understanding of the solid phase transformations during dissolution is achieved.

Jaakko Aaltonen is a Postdoctoral Fellow in the School of Pharmacy, University of Otago, New Zealand. He received his PhD in pharmaceutical technology from the University of Helsinki, Finland under the supervision of Professor Jukka Rantanen. Jaakko's research area is the solid state of drugs, with special interest on real-time analysis of processing-induced solid phase transformations using spectroscopy and chemometrics.

EXCIPIENT / API GLASS SOLUTIONS: IMPACT OF THE NATURE OF THE EXCIPIENT ON THE ULTIMATE STABILITY

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Pharmaceutical compounds are mainly in the solid state and can adopt either a crystalline or an amorphous form. Newly developed active pharmaceutical ingredients (API) are often poorly soluble in water. Consequently, the use of amorphous API becomes of great interest because these forms generally have enhanced biopharmaceutical properties like solubility and dissolution capability. The main drawback is their intrinsic physical instability compared with crystalline solids. The physical stability notion is strongly related with the value of the glass transition temperature (T_g). As a rule of thumb, more the T_g value is high compared with the room temperature (it is usually believed that the system should be physically stable at 50°C below T_g), more the amorphous compound is expected to be stable at room temperature. Consequently, a strategy is to find a formulation enabling to increase the glass transition of samples. One means is the formation of amorphous solid solutions between pharmaceutical excipients characterised by high glass transition temperatures and an API. These glass solutions can be performed by the classical melting/quenching process but also by spray drying, by extrusion or by co-milling. Among these processes, the melting/quenching and extrusion processes can be difficult to apply for materials which chemically degrade on heating. The main advantage of amorphizing by co-grinding is that it is a green process which doesn't need the use of solvent. It has been further demonstrated that milling amorphization is a really low temperature solid state process. It avoids the high temperature chemical degradations. An example is that of lactose which does not show any sign of mutarotation and caramelization [1].

In this presentation, we consider the formulation of an API currently in development which is water insoluble in the crystalline state.

This API can be vitrified by milling but, even 50°C below T_g , the glassy compound is not stable and slowly crystallizes towards a metastable phase.

We present the results of a stabilization study of this API by co-milling this compound with a pharmaceutical polymeric excipient and a sugar excipient both having higher T_g values than the API.

In both cases homogeneous glass solutions are formed. However important differences are observed with regard to the Gordon-Taylor plots and also with regard to the ultimate stability of the glass solutions. These points will be developed during the talk.

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EDUCATION: PhD IN MATERIAL SCIENCE

- 2005-2008 PhD in Material Science in collaboration with the SANOFI-AVENTIS group. The PhD takes place at the **University of Sciences and Technologies of Lille (USTL)** in the **Laboratory of Dynamics and Structure of Molecular Materials (LDSMM)** and is expected to be defended in October 2008. Thesis title: *Amorphous pharmaceutical compounds: milling, co-milling and stabilization*
- 2005 Engineering diploma from the **Superior National School of Chemical Industries (ENSIC)** of Nancy (post graduate level equivalent)
Master of Science "Process Engineering"

PROFESSIONAL EXPERIENCE

- 02/2005-09/2005 **Training period** at the ENSIC in the Laboratory of Macromolecular Physics Chemistry (LCPM)
Title: *Nanoparticulate systems with dextran to encapsulate API: synthesis and characterization*
- 07/2004-11/2004 **Industrial training period** in organic chemistry synthesis in the research area of the SANOFI-AVENTIS group

EXPERIMENTAL SKILLS

- Process: **Ball milling, jet milling**
- Thermal analysis: **Differential Scanning Calorimetry (DSC), Modulated Temperature DSC (MTDSC), TGA (Thermo Gravimetric Analysis)**
- Structural analysis: **X-Ray Powder Diffraction (XRPD)**

PUBLICATIONS

The Glass Transition of Molecular Driven Materials

M. Descamps, J.F. Willart, A. Aumelas

AIP Conference Proceedings 982 (2008) 53-61

The 5th International Workshop on Complex Systems 25-28 September 2007 Sendai (Japan)

Nanoparticles of hydrophobically modified dextrans as potential drug carrier systems

A. Aumelas, A. Serrero, A. Durand, E. Dellacherie, M. Leonard

Colloids and Surfaces B: Biointerfaces 59 (2007) 74-80

Utilization of dielectric Techniques in Pharmaceutical R&D: Application to the study of the amorphous phases and solid dispersions.

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It is known that the active pharmaceutical ingredients (API) as well as excipients are rarely of perfect crystallinity i.e. characterized by a long range order entirely devoid of any crystalline defects or amorphous phases. In addition to that, every manufacturing process (granulation, drying, compression etc...) involved in the preparation of a pharmaceutical drug product (DP) contributes to the loss of crystallinity. The pharmaceutical consequences are well-known: change in the mechanical properties, modified physico-chemical reactivity, enhanced solubility and the kinetics of dissolution etc... Regarding the amorphous phase properties, they can be seen as a disadvantage in terms of stability, but may provide a definitive advantage as far as the kinetics of dissolution are concerned and, ultimately, the bioavailability of the API. During the last two decades, a lot of publications have highlighted the interest of researchers for developing amorphous phases and solid dispersions to improve the bioavailability of new chemical entities, which have a trend to become increasingly less soluble.

For all these negative and positive reasons, there is a need to develop more and more physical techniques for assessing the crystallinity or conversely the amorphous content of materials. XRPD, ssNMR, IR, NIR, Raman and Terahertz Spectroscopy's, Microscopy and Calorimetry are known to be efficient tools in this domain. An approach that may be less-known than those cited above utilizes the dielectric properties of the materials which actually reflect the intra and inter molecular mobility of the molecules of which they are constituted.

In this presentation, two techniques will be described: Thermo-stimulated currents (TSC) [1] and dynamic dielectric spectroscopy (DDS) [2]. In both cases, a sample of the powder to be studied is introduced within the plates of a capacitor, to which an electrical field is applied and this may be either constant (TSC) or sinusoidal (DDS). This leads to the polarization of the electrical dipoles exhibited by the molecules which subsequently gives a macroscopic polarization. It will be shown during the lecture that these complementary dielectric techniques can provide information about the characteristic relaxation times τ_1 of the different kinds of molecular mobility, in addition to their behaviour as a function of temperature. Without entering into a rigorous mathematical treatment, it is easy to understand that this characteristic time τ_1 is related to the energetic interaction between the relaxing entities and their lattice, and will be affected by the crystalline and/or the amorphous character of the latter. During the lecture, after having introduced the principles of these two techniques, brief examples will be given of the possible applications:

- Crystallinity determination of an API,
- Comparative dielectric mapping of a material as crystalline or as an amorphous entity.
- Physical Status of an API in a formulation obtained by dissolving it in a molten hydrophilic polymer.

- Literature:

[1] C.Lacabanne and M.Bauer, Thermo stimulated Currents: A tool for Pharmaceutical Science, American Pharmaceutical Review, 10(2), and 2007, 66-72.

[2] J.Menegotto, M.Bauer, J.Alié, C.Mayoux, TSC and DDS, Solid State Characterization of Pharmaceuticals, Chapter 7, edited by Angelina & Marek Zakrzewski, (2006), assa® Inc. Danbury, Connecticut, published by Pergamon.

BIOGRAPHICAL NOTES

Dr Michel BAUER was born in 1943 and graduated in 1967 from l'Ecole Supérieure du Laboratoire in Paris. He received his Ph.D in 1972 from the Faculté des Sciences Paris VI in France and was awarded a Doctor of Sciences from the University of Toulouse (1987 – option Matériaux). After having worked in pharmaceutical R and D (Pharmuka, Pierre Fabre Laboratory) for 39 years, which included 16 years as world-wide Director of the International Analytical Department at Sanofi-Synthélabo, he now occupies a position of CMC scientific advisor to the International Direction for Development of Sanofi-Aventis. He is member of the French Pharmacopea and consulted as an Expert by the European Pharmacopea.

Michel is particularly interested in all domains concerned with analytical sciences and the statistical evaluation of data. Another discipline that is of special interest to him is the study of the solid state, in particular with respect to its importance in pharmaceutical development.

He has published articles about a range of subjects, including liquid chromatography, polymorphism, dielectric techniques, technology transfer, implementation of impurity specifications during development, dissolution, residual solvents etc... and has been invited to speak at different congresses and symposia concerning these disciplines. He gives courses in France on several topics including spectroscopic techniques, polymorphism, the amorphous phase, impurities and residual solvent in the framework of IFIS (Institut de Formations des Industries de Santé) in addition to giving lectures at schools of science and engineering.

USING XRF SPECTROMETRY FOR QUALITY CONTROL OF DRUG PRODUCTS

Detlef Beckers, Ian Campbell, Lieven Kempnaers, PANalytical B.V., Almelo, The Netherlands

X-ray fluorescence spectrometry (XRF) is a non-destructive technique with high elemental sensitivity and simple or no sample preparation. XRF can be used in the production and quality control to quantify major and minor elements in fillers, binders, lubricants, and other excipients. Traces of toxic compounds in excipients and final drug products can be detected and quantified down to ppb levels. Also traces of catalyst residues in final drug products can be quantified with high precision using XRF.

This paper presents a few examples for typical pharmaceutical applications like fingerprinting GUMs using a benchtop EDXRF spectrometer and screening catalysts residues in pharmaceutical end products using a high-end EDXRF spectrometer.

General Use Materials (GUMs) used in manufacturing are routinely analyzed by time consuming and complex instruments (such as titration and ion chromatography) for identity testing. It is desirable to simplify and speed up this process and make it more efficient. A PANalytical MiniPal 4 EDXRF spectrometer was evaluated for this purpose using several inorganic compounds commonly used on the GUMs list. This instrument is a relatively small, simple, low cost spectrometer. The XRF technique is inherently quick and simple, and requires virtually no sample preparation. The compounds tested can be identified qualitatively by comparison with reference spectra but this requires some expert knowledge of interpreting the spectra. The main technical objective of the evaluation was to establish the basis of a method that could reliably distinguish between compounds using a quantitative approach. This method should be suitable for relatively inexperienced operators with very little need to interpret the spectra. The evaluation also included the general suitability of the technique to a manufacturing environment.

XRF can also be used for screening and monitoring pharmaceutical end products concerning catalysts residues. Typical amounts for catalysts in end products should be below 10 $\mu\text{g/g}$ and can be quantified at even lower concentration level with high precision.

DETERMINATION OF SPECIFIC SURFACE AND PARTICLE SIZE DISTRIBUTION BY SMALL ANGLE X-RAY SCATTERING

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The Small-Angle X-ray Scattering (SAXS) technique allows structural analysis of amorphous and crystalline materials on a mesoscopic length scale ranging from approx. 1 - 150 nm. Powders or dispersions of organic and inorganic nano particles can be characterized with respect to their particle size distribution and inner structure. In case of porous materials the specific inner surface and pore size may be determined. The specific surface – e.g. between amorphous and crystalline domains - is also an important property of pharmaceutical compounds. It determines the thermodynamic stability of the material and therefore the dissolution properties of the compound.

We present SAXS measurements on a conventional X'Pert PRO X-ray diffractometer using a line focus in combination with collimating optics. Experimental results could be achieved within ca. 10 to 30 minutes.

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Ph.D. in physics at the Research Center Jülich, Solid State Physics Institute, Germany in 1996.

Joined PANalytical B.V. in 1996 (Philips Analytical B.V. at that time) in the position of project manager XRD (X-ray diffraction). At that time responsible for the management of hardware development projects and (pre-) development of new optical XRD modules.

Currently in the position of Market Segment Manager Pharmaceuticals, Food and Life Science with the responsibilities for applications and business development and the co-ordination of the pharmaceutical, food and life science market activities within the company.

**Application and development of NMR crystallography on pharmaceutical solids at natural isotopic abundance:
Utilization of ^1H - ^1H and ^1H - ^{13}C (^{15}N) dipolar couplings for structure refinement**

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Problems involving polymorphism of pharmaceutical compounds are widespread and cause great concern to industry. Unexpected transformations sometimes occurring during processing and storage can produce problems for patent establishment and protections that can result in complicated patent litigations. That is why any tool for precise solid-state characterization and recognizing polymorphs and solvates are a vital requirement.

NMR crystallography is an emerging discipline that is complementary to the traditional X-ray crystallography. Consequently in some attempts the diffraction techniques were extended and the information given by solid-state NMR was directly incorporated into the existing protocols for trial structure elucidation (Rietveld refinement). Basically this approach is based on calculation of shielding parameters using the fully periodic Gauge Including Projector Augmented Wave method and the current testing of CASTEP code is very promising. Unfortunately it has been shown that for the systems having two or more molecules in the asymmetric units and consisting of more than ca. 20 carbon atoms per molecule the CASTEP computation cannot be carried out on the complete crystal structure. That is why additional extension of the range of application of NMR crystallography toward larger systems would be valuable.

Obviously the additional information that may help in the crystal structure refinement is provided by dipolar couplings, the measurements of which yield direct information on internuclear distances. The requirement of labeled materials, however, renders application of standard ^{13}C - ^{13}C (^{15}N) techniques impractical for solution of some academic and industrial problems where synthetic effort necessary to selectively or uniformly label the molecules can be nearly daunting. That is why we focused our attention on the detection of dipolar coupling contacts involving ^1H atoms (^1H - ^1H (^{13}C , ^{15}N)). Recent advances in NMR spectrometers and probeheads design improved sensitivity and resolution ^1H frequency dimension in such way that a basic experimental concept of heteronuclear and homonuclear correlation involving new homodecoupling sequences (FSLG, PMLG, DUMBO, e—DUMBO etc.) can be successfully applied to acquire 2D ^1H - ^{13}C correlation spectra with resolution sufficient to separate correlation signals.

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6. Brus J., Jegerov A., THROUGH-BONDS AND THROUGH-SPACE SOLID-STATE NMR CORRELATIONS AT NATURAL ISOTOPIC ABUNDANCE: SIGNAL ASSIGNMENT AND STRUCTURAL STUDY OF SIMVASTATIN, *J. PHYS. CHEM. A*, 108(18); 3955, (2004).
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René CÉOLIN

born on the 10th of June 1944, in Paris.

Member of the National Academy of Pharmacy (France),
Corresponding member of the Royal Academy of Pharmacy of Catalonia (Spain),

Cursus:

Faculty of Pharmacy –Paris (1961-67): Diploma in chemistry (pharmacy),

Faculty of Science –Paris 1969: Post-graduate diploma in inorganic chemistry.

Faculty of Science –Paris (Pierre et Marie Curie University) 1974: PhD in physical science.

Positions:

House biochemist at the Hospitals of Paris (1965-69),

Assistant then senior lecturer (general chemistry) at the Faculty of Pharmacy –Paris (67-77),

Full Professor (general and inorganic chemistry) at the faculty of Pharmacy of Tours (77-94)

Full Professor (physical chemistry) at the Faculty of Pharmacy of the Paris-Descartes University (1994 - present).

Associate researcher of the Laboratoire Léon Brillouin (CEA, CEN Saclay).

Invited researcher at the Universitat Politècnica de Catalunya (2000, 2002, 2003, etc..., 2008).

Fluctuating interest in:

-Inorganic solid-state chemistry (Rare-Earth sulphides and arsenides),

-Local order of inorganic « covalent » liquids,

-Molecular solid-state physical chemistry (drugs and fullerenes),

-Phase diagrams, crystalline polymorphism and equilibrium thermodynamics of systems with non-negligible vapour pressure.

Publications

about 180 papers, among which:

Structure cristalline de l'oxysulfure de cérium et de bismuth CeBiOS₂.

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Polymorphism of even-numbered-carbon atom *n*-alkanes revisited through topological p-T diagrams.

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Abstract for presentation at: IWPCPS®-10, Tenth International Workshop on Physical Characterization of Pharmaceutical Solids, June 8-14, 2008, Hotel Residenzschloss Bamberg Bamberg, Germany.

To be presented by: Dr V. Brett Cooper, Merck Sharp & Dohme, Development Laboratories, Hertford Road, Hoddesdon, Herts EN11 9BU, Tel +44 1992452264.

The use of amorphous compounds in drug discovery and early development.

The amorphous state has advantages over the crystalline state that can lead to enhanced performance, increased exposure and better pharmacokinetics. However, there are several disadvantages and risks associated with the use of amorphous material. This presentation will discuss the use of amorphous compounds at different stages of discovery and early development, highlighting some of the issues that may be encountered.

Diversity: A Principle for Efficient Solid Form Screening

The requirement to identify suitable solid forms of drugs earlier in the development process, where the quantity of material available for experiments is limited, has influenced the nature of solid form screening in recent years. This requirement, along with the material limitations, has focused the emphasis on finding the most effective experimental designs to work within a limited number of experiments.

Maximum diversity in experimental design, including the range of crystallization methods employed as well as solvent types and crystallization conditions, will maximize the number of solid forms discovered within the limitations of solubility space, compound properties and the availability of material. Improved methods of preliminary solubility determination, in terms of both accuracy and speed, enable the above limitations to be defined more accurately and the range of acceptable conditions to be determined as input to the experimental design.

The advantages of diversity in experimental design include:

- A maximum range of conditions tailored to the compound in question, with the minimum usage of material.
- Experimental designs can focus on the most relevant issues of the investigation, for example, selection of forms suitable for further development.
- Different crystallization and work-up methods for future process development can be identified and assessed.
- The probability of finding solid forms will be maximized for the number of experiments performed.

A range of different crystallization methods that can be applied in screening for salts, polymorphs and co-crystals will be discussed, together with ways of selecting suitable conditions. The presentation will highlight case studies of the application of efficient screens designed according to the principles above, both to identify optimum solid forms for development and to overcome specific problems associated with previous, non-optimal form selections.

René Dam

Dr Dam received his PhD in organometallic chemistry from the Vrije Universiteit Amsterdam in 1997. He then went to UCLA to do a post-doc with Professor Fred Wudl in polymer chemistry and physical-organic chemistry, after which he returned to the Netherlands. For the past 6 years he has been working for several CRO's to the pharmaceutical industry. Currently he is employed by Avantium Technologies BV in Amsterdam, the Netherlands and responsible for the Technology Development of the Pharma Business Unit.

The solvate formation of Ethinyl estradiol - a rational insight

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A detailed investigation of pseudo-polymorphism of Ethinyl estradiol, an estrogen analogue, which shows remarkable solvate forming abilities, was performed.

Ethinyl estradiol is a synthetic estrogenic steroid that has therapeutic uses (e.g. oral contraception) and is one of the most potent estrogens. It has a common steroid ring skeleton with an ethinyl substitution at c17 which greatly increase oral potency by inhibiting first-pass hepatic metabolism.

The compound is known to have different pseudo-polymorphic forms (solvates), whereas other similar structures do not show pseudo-polymorphism. In this study several (new) solvates of Ethinyl estradiol were found and characterized by single-crystal X-ray diffraction. All forms have been compared to each other with respect to the crystal packing and hydrogen bonding behavior. Ethinyl estradiol forms solvates mainly with solvents having H-bond accepting or with both accepting and donating propensity. The solvates formed show a remarkable difference in H-bonding patterns, which are shown and described here. Differences are observed in the dimensions of the H-bond network and in the packing patterns of the molecules.

Compounds similar to Ethinyl estradiol, like Estradiol, show the same behavior of forming solvates, whereas other similar structures, like Mestranol, do not. The structures and crystal packings of such compounds are analyzed and a comparison with Ethinyl estradiol is made.

Applying Lessons from Litigation to Defining the Pharmaceutical Invention

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Current trends in patent litigation, including the U.S. Supreme Court's recent changes to the law of obviousness standard, appear to have heightened the standards for successfully enforcing pharmaceutical patents. This issue is particularly pertinent for patents directed to compositions and methods based on preexisting active ingredients. These litigation trends, together with court decisions addressing what is and what is not sufficient proof of infringement, can provide guidance to early stages of both product development and the patenting process to define the pharmaceutical invention.

Mark J. Feldstein, Ph.D.

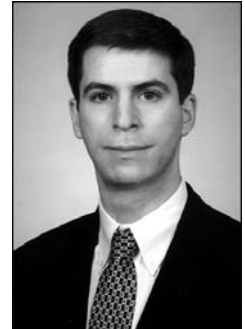
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Mark Feldstein is an patent attorney with the Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, focusing on U.S. district court litigation, primarily concerning the enforcement of U.S. patent rights and trade secret issues. He also maintains an active patent prosecution practice, preparing and prosecuting U.S. patent applications on behalf of domestic and foreign clients. In addition, Dr. Feldstein provides counseling to clients with opinions and strategic guidance on infringement, validity, enforceability, and clearance matters.

Dr. Feldstein's practice encompasses a range of technologies, including pharmaceuticals, polymers, small molecule chemistry, nanotechnology, optics, and medical and analytic devices. His proficiency in these areas is supported by extensive research experience. For example, prior to his legal career, Dr. Feldstein conducted research in ultrafast laser spectroscopy and scanning probe microscopy analysis of metallic, nano-structured, and conducting polymeric systems. As a National Research Council Post-Doctoral Associate, Dr. Feldstein also designed and developed optically transduced biosensors and related signal processing software for the U.S. Naval Research Laboratory.



In addition to his law practice at Finnegan Henderson, Dr. Feldstein is an Adjunct Professor of Law at Georgetown University Law Center, teaching courses in patent prosecution practice and IP management. He also speaks regularly to national and international audiences of both attorneys and scientists on issues of patent litigation and prosecution.

Dr. Feldstein's pro bono activities include military veteran representation before the United States Court of Appeals for Veterans Claims. Professionally, Dr. Feldstein is on the steering committee of the IP Focus Group for the American Association of Pharmaceutical Scientists (AAPS) and maintains active memberships in several legal and technical professional organizations.

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Education:

Georgetown University (J.D., *cum laude*, 2001); University of Pennsylvania (Ph.D., Physical Chemistry, 1997); University of Chicago (M.S., Chemistry, 1992); The George Washington University, (B.S., Chemistry; B.A., Philosophy, *cum laude*, 1991).

Solid-state method development and validation: The Rationale of a Staged Approach. What is necessary from a "submission" point of view related to the different stages of development?

Cornelia Field, MS

Boehringer Ingelheim Pharmaceuticals, Inc.

Appropriate characterization and understanding of the solid-state properties is vital to the successful development of drug substance and drug product. Usually in the early phase of development, results from techniques used to characterize the solid-state properties are interpreted qualitatively rather than quantitatively. When it becomes apparent that the control of a solid-state property is necessary because it has a significant impact on the performance and/or safety it is necessary to develop and validate an appropriate quantitative method. Solid-state method development and validation are often difficult because the “typical” validation parameters differ from those used in chemical purity analyses. The following presentation proposes a strategy to a staged approach for the method development and validation of solid-state properties, along with some examples, with emphasis on what is really necessary for submission documents

Magnetic Resonance Studies of Pharmaceutical Delivery Systems

Lynn F. Gladden

Department of Chemical Engineering, University of Cambridge, Pembroke Street,
Cambridge CB2 3RA, UK.

In recent years there has been increasing interest in applying magnetic resonance techniques in areas of engineering and chemical technology. This presentation will review some of the most significant recent developments with particular reference to the pharmaceutical industry. Particular examples will be taken from the following four areas of research activity:

- Measurement of evolving pore size distributions in delivery systems.
- Development of numerical models of release based on novel magnetic resonance data.
- Development and use of ultra-fast, spatially resolved, magnetic resonance imaging (MRI) techniques to give quantitative insights into the dissolution behaviour of *medium* and *fast* controlled drug release systems.

The presentation will also describe other areas of activity within our group, which include MRI studies of material processing operations such as extrusion and gas-solid fluidisation, along with rapid characterisation of multi-phase systems such as emulsions.

Lynn Gladden FRS FREng

Professor Lynn Gladden is currently Shell Professor and Head of the Department of Chemical Engineering at the University of Cambridge. She is also Director of the Magnetic Resonance Research Centre, which is part of the Department of Chemical Engineering. Prior to moving into the field of chemical engineering in 1987 she had graduated in Chemical Physics at the University of Bristol and studied for a PhD in the Department of Physical Chemistry at Cambridge. Currently her major research interests lie in the development and application of magnetic resonance techniques in chemical engineering, with a particular interest in applied catalysis, oil recovery and pharmaceutical delivery systems. She also has an emerging interest in TeraHertz spectroscopy and its use alongside magnetic resonance techniques.

In 1996 she was awarded a Miller Visiting Professorship at the University of California, Berkeley and in 2000, the Tilden lectureship and silver medal of the Royal Society of Chemistry. She is a member of the International Advisory Board of the MacDiarmid Institute for Advanced Materials and Nanotechnology, New Zealand, and has published over 200 research papers.

Development and Validation of Quantitative Methods Using Solid-State NMR

Eric M. Gorman, Dewey H. Barich, Eric J. Munson
Department of Pharmaceutical Chemistry, The University of Kansas

Purpose: To determine the feasibility and necessary parameters for quantitation of physical forms of pharmaceuticals in pure API, formulations, and more complex systems (i.e., proteins) using solid-state NMR spectroscopy (SSNMR).

Methods: Two anhydrous neotame polymorphs were generated and mixed with either one another or amorphous neotame to create binary mixtures of known composition. The composition of each mixture was then determined by SSNMR. Anhydrous polymorphs of cortisone acetate (CortA) were generated and then mixed. These mixtures were subsequently diluted in starch 1500 to produce model formulations and the relative amounts of each polymorph within each formulation were measured by SSNMR. Crystalline and amorphous insulin were generated and combined in binary mixtures of various compositions and analyzed by SSNMR to determine the relative amounts of crystalline and amorphous material that were present.

Results: The TOSS sequence was used to suppress the spinning sidebands, and it was found to have little effect on the ability to quantitate the polymorphs. The composition of the binary neotame mixtures measured by SSNMR agreed well with the known composition. In addition, SSNMR was able to reveal that each of the anhydrous polymorphs contained some amorphous material. Even when the CortA composed only ~2% of the entire formulation, the levels of each CortA component measured by SSNMR were within 3.7% of the known concentrations based on the prepared mass. Differences in the SSNMR spectra of crystalline and amorphous insulin have been identified and work is currently under way to determine the best way to quantify the composition of the mixtures.

Conclusions: SSNMR can be used to quantitate polymorphs, even when pure standards are unavailable, and the preparation of a calibration curve is usually not necessary. If non-quantitative conditions are used to shorten the total experiment time the peak areas can subsequently be corrected for relaxation effects to yield quantitative measurements if the relaxation constants are known.

Assessing prediction parameters for the stability of amorphous pharmaceutical compounds

K. Graeser (School of Pharmacy, University of Otago, New Zealand, GlaxoSmithKline R&D, UK), **J. Patterson** (GlaxoSmithKline R&D, UK), **T. Rades** (School of Pharmacy, University of Otago, New Zealand)

Introduction: Improved dissolution properties of amorphous materials are a result of the metastable nature of the amorphous form. Unfortunately this may also result in physical instability and accelerated chemical degradation. Understanding the parameters associated with physical instabilities is therefore crucial. To date stability is predicted based mainly on time consuming stability studies. However, recently attempts have been made to predict stability on the basis of thermodynamic (configurational entropy and/or enthalpy) or kinetic considerations (fragility, relaxation time).

Materials: Drugs used in this study were tolbutamide, simvastatin, acetaminophen, nifedipine, indomethacin, lacidipine, troglitazone, DRUG A, GW406381X, donepezil, cefuroxime axetil and griseofulvin.

Methods: Drugs were made amorphous by melt - quenching in the DSC instrument. Configurational heat capacity was measured and used to calculate configurational entropy (Sconf) and enthalpy (Hconf). The kinetic values were obtained by measuring the temperature dependence of the glass transition. For the stability storage experiments, drugs were stored at Tg-20 K and analysed using DSC.

Results: Stability experiments showed that the most stable drugs were cefuroxime axetil and GI262570X. The least stable drugs were acetaminophen followed by nifedipine.

The Sconf and Hconf data for all drugs were obtained from DSC experiments. Results suggest that a higher Sconf should result in greater physical stability (as seen for cefuroxime axetil and GI262570X). Differences in Hconf values for the drugs are not as pronounced and Hconf therefore is regarded as less influential for recrystallization.

Based on mobility it is predicted that donepezil and acetaminophen should be the most stable drugs and tolbutamide and indomethacin should be the least stable drugs. Cefuroxime axetil showed very different behaviour from that predicted. It was shown to be the most stable amorphous form, but initial relaxation time values predicted it to be the least stable drug. Furthermore, the increase in relaxation time with increasing temperature was not as pronounced as for the other drugs. This indicates, that compared to the other glasses, cefuroxime axetil shows 'strong' behaviour and its initial relaxation time could not be used as a means of predicting stability compared to the other drugs that show fragile behaviour.

Fragility values for all of the drugs were quite variable. Different fragilities indicate different temperature dependence of molecular mobility. As the drugs do not fall precisely into the category of either 'strong' or 'fragile', the concept of strength and fragility in pharmaceutical glasses may have to be reconsidered to allow for better differentiation of the observed behaviour.

It was found that no single method was able to predict stability reliably for the drugs apart from troglitazone, which was shown to exhibit good physical stability as predicted by all methods individually. Based on study findings to date, it appears that a combination of different parameters (thermodynamic and kinetic) is needed to be able to predict physical stability.

Conclusion: The methods presented show the current limitations of single prediction techniques used, as recrystallization is a complex process. Various factors such as Tg, fragility, configurational heat capacity and thermodynamic parameters such as the entropy and enthalpy all have to be taken into account as it may be compound specific how big each individual influence is on stability.

Local mobility and factors such as hygroscopicity and hydrogen bonding may well also influence the stability and are currently being investigated.

Kirsten Graeser

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School of Pharmacy
University of Otago

Academic Education

- 2000 – 2005 Enrolment at the Technical Braunschweig, Germany, in Pharmacy
2005 Registration as a full qualified Pharmacist
2006 DPhG financed 4 months research assistant at the University of Bonn in
 Pharmaceutical Chemistry with Prof. C.E Mueller
2006 - present PhD student at the School Pharmacy, University of Otago, New Zealand
 Thesis topic: Investigation and characterization of amorphous systems and
 possibilities of their stabilization
2007 – 2008 currently working at GSK R&D, UK as part of the PhD

Scientific proceedings

Poster Presentations

“Investigation of physico-chemical properties and stability of two amorphous forms of simvastatin”
Kirsten A. Graeser, Clare J. Strachan, James E. Patterson, Keith C. Gordon, Thomas Rades
CRS, Long Beach, September, 2007

“Amorphous simvastatin – stability and physico-chemical properties of two differently prepared amorphous forms”
Kirsten A. Graeser, James E. Patterson, Keith C. Gordon, Thomas Rades
AAPS, San Diego, November, 2007

“Configurational properties of amorphous drugs and initial relaxation time as predictors of physical stability”
Kirsten A. Graeser, James E. Patterson, Thomas Rades
6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, April, 2008

Oral Presentations

“Introduction to solid state studies”

Kirsten Graeser

FDD meeting, Otago University, NZ, Oct 2006

“Investigation and characterization of amorphous systems and possibilities of their stabilization”

Kirsten Graeser, Clare Strachan, James Patterson, Keith Gordon, Thomas Rades

Initial presentation, SOP, University of Otago, NZ, January 2007

“Solid-state studies; an introduction into the investigation and characterization of amorphous systems”

Kirsten Graeser, James Patterson, Thomas Rades

Aston University, Birmingham March, 2007

“Amorphous simvastatin – stability and physico-chemical properties of two differently prepared amorphous forms”

Kirsten A. Graeser, Clare J. Strachan, James E. Patterson, Keith C. Gordon, Thomas Rades

1st PSSRC symposium, Duesseldorf, September, 2007

Journal articles

“Physico-chemical properties and stability of two differently prepared amorphous forms of simvastatin”

Kirsten A. Graeser, Clare J. Strachan, James E. Patterson, Keith C. Gordon, and Thomas Rades, Journal of Crystal Growth and Design V8 (1):128-135 (2008).

Structure & Dynamics of Pharmaceutical Solvates, studied by NMR

Robin K. Harris

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Solvates, especially hydrates, are of enormous importance in pharmaceutical industry. However, it is not trivial to obtain details of their crystal structures or of the mobility of their constituent molecules. This is partly because of the variety of solvate types and stabilities. Questions of molecular-level mobility, spatial or temporal disorder, variable stoichiometry and instability raise difficulties for diffraction techniques. Incorporation into formulated products gives further problems. Solid-state NMR can address many of these issues because it operates on different spatial and temporal scales from diffraction. The lecture will give examples of cases where NMR, sometimes in conjunction with XRD, gives detailed information on the above questions. Among the examples discussed will be sildenafil citrate, finasteride and formoterol. Deuterium NMR will be shown to be particularly useful in examining solvates.

Structure & Dynamics of Pharmaceutical Solvates, studied by NMR

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Professor Robin K. Harris

A short biography

Professor Harris studied at Magdalene College, Cambridge (U.K.) for his degrees – a B.A in Natural Sciences and a Ph.D. (supervised by Dr. Norman Sheppard) on the subject “High-resolution NMR spectroscopy”. He was awarded a Sc.D. by Cambridge in 1978 on the basis of his research publications. Following his doctorate he spent two years as a research fellow at the Mellon Institute, Pittsburgh. He subsequently became a lecturer at the then-new University of East Anglia, where he rose to the position of Professor. His first period of sabbatical leave was spent at the University of Utah with Professor Dave Grant studying ^{13}C NMR before the days of FT. In 1984 he moved to take charge of the Physical & Theoretical Chemistry Section of the Chemistry Department at the University of Durham, where he now holds the title of Emeritus Professor. From the early 1980s until 2004 he directed a national solid-state NMR research service for U.K. universities and industry.

His research interests concern the development and chemical applications of NMR. After a productive decade and a half working on solution-state NMR (especially on spectral analysis and the use of the ^{29}Si nucleus), he jointly pioneered in the U.K. (with Dr. Ken Packer) the cross-polarisation, magic-angle spinning techniques for obtaining high-resolution NMR spectra of solids. His research since then has involved a wide range of chemical areas, and has included the use of heavy-metal spin- $\frac{1}{2}$ nuclei, spinning sideband analysis, polymorphism and (latterly) NMR crystallography. He has published over 500 research papers and co-authored a textbook entitled “NMR: A Physicochemical View”. He is senior editor-in-chief of the 9-volume “Encyclopedia of NMR”, which is now on-line and in the process of being continually updated. The RSC gave Professor Harris its awards for “Chemical Instrumentation” (1985) and for “Analytical Spectroscopy” (1998).

New Possibilities for X-ray Diffractometry

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The latest developments in new X-ray microfocus sources lead to new possibilities in X-ray diffractometry. Using the new Incoatec Microfocus Source ($I\mu S^{\text{TM}}$) with the latest kind of two dimensional focussing Montel optics, the so called QuazarTM optics, in combination with a two dimensional detector allows high quality diffractometry measurements with very good resolution of very small and weakly scattering samples in the home-lab in short time.

The advantages of the new 30 W air cooled $I\mu S^{\text{TM}}$ with a focal spot size below 50 μm are presented. $I\mu S^{\text{TM}}$ has all the advantages of a sealed tube system, and a performance exceeding combinations of traditional rotating anodes with multilayer optics. With a 2-dim focussing mirror $I\mu S^{\text{TM}}$ achieves in a single crystal diffraction set-up a flux above $3 \cdot 10^8$ cps in a 250 μm spot with Cu- K_{α} or a flux above 10^7 cps in a 110 μm spot for Mo- K_{α} radiation.

Examples of new application measurements on X-ray standard samples and pharmaceutical compounds are shown. The figure shows the X-ray powder diffraction patterns of ibuprofen recorded with a typical parallel beam sealed tube set-up (left) and with $I\mu S^{\text{TM}}$ (right) in transmission setup.

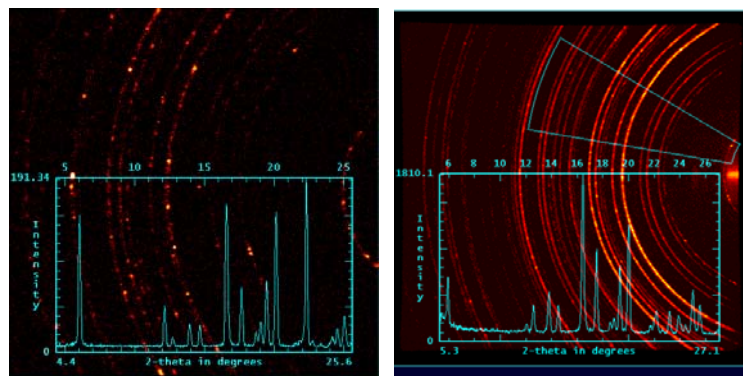


Figure: Diffraction pattern of Ibuprofen recorded with a parallel beam sealed-tube set-up (left) and an $I\mu S^{\text{TM}}$ (right), both with a Bruker D8 GADDS. The exposure times were 120 sec (left) and 15 sec (right) respectively.

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Curriculum vitae

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Application Scientist for X-ray diffraction at Incoatec

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Beamline scientist at an instrument for position sensitive diffractometry at HASYLAB/DESY (Beamline G3, photon energies of 6 to 20 keV) and project work for the design and setup of a new detector for position sensitive diffractometry at photon energies up to 100 keV at the HARWI-2 beamline.

01/1999 to 08/2001

PhD thesis in inorganic chemistry at the Universities of Hamburg and Bochum in the Group of Prof. Dr. M. Epple (now University of Duisburg-Essen) titled "Solid state chemical investigations on biominerals and alkaline-S-2-chloro propionates" (written in German)

04/1994 to 12/1998 Studies of chemistry at the University of Hamburg
September 28, 1973 Born in Hamburg/Germany

List of reviewed publications in scientific journals:

1. B. Hasse, M. Epple, „Kontrollierte Kristallisation von Strontiumsulfat, Bariumsulfat und deren Mischkristallen in einer Polymermatrix“, Freiburger Forschungshefte A853 (1999) 137-146.
2. H. Ehrenberg, B. Hasse, K. Schwarz, M. Epple, „Structure determination of lithium chloroacetate, lithium bromoacetate and lithium iodoacetate by powder diffraction“, Acta Crystallographica B55 (1999) 517-524.
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12. T. Wroblewski, A. Bjeoumikhov, B. Hasse, „Micro Diffraction Imaging of Bulk Polycrystalline Materials“, *Mater. Sci. Forum* 524-525 (2006) 273-278.
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(IWPCPS-10, Bamberg, June 8-14, 2008)

How to Select the Optimal Salt, Co-Crystal or Polymorph

Rolf Hilfiker, Solvias AG, Basel, Switzerland

The selection of the solid form for a new active pharmaceutical ingredient (API) is a decision of paramount importance that usually has to be made at an early stage, i.e., at a time when the clinical research results and the success of the future drug product are yet unknown. Therefore, it is crucial to evaluate the most suitable solid form of a drug substance in a timely and cost effective manner.

For a new API with acidic or basic functional groups, a screening for crystalline salts is generally followed by a screening for polymorphs, hydrates and solvates of one or several salt candidates which have been identified during the initial salt selection process. For substances, where salt formation is not feasible, generation of co-crystals can be a very effective alternative to design solids with suitable properties.

High throughput screening is a powerful tool to support the selection of the most suitable form. But in addition to identifying solid forms, a thorough characterization which includes thermodynamic considerations and kinetic investigations is essential in order to be able to select the optimal form.

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Rolf Hilfiker is Head of the Department Solid-State Development at Solvias AG. Solvias AG is a scientific services company focused on leveraging expertise in various scientific disciplines to accelerate the drug discovery and development process. The department of some 25 people does contract research and development in the solid-state area, i.e. polymorphism studies, crystallization optimization, etc.

Rolf obtained his Ph.D at the University of Basel, Switzerland. From 1987-89 he was Post Doc at SUNY, New York and from 1989-1992 Senior Research Fellow at the University of Basel. He has more than fifteen years of experience in an industrial R&D environment at Ciba-Geigy, Novartis, and Solvias. In the last 8 years he has substantially expanded the solid-state department.

He is author of about 50 scientific publications in various areas of physical chemistry and editor of "Polymorphism – In the Pharmaceutical Industry", Wiley-VCH, 2006.

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Terahertz pulsed imaging as a process analytical technique for tablet film coating

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5 Department of Chemistry, University of Otago, Dunedin, New Zealand

6 Department of Electrical Engineering and Electronics, University of Liverpool, UK

7 Department of Chemical Engineering, University of Cambridge, UK

Abstract

As a process analytical technique, terahertz pulsed imaging (TPI) exploits radiation that resides in the far-infrared region of the electromagnetic spectrum (2 cm^{-1} – 120 cm^{-1}). This radiation is able to penetrate through most pharmaceutical excipients allowing the non-destructive analysis of tablet coating quality. TPI can detect tablet coating defects, coating thickness, uniformity and batch-reproducibly [1]. 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 [2]. 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 [3]. 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.

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Applications of terahertz pulsed spectroscopy to pharmaceutical solid-state analysis – an overview

1,2,3 1

Louise Ho and Thomas Rades

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2 Cavendish Laboratory, University of Cambridge, Cambridge, UK

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Abstract

Terahertz radiation corresponds to the far-infrared region of the electromagnetic spectrum (3-333 cm⁻¹ or 100 GHz-10 THz). Radiation from this region of the electromagnetic spectrum was traditionally difficult to generate and required cryogenic cooling. With the advent of specially-engineered photoconductive semiconductor antenna switches and ultra-short femtosecond lasers, terahertz radiation can now be generated and detected effectively at room temperature for both spectroscopic and imaging use [1]. Modern terahertz pulsed spectroscopy (TPS) generally exploits the frequency range between 60 GHz to 4 THz (2-130 cm⁻¹), to directly probe inter-molecular vibrations and translations in solids. In the field of pharmaceutical solid-state research, TPS has demonstrated potential in characterising and quantifying polymorphic forms and is also readily employed to study phase transitions of active pharmaceutical ingredients [2-4]. This short-talk is designed to give an overview of the terahertz technology and illustrate our current applications of TPS to pharmaceutical solid-state analysis.

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pulsed spectroscopy to quantify pharmaceutical polymorphism and crystallinity. *Journal of Pharmaceutical Sciences* 94(4) (2005) 837-846.

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Louise Chia-Hua Ho

PhD candidate in Pharmacy

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PhD affiliations

- National School of Pharmacy, University of Otago, Dunedin, New Zealand.
- Cavendish Laboratory, University of Cambridge, Cambridge, United Kingdom.
- TeraView Limited, Cambridge, United Kingdom.

Professional memberships

- PSSRC, Pharmaceutical Solid State Research Cluster
- APSGB, The Academy of Pharmaceutical Sciences of Great Britain
- ISPE, International Society for Pharmaceutical Engineering
- PSNZ, Pharmaceutical Society of New Zealand
- SAS, Society of Applied Spectroscopy
- IRDG, Infrared and Raman Discussion Group

Qualifications/Training Course Attended

- Colorcon® coating school, Dartford, United Kingdom, 05/2007
- Registration as Pharmacist, Pharmacy Council, New Zealand, 12/2005
- BPharm, National School of Pharmacy, University of Otago, New Zealand, 12/2004

Awards/Scholarships

- Pharmaceutical Sciences Poster Award at the British Pharmaceutical Conference, Manchester, United Kingdom, 09/2007
- Poster Award at EuPAT 1 conference, Gothenburg, Sweden, 11/2006
- PhD stipend from National School of Pharmacy, University of Otago, New Zealand, 03/2006-
- NZHPA Syd Little Memorial Prize (final year pharmacy student with the best performance in the sterile dispensing), 12/2004
- Adis Press Pharmacy Prize for Pharmacy Elective Project (final year pharmacy student who produced the most publication-worthy elective project), 12/2004
- National School of Pharmacy Summer Student Research Scholarship, University of Otago, New Zealand, 12/2003
- Division of Health Sciences Summer Student Research Scholarship, University of Otago, New Zealand, 12/2002

Research Interests

The integral part of my PhD comprises of using terahertz pulsed imaging (TPI) to analyse various

aspects of tablet coating quality. TPI utilises radiation that resides in the far infrared region of the electromagnetic spectrum (2 cm⁻¹ – 120 cm⁻¹). Radiation from this region is able to penetrate through most pharmaceutical excipients, thus allowing the non-destructive analysis of tablet coating quality. I demonstrated for the first time how the technique can be applied to a batch of sustained-release coated tablets to generate information on coating layer thickness, coating uniformity and batch variability. The coating layer thickness generated with TPI is validated with microscopy imaging. Moreover, defects like blisters and craters can also be detected and mapped out with three dimensional terahertz tablet models. This gives information on the exact location, size and depth of these flaws. I am currently using this knowledge to investigate the relationship between the terahertz coating images and product performance (dissolution). This will lead to a better understanding of the spray-coating process during scale up and control the quality of the tablet coating.

International Collaborations

- **Germany**, Prof. Peter Kleinebudde and Dr. Ronny Müller, Institute of Pharmaceutics and Biopharmaceutics. Heinrich-Heine University of Düsseldorf. Analysis of coating quality using terahertz pulsed imaging, 07/2006 –
- **Finland**, Dr. Jyrki Heinämäki and Ms Meike Römer, Division of Pharmaceutical technology, University of Helsinki. Analysis of terahertz refractive index and its relationship with coating quality, 07/2006-
- **France**, Prof. Juergen Siepmann and Bianca Glaessl, College of Pharmacy, Université de Lille, Lille. Analysis of coating quality on pellets using terahertz pulsed imaging, 11/2006-

Publications

International peer-reviewed journal articles

- **Louise Ho**, Ronny Müller, Keith C Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F. Taday and J. Axel Zeitler. "Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance." *Accepted. Journal of Controlled Release. DOI: 10.1016/j.conrel.2008.01.002*
- **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 and J.A Zeitler. "Analysis of sustained-release tablet film coats using terahertz pulsed imaging." *Journal of Controlled Release*, 119 (2007) 253-261
- Cushla M. McGoverin, **Louise C. H. Ho**, J. Axel Zeitler, Clare J. Strachan, Keith C. Gordon and Thomas Rades. "Quantification of binary polymorphic mixtures of ranitidine

hydrochloride using NIR spectroscopy." *Vibrational Spectroscopy*, 41 (2006), 225-231

Invited professional publications

- **Louise Ho**, Keith C. Gordon, Thomas Rades and Phil Taday. "Tune into Terahertz – terahertz pulsed imaging could potentially advance tablet coating quality analysis." *Pharmaceutical Formulation and Quality*, April/May (2007) 48-52
- **Louise Ho**, J. Axel Zeitler, Keith C. Gordon, Clare J. Strachan and Thomas Rades. "Terahertz pulsed spectroscopy – potential for analysis of pharmaceutical ingredients". *G.I.T Laboratory Journal*, July (2006) 2-4.
- Clare J. Strachan, **Louise Ho**, J Axel Zeitler, Keith C. Gordon, Thomas Rades and Jukka Rantanen. "Terahertz applications for the analysis of solid dosage forms". *Pharmaceutical Technology Europe*, 18 (2006) 27-33.

Patent

- **Louise Ho**, Yaochun Shen and Philip F. Taday. *Patent submitted.*, August 2007

Conference Contributions

- **Louise Ho**, Ronny Müller, Keith C. Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F. Taday and J. Axel Zeitler. "Terahertz pulsed imaging as a process analytical technique for tablet film coating during scale-up" *Submitted for oral presentation at the 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, Barcelona, Spain, 7-10 April, 2008.
- **Louise Ho**, Ronny Müller, Keith C. Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F. Taday and J. Axel Zeitler. "Terahertz pulsed imaging as a process analytical technique for sustained release tablets" *Accepted for oral presentation at the 59th Pittsburgh Conference on Analytical and Applied Spectroscopy (PITTCON)*, New Orleans, Louisiana, U.S.A, 1-7 March, 2008.
- **Louise Ho**, Ronny Müller, Keith C. Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F. Taday and J. Axel Zeitler. "Terahertz pulsed imaging as an analytical technique for tablet film coating during process scale-up" *Accepted for oral presentation at the International Foundation Process Analytical Chemistry Annual Meeting (IFPAC)*, Baltimore, Maryland, U.S.A, 27-30 January, 2008.
- **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 and J.A Zeitler. "Terahertz pulsed imaging as a coating quality analytical tool for sustained-release tablets" *Accepted for poster presentation at the American Association of Pharmaceutical Scientists Annual Meeting and Exposition (AAPS)*, San Diego, U.S.A, 11-15 November, 2007.
- **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 and J.A Zeitler. "The application of terahertz pulsed imaging to the analysis of tablet coating quality" *Accepted for oral presentation at the 46th Annual Eastern Analytical Symposium and Exposition (EAS)*, New Jersey, U.S.A, 12-15 November, 2007.

- **Louise Ho**, Ronny Müller, Keith C. Gordon, Peter Kleinebudde, Michael Pepper, Thomas Rades, Yaochun Shen, Philip F. Taday and J. Axel Zeitler. "Terahertz pulsed imaging as a process control technique for tablet film coating during scale-up" *Accepted for oral presentation at the second Pan-European PAT scientific conference (EuPAT 2)*, Copenhagen, Denmark, 13-14 November, 2007.
- Philip Taday, Alessia Portieri, Yaochun Shen, **Louise Ho**. "Uses of terahertz pulsed spectroscopy and imaging in industry" *Accepted for oral presentation at the 34th Federation of Analytical Chemistry and Spectroscopy Societies' conference (FACSS)*, Memphis, U.S.A, 14-18 October, 2007
- **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 and J.A Zeitler. "Analysis of tablet film coating quality using terahertz pulsed imaging" *Oral and poster presentations at the British Pharmaceutical Conference (BPC)*, 10-12 September, 2007.
- **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 and J.A Zeitler. "Terahertz pulsed imaging as an analytical tool for tablet coating quality" *Poster presentation at the joint 32nd international conference on infrared and millimetre waves and the 15th international conference on terahertz electronics (IRMMW-THz)*, Cardiff, United Kingdom, 2-7 September, 2007.
- **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 and J.A Zeitler. "Terahertz pulsed imaging for the analysis tablet film coating" *Oral presentation at the 9th Martin & Willis Meeting and Infrared and Raman Discussion Group Meeting (IRDG)*, Sheffield, United Kingdom, 4-5 April, 2007
- Yao-Chun Shen, **Louise Ho**, Alessia Portieri, Jelena Obradovic, Philip F. Taday. "Terahertz Pulsed Imaging for non-destructive Analysis of Hydration dynamics of Functional Coatings and Controlled Release Products" *Poster presentation at the 34th annual meeting and exposition of the Controlled Release Society (CRS)*, Long Beach, U.S.A, 7-11 July, 2007.
- **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 and J.A Zeitler. "Advances in terahertz pulsed imaging as process analytical technology for tablet film coating" *Poster presentation at the 34th annual meeting and exposition of the Controlled Release Society (CRS)*, Long Beach, U.S.A, 7-11 July, 2007.
- **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 and J.A Zeitler. "Investigation of terahertz pulsed imaging as an analytical tool for film coating process" *Oral presentation at the International Foundation Process Analytical Chemistry Annual meeting (IFPAC)*, Baltimore, U.S.A, 28-31 January, 2007.
- **L. Ho**, R. Müller, K.C. Gordon, J Heinämäki, P. Kleinebudde, M. Pepper, T. Rades, Y.C. Shen, C.J. Strachan, P.F. Taday and J.A Zeitler. "Terahertz pulsed imaging as an analytical tool for tablet film coating" *Poster presentation at the first Pan- European PAT scientific conference (EuPAT 1)*, Gothenburg, Sweden, 21-22 November 2006.

References

References available on request.

Solid-state characterization of co-crystal prepared by co-grinding and co-precipitation methods

Ibrahim, A., Grimsey, I., Bonner, M. C., Blagden, N. and Forbes, R.T.

Introduction

Reactions of drugs in the solid-state came to be investigated for the preparation of crystalline materials (Caira, et al., 1995). Several methods exist to characterize co-crystals and excellent reviews have been published (e.g. X-ray powder diffraction, Raman spectroscopy, solid-state nuclear magnetic resonance, differential scanning calorimetry and scanning electron microscopy). In this study we used XRPD, Raman spectroscopy and differential scanning calorimetry to characterize urea/ 2-methoxybenzamide co-crystal prepared by co-grinding and co-precipitation

Methodology

1. Preparation of co-ground mixture of urea/ 2-methoxybenzamide (2-MB)

0.8g of 2-MB was added to 0.4g of urea in a glass mortar and ground with 5ml ethanol for 30 min.

The mixture was then collected on filter paper and dried at room temperature for 24 h.

2. Preparation of co-precipitated mixture of urea/ 2-methoxybenzamide (2-MB)

1.6g of 2-MB was dissolved in 40 ml ethanol and heated to 60°C. After the addition of 0.8g of urea, the solution was stirred for 10 min. Then the solution was stored at 25°C for 24 h to obtain the crystals. The precipitated product was collected on a filter paper and dried at room temperature for 24 h.

3. Analytical techniques

The Bruker D-8-X-ray diffractometer, Bruker IFS 66 Instruments with an FRA 106 and the Q 2000, TA Instruments Limited Crawley UK were used to obtain XRPD spectra, Raman spectra and DSC profiles, respectively.

Results and discussion

The X-ray powder diffraction patterns presented in this work show that both co-ground- and co-precipitated mixtures possessed new peaks at $2\theta = 9^\circ$, 14.9° and 18.9° . On the other hand, Raman spectra show noticeable differences between both mixtures and starting materials in the wave number region (1750- 1275 cm^{-1}). The amide 1-vibration band of 2MB at around 1630 cm^{-1} and 1595 cm^{-1} observed in the intact crystal were shifted to higher wave number at 1660 cm^{-1} and 1606 cm^{-1} , respectively. In addition, the position of N-H vibration band of urea was changed. The melting points of co-ground mixture and co-precipitated mixture are 136°C and 137°C respectively, which are different from those of starting materials (urea = 133°C, 2MB = 129°C). The XRPD and DSC results were in agreement with results already published by Moribe, et al., (2005). As for Raman, to my understanding, this the first reported Raman spectroscopy on co-crystals.

Conclusion

In conclusion, the data reveal that co-crystal of urea/ 2MB could be prepared both by Co-precipitation as well as by co-grinding. The XRPD, Raman spectra and DSC results were consistent with each other. However, small intensity of XRPD peaks of co-ground mixture compared with that of co-precipitated mixture may be due to grinding, as it is known to decrease XRPD peaks intensity (Ohashi, et al., 2000).

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- 3.Moribe, K., Tsuchiya, M., Tozuka, Y., Yamaguchi, K., Oguchi, T. and Yamamoto, K. (2006) *J.Inc.Phenom.*, **54**, 9-16.

Personal Details

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Education

University of Bradford **2006** –
2008
Post Graduate in Pharmacy (Pharmaceutical technology)

University of Martin Luther (Germany) **1996** –
1997
MSc in Pharmacy (Diplomarbeit)

University of Martin Luther (Germany) **1990** –
1996
BSc in Pharmacy (zweite Staatsexam)

Employment History

Omdurman University **Lecturer** **1999** –
2006
(Sudan)

University of Gezira **Lecturer** **2002** –
2004
(Sudan)
During my employment at these Universities, I was a Lecturer of Pharmaceutical Technology.

El Mundara Pharmacy **Pharmacist** **1999** –
2006
(Sudan)

Whilst working as a Pharmacist, my duties and responsibilities constituted of the following:

- Customer service duties
- Dispensing medicine

- Cash handling
- Liaising with medical reps, doctors and hospitals
- Attending management meetings
- Completing the necessary paperwork
- Stock Take and stacking shelves
- General cleaning duties

Humanities Pharmacy
1998
(Germany)

Pharmacist

1997 –

Whilst working at the above establishment, my duties included:

- Service customers
- Cash handling
- Dispensing medicine
- Operating the till
- Liaising with doctors, hospitals and medical reps
- Attending meetings
- Completing paperwork

Pharmacy of University Hospital
Alte Pharmacy (Apotheke)
(Germany)

Pharmacist
Pharmacist

1998 – 1999
1998 – 1999

During my employment at the above two establishments, I was responsible for working within the Hospital, where my duties included:

- Dispensing medicine
- Customer service duties
- Cash handling
- Operating the till
- Liaising with doctors, hospitals and medical reps
- Attending meetings and taking minutes
- Completion of paperwork
- General cleaning duties

General Skills

- *Negotiation and Sales skills learnt from liaison with suppliers*
- *Ability of working as part of a team as well as working on my own initiative*
- *Problem solving ability with a logical and methodical approach to all tasks undertaken*
- *Excellent report writing skills with a high level of literacy and numeracy*
- *Bi-lingual in German and Arabic*
- *Experience of working to tight deadlines and working under pressure*

Interests

During my spare time I like to partake in various activities. I have a keen interest in reading. I have a large circle of friends and family and therefore enjoy socialising with them. To keep up to date with current affairs I like to watch television and read newspapers.

References

Professor Rob T Forbes
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Dr Michael Bonner
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Determination of amorphous content in lactose using microcalorimetry.

Kjell Jarring, AstraZeneca R&D, Lund, Sweden

The determination of amorphous content in lactose using isothermal microcalorimetry has been described in several papers in the scientific literature. However, validation data are usually lacking and in the cases where these exist, they usually rely on physical mixtures of pure amorphous and crystalline phases of lactose rather than real samples from e.g. milling or micronisation.

Lactose exists in two anomeric forms α and β and can exist in several solid state modifications, which all need to be considered when developing a microcalorimetric method for amorphous content.

The presentation will highlight the importance of preparing calibration standards that are relevant to the “real samples” to be analysed. Method development and validation aspects regarding limit of detection, limit of quantitation, linearity, precision and robustness will be discussed.

Determination of beta lactose content in alfa lactose monohydrate by XRPD.

Kjell Jarring, AstraZeneca R&D, Lund, Sweden

A method for determination of β -lactose in mixtures with α -lactose monohydrate have been developed and validated. The quantitation of β -lactose relays on peak ratios of resolved β - and α -lactose peaks in the diffractogram of the mixture. A calibration curve was prepared for physical mixtures of the two pure forms. Two different scan rates were investigated to compare the quality of the determination to the time it takes to perform the measurement.

The method was validated for both scan speeds regarding accuracy, linearity, precision, limit of detection and limit of quantitation.

Transfer of methodology to a quality control laboratory and practical aspects such as sample preparation will also be discussed in the presentation.

Kjell Jarring

Kjell Jarring is a Principal Scientist within Analytical Development at AstraZeneca. He is situated in Lund, Sweden, but has a global role in supporting project teams with solid state expertise and to train and coach staff doing solid state characterisation.

A lot of his time is devoted to aid in formulation development with characterisation work and knowledge in order to understand APIs and excipients and how their properties affect formulation processes and product performance. Special focus lately has been on how solid state properties relate to chemical degradation.

Kjell has a background in Inorganic Chemistry and Thermodynamics. He received a Ph.D at the University of Lund, Sweden in 1988 and was employed at AstraZeneca the same year. He has worked in all phases of development from early drug substance development to regulatory applications for drug products.

Prediction of Materials' Properties based on Thermokinetic Evaluation of Dehydration and Decomposition Reactions

Dr. Gabriele Kaiser, NETZSCH-Gerätebau GmbH, Selb/Germany

In all branches where production and storage of substances are temperature dependent, like e.g. in chemistry or pharmacy, the software packages NETZSCH Thermokinetics, Component Kinetics and Thermal Simulations have proved to be extremely useful for modeling and optimizing chemical processes like dehydration, degradation or decomposition. With Thermokinetics, these processes can be formally characterized while their conventional solution usually requires much more effort or time or might even be unachievable.

The aim of the kinetic analysis is to find a set of kinetic parameter to describe the temperature-time influence on the reaction. Typical kinetic parameters are the number of reaction steps, the contribution of each step to the total effect of the process, the reaction type, the activation energy, the pre-exponential factor and the reaction order.

Based on the calculated results, it is possible to get information about the properties of a relevant material, about its stability (also long-term stability) during storage, or – by means of Thermal Simulations - about its potential hazard (self-ignition etc.).

The new software module "Component Kinetics" goes even one step further and allows processing of complex reactions by taking different compositions of reaction mixtures or the presence of variable amounts of e.g. solvents into account.

The measurement data used for calculation can be derived from different kinds of analysis systems, like dynamic scanning calorimeters – DSC, thermobalances – TG, dynamic mechanical analyzers – DMA, thermo-mechanical analyzers – TMA, micro-calorimeters, rheometers etc.

The present lecture refers to DSC and TG measurements carried out on various sugars/sugar hydrates – used as excipients, cyclopentadiene and energetic material.

Development and Validation of Quantitative Methods using XRPD

V.Kogan, DANNALAB, The Netherlands

D.Beckers, PANalytical B.V., The Netherlands

The use of X-ray powder diffraction (XRPD) in the analysis of pharmaceutical materials has greatly increased over the last decade due to its unique capability to discern polymorph crystalline phases in samples that are otherwise chemically identical. One of the common uses for XRPD in the analysis of pharmaceutical materials is quantifying the amount of a phase in a sample, from API content to detection of polymorphs and/or impurities. Also due to increasing regulatory requirements in recent years, there is a need for unified approach to validation of XRPD methods.

We will present the case study of quantitative XRPD methods applied for characterisation of drug products at different production steps.

"Large Sample Analysis with an Automated Confocal and Raman Atomic Force Microscope Combination"

Matthias Kress, Ute Schmidt, Thomas Dieing, Andrea Jauss

The combination of a Confocal Raman Microscope and an Atomic Force Microscope allows chemical and surface topography imaging on large samples without any ongoing process control by an operator. In confocal Raman imaging, a complete Raman spectrum is recorded at each image pixel with confocal resolution while the sample is scanned. An optimized spectrometer setup in conjunction with the latest detector technology reduces the acquisition time for a Raman spectrum to less than one millisecond. Raman images consisting of tens of thousands of spectra can thus be obtained in approximately one minute. The evaluation of spectral features such as peak intensity, peak position etc, provides images revealing either chemical or stress distributions within the analyzed materials. The automated sample stage allows the execution of predefined measurement sequences at any user-defined number of measurement points on the sample. By rotating the microscope turret, the confocal Raman microscope can be transformed into an AFM. This allows the system to acquire high resolution topographic images from the same pre-selected positions on the sample. The presentation will introduce the measurement principles of Confocal Raman Imaging and Atomic Force Microscopy. Examples of automated measurements and large area investigations will be discussed.

Matthias Kress graduated in the field of Medical Engineering from the University of Applied Sciences in Ulm, Germany. After finishing his diploma thesis in the field of confocal laser scanning microscopy he joined WITec in 2001 to cover new applications and the field of customer support. Since 2007 he is responsible for the WITec sales activities in Asia.

DEVELOPMENT AND VALIDATION OF QUANTITATIVE METHODS USING SAXS, SWAXS, AND GISAXS

Peter Laggner, Philipp Hernegger , Manfred Kriechbaum
Institute of Biophysics and Nanosystems Research, Austrian Academy of Sciences
and
Hecus X-Ray Systems GmbH
Graz , Austria

Small-angle X-ray methods for the structure analysis in bulk or at surfaces of nanostructured materials bear great promise for technologically important applications, e.g. in the characterization of solid state pharmaceutical materials. The broader application in industrial routine analytics has been hindered so far by relatively complex instrumentation and/or the necessity to perform specific numerical corrections that were critically dependent on the specific experimental conditions (desmearing). Ideal point-beam geometry, which produces ‘true’ diffraction patterns, was difficult to achieve at the scale of laboratory instrumentation, and was therefore mainly used at synchrotron facilities. This obstacle has been overcome by the introduction of highly brilliant point-focussing sources and optics that provide a photon flux close to that of most of the existing synchrotron SAXS beamlines. With the development of such instrumentation, the validation of SAXS measurements for the measurement, e.g. of nanoparticle size, pore size, specific inner surface, becomes practicable not only for R&D laboratories, but also for the use in routine QC or PAT applications. The second advantage of this new development is the compactness and small energy consumption: due to the high efficiency of source and optics, the system operates at a power of only 50 (fifty) Watt, without the need of external water cooling, and can therefore be installed in every non-specialist laboratory, even in mobile or on-line test stations. Nanometric parameters are therefore accessible within seconds to minutes.

BIOGRAPHY

Prof. Dr. Peter Laggner

Peter Laggner received his Ph.D. degree in Chemistry and Physics from the Karl-Franzens University Graz, Austria, in 1971 supervised by Otto Kratky. From 1973-1974, he was a Postdoctoral Fellow (EMBO) at Unilever Research Laboratory, GB. From 1974-1981 he worked as a Staff Scientist at Inst. f. Röntgenfeinstrukturforschung, OEAW, Graz, Austria and from 1981-1983 as a Staff Scientist at the EMBL/DESY, in Hamburg, Germany. In 1976, he received Sandoz Award for Chemistry and in 1977, together with K. Müller, the Research Award of the Styrian Government followed by the Rudolf-Wegscheider-Award of the Austrian Academy of Sciences in 1979. After his habilitation in biochemistry in 1977, he started to teach as a Professor for Biochemistry/Biophysics at the Technical University Graz, Austria. Since 1978 he fulfilled numerous visiting professorships in Sweden, Finland, Minneapolis, Malaysia and China. He is a member of various societies: German Biophysical Society, European Colloid and Interface Society, European Synchrotron Radiation Society, American Chemical Society and The Biophysical Society. Since 1996, he functions as an Austrian Delegate to the IUPAB and as Vice President of the Erwin-Schrödinger-Gesellschaft for Nanosciences. Peter Laggner is currently the Managing Director at the Institute of Biophysics and Nanosystems Research of the Austrian Academy of Sciences in Graz as well as the Project Leader of the Austrian SAXS beamline at ELETTRA in Trieste, Italy. In addition, he is Co-Founder and Director of Hecus X-Ray Systems GmbH, Graz. He has published more than 200 original papers and reviews in scientific journals and books. His field of interest comprises the elucidation of structure-dynamics-function relationships in supramolecular nanosystems as they occur e.g. in biological membranes and lipoproteins. Another intention of his research lies in the area of biomedicine, especially in the investigation of the molecular basis of diseases.

Patenting Pharmaceutical Solids

Jeffrey A. Lindeman, Ph. D., Esq.
Nixon Peabody LLP
Washington, DC

Patenting the solid forms of pharmaceutical compounds presents unique challenges to patent applicants. The solid form, be it crystalline or amorphous, must carry the weight of its patentability, distinguishing it from any solid form of the compound in the prior art. Drafting effective patent claims to crystalline forms differs from drafting traditional pharmaceutical patent claims. Claims to crystalline forms should provide confident and accessible characterization of the specific crystalline form, especially when distinguishing among polymorphs. This presentation discusses the various aspects of patentability uniquely impacting pharmaceutical solids, provides guidance on drafting claims, and discusses differences in examination as between the USPTO and the EPO.



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Practice Technology and Intellectual Property

Experience

Jeffrey A. Lindeman's practice involves patent matters with a focus on counseling clients in the pharmaceutical, chemical, material sciences and other chemistry-related industries. His practice spans the entire life cycle of an invention – from patenting to commercialization. Dr. Lindeman is currently the Practice Group Leader of Nixon Peabody LLP's Patent Practice Group.

A strength of Dr. Lindeman's practice is characterized by establishing rapport with his clients and using his experience to address their needs in both client counseling and patent litigation. Dr. Lindeman has experience in all aspects of patent preparation and procurement – from drafting patent applications and shepherding them through the patent office, including reissue applications and reexamination to designing patent portfolios and strategies. Dr. Lindeman regularly prepares patent opinions on issues of patentability, infringement, validity and freedom to practice. Dr. Lindeman also works with clients on patent litigation matters and in transactional areas such as intellectual property due diligence and licensing.

Dr. Lindeman is a frequent speaker on patent matters and has authored articles published in both scientific and legal journals. Dr. Lindeman also worked for the U.S. Patent & Trademark Office as a Chemical Patent Examiner specializing in electrophotographic art and in the Office of Legislative & International Affairs. He was also a general chemistry instructor and teaching assistant in nuclear magnetic resonance.

One unique focus of Dr. Lindeman's practice relates to the patenting of crystalline forms of compounds, *e.g.* polymorphic and co-crystalline forms of active pharmaceutical ingredients, API's. In addition to preparing and prosecuting patent applications on crystalline forms, Dr. Lindeman has made numerous presentations on this topic in the past several years.

Dr. Lindeman also works in areas of formulation chemistry, including industrial microbicides and herbicides, polymers, and nanotechnology.

Dr. Lindeman is an adjunct professor at the Washington College of Law at American University. Dr. Lindeman teaches classes on U.S. patent prosecution and international patent law.

Education

Georgetown University Law Center, J.D., *Cum Laude* (1992)
University of South Carolina, Ph.D. Chemistry (1988)
West Virginia University, B.A. Chemistry (1983)

Admissions

Admitted to practice in Virginia, the District of Columbia, and Tennessee, and before the U.S. Patent and Trademark Office.

Affiliations

Member of the American Bar Association; American Intellectual Property Law Association, (Currently Chair of the AIPLA Chemical Practice Committee); Christian Legal Society; and American Chemical Society.

Publications/Presentations

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Abstract Submission for:

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“Assessment of the impact of crystal form on bioavailability using pharmacokinetic modeling.”

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The consequences of polymorphism and crystal form alteration have well recognized implications on bioavailability. Because of the free energy difference between two crystal (or solid) forms, their solubilities and hence dissolution rates can be different. This can potentially have an impact on safety and efficacy because of a change in the rate and/or extent of absorption. An alternate crystal form may be intentionally or unintentionally introduced during the drug development process. A change in form may be necessitated by the discovery of a more stable crystal form, the inability to obtain a previous polymorph or a switch to a form with more advantageous properties for achieving manufacturability (API or dosage form) or bioavailability. However, despite many literature studies indicating that crystal form has an impact on bioavailability, predictive methods that can be used to assess the impact of a change are lacking. Pharmacokinetic simulations offer a method to gain insight into the risk of altering bioavailability due to introduction of a new form and identify whether the new crystal form may have an impact on AUC or C_{max}. In this presentation, GastroPlus™ (Simulations Plus, Inc.) was used to simulate drug absorption using a generalized model for non-ionizable compounds. The impact of high and low permeability values, solubilities of 0.001mg/ml to 1mg/ml and doses from 1 to 250 mg were examined. The % change in AUC or C_{max} was calculated at any solubility ratio for a given dose, permeability, and reference state solubility. Analysis of the data in this form allowed the expression of a “Solubility Window” or region of solubility ratio where AUC or C_{max} did not change more than 10%. From this analysis it was possible to estimate whether a new form would significantly influence bioavailability, across wide span of dose and solubility. Examples are presented that show the utility of the estimation method in risk assessment when switching to a lower energy or higher energy form (i.e. amorphous or solvate) of known solubility, when estimating the solubility of a new form and when conducting probabilistic estimates based on the frequency of solubility ratios in the literature. The estimation method can be useful in developing justification for a crystal form switch, providing rationale for an IND amendment and conducting a clinical BA study between the two forms. Additionally, these types of calculations can be used to determine whether prior modulation of the input crystal form composition in drug product can be used to achieve a therapeutic advantage.

Paul E. Luner, Ph.D.

Biographical Sketch

Dr. Luner received a B.S. in Chemistry in 1984 from Syracuse University (Syracuse, NY) and subsequently obtained his M.S (1986) and Ph.D. (1990) in Pharmaceutics from The University of Michigan, College of Pharmacy (Ann Arbor, MI) where he worked with Prof. Gordon Amidon. Dr. Luner worked in the areas of preformulation and physical characterization for Parke-Davis/Warner Lambert in Morris Plains, NJ from 1990-1995. Dr. Luner's research interests at Parke-Davis included bile salt solubilization and the wetting of drug surfaces by surfactants. In 1995 he joined the Pharmaceutics faculty at the University of Iowa, College of Pharmacy as an Assistant Professor. His research focus at Iowa included the application of near-infrared spectroscopy to solid-state characterization, surface characterization of pharmaceutical materials, and the influence of the gastrointestinal environment on APIs and dosage forms. Dr. Luner developed and taught a Pharmaceutics Graduate course on solid-state properties of pharmaceutical materials and their physical characterization and taught physical chemistry of pharmaceutical systems in the PharmD. curriculum. In 2002 he joined the Solids Development Group at Pfizer (Groton, CT) and was responsible for immediate release tablet formulation development (Phase I through Commercial Image) and utilization of API sparing techniques in formulation development. In 2006 he transferred to the newly formed Material Science department and is presently Senior Principal Scientist. His current responsibilities include API solid-state characterization, form screening and selection for early and late-stage compounds and representing Material Science at the project team level for compounds in development. Dr. Luner has published over 20 refereed journal articles and presented more than 30 abstracts/invited talks, spanning a wide range of pharmaceutically relevant areas from solid state characterization to formulation development. He is a contributor of several monographs to the Handbook of Pharmaceutical Excipients, and a reviewer for journal such as *Pharmaceutical Research*, *Journal of Pharmaceutical Sciences* and *Colloids and Surfaces A*. Dr. Luner has presented invited lectures at leading academic institutions, educational conferences and the FDA (ONDQA). He is long time member of AAPS and was recipient of the Pharmacy Faculty New Investigator Award sponsored by the American Association of Colleges of Pharmacy/American Foundation for Pharmaceutical Education.

Modeling dissolution of drugs in stomach environment

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Abstract

We developed a mathematical model for predicting dissolution of drugs in physiological stomach environment. The model takes into account time-varying pH values of stomach environment after food or liquid consumption and emptying of stomach contents into duodenum. We simulate both, fasted and fed state of stomach. The model can predict the influence of solubility, particle size and formulation disintegration properties on the dissolution of drug. The model is particularly useful for modeling the dissolution of drugs which exhibit strong solubility variation within physiological pH-range of stomach. It can be applied to analyze the release of drug from pharmaceutical formulations where the governing factor of the release is the drug dissolution. We present the simulated results on a model drug compound.

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Robotic Screening in Discovery: a Salt Screening case study

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The tendency to reduce timelines for Research and Development of New Chemical Entities represents a major concern for pharmaceutical companies. Sanofi aventis is no exception and is faced with the important challenge of making a large number of new Active Pharmaceutical Ingredients (API) druggable, in a minimum amount of time. This challenge is further accentuated by the very small quantity of product available, generally no more than a few hundred milligrams, to perform a large number of tests at the earliest stage in development.

During the past five years, different robotic platform systems have been designed to automate complex tasks involved in crystallization processes of drug substance (liquid and powder distributions, evaporation, thermal cycle, filtration, ...). These highly technological platforms help to reduce every day the time spent manually on basic tasks but also allow work to be carried out relatively easily using a very small amount of API (mg scale by trial).

The scope of this presentation is to expose a salt screening case study performed in the Discovery Analytics department in Sanofi aventis. Counterions, crystallization solvents, stirring and thermal parameters selected to design the robotic screening will be discussed, together with the different unavoidable compromises related to the limited number of possible trials. Automatic XRPD and Raman characterizations of obtained products that are performed to identify potential crystalline or amorphous salt hits will be presented. The workflow that follows this Robotic screening implying i) the salt hit confirmation, ii) the scale-up phases and iii) the solid state characterization of salts involving first accelerated physical and chemical stability studies will be exposed.

The powerful and versatile tools present on the Robotic system also enable it to be used for other interesting applications such as solvent screening (a simplified Polymorphism screening) and chiral screening. These different applications will be rapidly mentioned.

The aim of this talk is to demonstrate that the robotic studies, even if often disparaged for their empirical approach, are now essential in modern pharmaceutical sciences. However, because of the failings that may be arise from using a systematic approach, the robotic system must be considered as just one of the many tools available.

From 2001 to 2006, Jerome Menegotto held the position of scientist in the Analytical Development Department of Sanofi aventis at Toulouse, France. He was responsible for dielectric characterization of amorphous and crystalline phases of active ingredients and pharmaceutical products in development in Sanofi aventis. Since 2006, Jerome holds the position of head of the Solid State Laboratory of the Discovery Analytics department of Sanofi aventis at Toulouse, France. He is in charge of salt screening and salt characterization studies and more generally of Solid State characterization of drug substance at earliest stage of development.

Jerome obtained his BA and his Master degree in Physics in 1994 and 1995 respectively and received his Ph.D in 1999 from the P. Sabatier University of Toulouse in Polymer Physics. From 1999 to 2001, he holds a Post-doc position in Polymer Physics at the P. Sabatier University of Toulouse. His research interests include amorphous dynamics and stability, crystallization in liquid and solid state and salts, polymorphs, co-crystal, chiral screening and characterization. His skills are Dielectric Spectroscopies, Thermal analyses (DSC-MDSC, TGA), Microscopy, Hygroscopicity measurement, X-ray powder diffraction (high throughput but aslo structure resolution), Particle size distribution, Infrared spectroscopy and microscopy, Raman microscopy, Development of Robotic methods.

**Quantitative Determination of Crystal Modifications in Active Pharmaceutical Ingredients by
FT-IR, NIR and XRPD**

Gert Klein, Sander Graswinckel, Marco Ruijken, Piet Hoogkamer, Marian ter Horst,
Jan Winder and Pim Muijselaar

*Solvay Pharmaceuticals, Chemical and Pharmaceutical Development,
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If different crystal modifications of an active pharmaceutical ingredient exist, robust and sensitive methods are required for the quantitative determination of these crystal modifications in order to support the drug development process. In this study FT-IR, NIR and XRPD have been evaluated for the quantitative determination of the crystalline purity of a new chemical entity. Calibration models were constructed using mixtures with known amounts of crystal modifications α and β . All three techniques showed good specificity and an appropriate limit of detection to determine the β modification in the bulk of the α modification. The influence of differences in particle size distribution for FT-IR and NIR as well as preferred orientation for XRPD will be discussed.

Pim Muijselaar

Pim Muijselaar studied chemical engineering at the Eindhoven University of Technology. After having obtained his Ph.D. in 1996 at the Laboratory for Instrumental Analysis, he worked as a post-doc at the Himeji Institute of Technology in Japan for one year.

After returning to the Netherlands he took a position at Solvay Pharmaceuticals as senior analytical scientist within pharmaceutical development. There he has been involved in analytical method development and validation as well as impurity profiling in different stages of drug development. In addition, he has been involved in dissolution testing of drug products.

In 2007 he changed jobs and started working within chemical development on pharmaceutical solids. In this position he is working on solid state characterization of active pharmaceutical ingredients as well as formulated products.

Dr. Norbert Nagel studied chemistry and received his Ph.D. in 1999. After being a post-doctoral fellow at Hoechst-Marion-Roussel, he joined Aventis Pharma in 2002, being initially head of the X-Ray Crystallography lab and later on head of the Polymorphism lab. With the formation of Sanofi-Aventis in 2005, he became head of the Solid State Characterization unit within the Analytical Sciences department in Frankfurt, Germany.

Christian Näther

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Polymorphism, which is defined as the ability of a compound to exist in more than one crystalline modification is a widespread phenomenon and is of special importance in pharmaceutical development. This also includes hydrates or generally solvates, which frequently occur during the preparation of a drug. In this context also the polymorphism of very old drug substances can be of great interest, which in most cases has not been investigated satisfactorily. This has been observed by us in the case of several glucocorticoids like e. g. triamcinolonacetonide, hydrocortisone or prednisolone, which are used in therapy for a very long time. As part of an overall programme in this area we have initiated systematic investigations on the polymorphism of glucocorticoides and the results of these studies will be presented in this talk.

This will include a brief introduction into the field and into the different methods used for the investigations. For each compound a complete polymorphic screening was performed in order to check how many forms exist, how they are related and how they can be prepared and transformed into each other. Finally the consequences of our investigations onto the processing of these drugs by sterile filtration are discussed.

In these investigations several new polymorphs and solvates were discovered and structurally characterized for the first time. For triamcinolonacetonide it was found for example that the drug which is marketed since several years does not represent a solvent free form. It contains a small amount of water which is needed for the stability of this form. If the water is removed a transformation into a solvent free form is observed.

For triamcinolone for example we have found two crystalline modifications and one hydrate. Surprisingly the commercial products are thermodynamically metastable at room-temperature and can only be prepared by decomposition of the hydrates.

For hydrocortisone three polymorphic modifications and several solvates were discovered. The different polymorphic forms can be prepared by thermal treatment of the solvates. The polymorphic form which is obtained by this procedure depends strongly on the actual crystal structure of the solvate.

Curriculum

Christian Näther was born in 1962 in Frankfurt, Germany. He was educated as a chemical assistant at the Metallgesellschaft AG. Afterwards he studied chemistry and finished his PhD in 1994 at the University of Frankfurt. In 1996 he moved to Kiel for habilitation and since 2003 he has a permanent position as lecturer in the Institute of Inorganic Chemistry. His scientific interests are in the area of solid state chemistry and focus on investigations on the polymorphism of drugs as well as on the synthesis and characterization of coordination compounds. He is a specialist in single crystal structure analysis but he also uses different diffraction and thermoanalytical methods for his investigations. He is also still active in chemistry education and he carried out several workshops and courses on crystallography and solid state chemistry in Germany and other countries. He is a member of the advisory board of the Journal for Chemical Sciences and coeditor for Acta Crystallographica E. In 2006 he was awarded with the Heyrovsky-Ilkovic-Nernst Lectureship of the GDCh and of the Slovak and Czech Chemical Society. He is author and coauthor of more than 350 publications and 130 contributions to conferences.

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Rapid Raman imaging of pharmaceutical tablets using a novel continuous readout technique

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Raman spectroscopy is being used increasingly in the pharmaceutical industry. Its key benefit is the ability to analyse both APIs and excipients with sub-micrometer spatial resolution, completely non-destructively.

Raman spectroscopy can be used to generate chemical images by acquiring spectra from an array of positions and then processing them to reveal the components of interest. The most common imaging technique is point-by-point mapping, where spectra are collected sequentially from a large number of single points in a raster pattern. This technique requires long total measurement times if an appreciable area is to be imaged; this has limited its use within the pharmaceutical industry.

Alternative approaches use narrow band filters (angle-tuned, acousto-optical, or liquid-crystal) to generate images. These methods can give short data acquisition times, but their use has been limited for a variety of reasons, including non-confocality, reduced spectral resolution, and limited image contrast.

We have developed a novel method of acquiring confocal Raman images that produces uncompromised data and images for both small and large areas, at speeds much greater than possible with the other methods.

The benefits of this method will be illustrated with a variety of pharmaceutical tablet imaging examples.

191 words

Differentiating surface and bulk properties of solids in relation to functionality

Rodolfo Pinal, Sai P. Chamrthy, Rama A. Shmeis, Garry Etherington and Pierre Le Parlouer

Abstract

Variability in the functionality of solid particulate materials is a major source for inconsistency in the performance of pharmaceutical dosage forms. Even though it is widely recognized that different physical characterization techniques provide complementary information, the achievement of *sameness with respect to functionality* in pharmaceutical materials remains something of a challenge. Similar results from physical characterization between specimens do not necessarily translate into the same functionality. By the same token, similar functionality between lots of pharmaceutical materials does not necessarily imply similar characterization results. We present experimental cases that illustrate the contrast between physical and functional sameness in pharmaceutical materials. Exploring surface and core-particle properties of solids leads to objective assessment of functionality. We investigated the changes in surface energy, thermal properties and molecular mobility of solids when subjected to different pharmaceutical processes. At the first stage, comparative surface and thermal analysis can effectively differentiate between lots in terms of functionality. Thermal depolarization methods provide direct molecular mobility information capable of differentiating functional characteristics of materials that are seemingly indistinguishable on the basis of their thermal properties. The three-pronged characterization approach effectively relates physical characterization to functionality.

BIO-DATA

Rodolfo Pinal, Ph.D.

Rodolfo Pinal is Assistant Professor in Industrial and Physical Pharmacy at Purdue University, he has a B.S. in Pharmaceutical Chemistry from the National University of Mexico and a Ph.D. in Pharmaceutics from the University of Arizona.

Prior to joining the faculty at Purdue, Rodolfo Pinal worked for thirteen years in the pharmaceutical industry. He was Research Leader at Hoffmann–La Roche, heading the Solid State Pharmaceutics group, where he was responsible for writing the NDA section on crystal polymorphism and the physical characterization of drug substances, excipients and intermediate blends. Prior to that, Dr. Pinal worked in the sterile dosage forms development group at Roche, where he was responsible for the liquid formulation of poorly soluble drugs, including small molecules and peptides. Rodolfo Pinal started his career in the pharmaceutical industry as a preformulation scientist at Roche, where he was responsible for the physicochemical characterization of new chemical entities. Before joining Roche, Dr. Pinal did postdoctoral research work at the University of Florida, focusing on solution chemistry and modeling the fate and transport of EPA's high-priority organic pollutants.

Rodolfo Pinal's research interests include some of the most prevalent problems encountered during pharmaceutical product development, such as solubility, solubilization and their impact on drug delivery. His research area includes the physical stability of amorphous systems as well as micro- and nanoparticles as drug delivery systems. Dr. Pinal's research also focuses on the physical functionality of pharmaceutical materials, specifically, excipient variability.

A Structured Approach to Investigate and Develop Amorphous Systems

T. Rades, University of Otago; New Zealand

In this presentation I will initially give an overview of the various techniques to formulate glass solutions and amorphous suspensions including solvent methods, melt methods, mechanical activation, and melt-extrusion.

Then a practical guide to assess the suitability of drug-polymer mixtures for formation of glass solutions will be presented based on determination and characterisation of

- excipient selection
- thermal stability
- amorphousness
- glass transition temperature
- drug-polymer interactions
- dissolution rate & solubility
- physical stability.

I will also 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) and X-ray powder diffraction particular emphasis will be placed on modern techniques such as terahertz pulsed spectroscopy (TPS).

Determination of Hydrate Formation During the Dissolution Process

T. Rades, University of Otago; New Zealand

In the first part of this presentation we will investigate hydrate formation kinetics of carbamazepine polymorphs CBZ forms I, II and DH were prepared from form III and all forms were characterized by various physicochemical techniques (XRPD, DSC, SEM, PLM, DRIFTS and true density). Two source materials were used for preparing form I and the resulting 1st and 2nd batches showed different crystal morphology. The particle size range of all forms was restricted to $180 \leq x \leq 250 \mu\text{m}$ and one source of form III with a particle size of approximately $5 \mu\text{m}$ was also used. For each sample, the pure form and the mixture of form I and III (1:1) were dispersed separately in water, and then recovered and measured by FT-Raman spectroscopy. PLS was used to build quantitative models for binary mixtures of each pure form and the DH, and for ternary mixtures of forms III, I and the DH. Pseudo first order kinetics with an unconverted portion were well fitted for all the forms ($R^2 \geq 0.95$). 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. Particle size also had an effect on the conversion since all the forms of large particle size did not completely convert, but the smaller particles of form III converted completely. Furthermore, the conversion of forms III and I was not influenced when dispersed together. The conversion of carbamazepine polymorphs in water can be monitored by combining FT-Raman spectroscopy with multivariate analysis.

In the second part of this presentation we will investigate the interactions of excipients and carbamazepine. Ten excipients having functional groups which are potentially able to form hydrogen bonds with CBZ (group 1: methylcellulose (MC), hydroxymethylcellulose (HPMC), hydroxypropyl cellulose (HPC), 2-hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (CMC), cellobiose; group 2: poly(vinyl pyrrolidone) (PVP), polyvinyl pyrrolidone-vinyl acetate copolymer (PVP/VA) and N-methyl-2-pyrrolidone; group 3: polyethylene glycol (PEG) and polyethylene oxide-polypropylene oxide copolymer (PEO/PPO)) were selected. CBZ (forms III and I) was dispersed into each excipient solution (0.1% w/v) at room temperature, and recovered after 30 min. Qualitative analyses of the recovered samples were determined by X-ray powder diffraction (XRPD), Differential Scanning Calorimetry (DSC) and Raman spectroscopy. Quantitative studies were also carried out using Raman spectroscopy combined with multivariate analysis – partial least squares. Excipients in groups 1 and 2 which have both low solubility parameters ($< 27.0 \text{ MPa}^{1/2}$) and strong hydrogen bonding groups (MC, HPMC, HPC, PVP/VA and PVP) could completely inhibit the conversion of both CBZ forms III and I to the DH in 30 min dispersion. With increasing solubility parameter, inhibition ability decreased for the excipients in group 1, especially for CBZ form I, which consists of needle-like crystals and thus has a higher specific surface area. Also, the excipients of group 3 (PEG and PEO/PPO) lacking strong hydrogen bonding groups, showed poor inhibition although their solubility parameters were less than $21.0 \text{ MPa}^{1/2}$.

Thomas Rades

Prof. Thomas Rades (PhD 1994, Braunschweig, Germany) is the Chair in Pharmaceutical Sciences at the New Zealand National School of Pharmacy, University of Otago, Dunedin, New Zealand. His research interests are in formulation and drug delivery and physical characterisation of the solid and liquid crystalline state of matter. The research in both areas aims to improve drug therapy through appropriate formulation of medicines and to increase our understanding of the physico-chemical properties of drugs and medicines. It combines physical, chemical, and biological sciences and technology to optimally formulate drugs for human and veterinary uses. Specific research interests are: *Colloidal delivery systems for bioactives* and the *Solid state of drugs and dosage forms*.

Prof Rades has worked in both Academia (in Germany and New Zealand) and the Pharmaceutical Industry (F. Hoffmann-La Roche, Basel, Switzerland). He also is a visiting Professor at the University of Adelaide, and Aston University, Birmingham. He has published more than 140 papers in int. peer reviewed journals, more than 300 conference presentations and is the inventor on several patents.

MORPHOLOGY INFLUENCE ON THERMAL BEHAVIOR OF ARIPIPRAZOLE MONOHYDRATE

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Numerous active pharmaceuticals ingredients (API) exist as hydrated pseudopolymorphic crystal form. Stability and dissolution rate of hydrates can vary widely due to crystal shape variation i.e. variation of the surface molecular arrangement and energies for different crystal plane. Hydration or dehydration on particular crystal plane may occur during processing or storage of pharmaceuticals which could change dissolution rate and bioavailability of formulated drug. Thus the knowledge of the thermal behavior is essential to develop stable pharmaceutical formulations. The kinetics of the thermal dehydration of different solvates has been extensively studied but little work has been done on understanding how particle shape impact dehydration process.

The aim of this work is to study the morphology influence on dehydration kinetic of aripiprazole monohydrate. The crystal structure and morphology of the aripiprazole monohydrate have been analyzed by X-ray diffraction (XRPD) and scanning electron microscopy (SEM) while the dehydration process have been investigated by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

The plate-like and rod-like crystals of aripiprazole monohydrate show different dehydration characteristics under same applied conditions in TG and DSC experiments. The plate-like crystals show a single-step, while the rod-like ones express three-steps in TGA curve. The dehydration process difference was observed in DSC curve as well.

The kinetic parameters of aripiprazole monohydrate dehydration (based on calculated data obtained by isothermal TGA, and non-isothermal TGA) were correlated to particular crystal planes. This study supports the concept of surface morphology influence on aripiprazole monohydrate thermal behavior. The observations are important for the interpretation and prediction of aripiprazole monohydrate stability.

CURRICULUM VITAE

Personal data

First name: **Maša**
Last name: **Rajić Linarić**
Date of birth: **October, 7, 1973**
Place of birth: Zagreb, Croatia
Nationality: **Croatien**
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Current Address: **M. Divkovića 11, 10000 Zagreb, Croatia**
Current phone: 385-1-3721-827
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Education:

1980 - 1988 Elementary school
1988 - 1992 Secondary school, degree - chemical technician
1992 - 1996 Studies of chemical science at the University of Zagreb, Faculty of Science, Department of chemistry degree – ***B. Sc. in Chemical engineering***
1997 - 2000 Postgraduated studies of chemical science at the University of Zagreb, Faculty of Science, Department of chemistry degree – ***M. Sc. in Natural Science***
2000 - 2005 Doctoral studies of chemical science at the University of Zagreb, Faculty of Science, Department of Chemistry

References:

1996 - 1997 Graduated student at Rugjer Bošković Institute
1997 - 2000 Postgraduated student at Brodarski Institute – Marine Research & Special Technologies
2000 - 2005 Doctoral student at Brodarski Institute – Marine Research & Special Technologies
2005 – 2007 Postdoctoral student at Brodarski Institute – Marine Research & Special Technologies
2007 - 2008 Senior Research at Pliva Croatia, Research and Development
2008 - Technical Group Leader at Pliva Croatia, Research and Development

Active Member of:

1. The Croatian Chemical Society
2. Croatian Society of Chemical Engineering and Technologies

Mother Tongue:

Croatian

Other Languages:

English

German (fundamentals)

Scientific and Professional Experience:

Techniques:

Thermal analysis:

- differential scanning calorimetry, DSC
- differential thermal analysis, DTA
- termogravimetric analysis, TGA

Materials:

- pharmaceuticals
- explosive materials
- glasses
- metal alloys
- other organic and inorganic materials

Field of interest:

- Characterization and kinetic of thermal properties (isothermal and non-isothermal) of materials

SPM based photothermal spectroscopy: principles and applications

L Harding, M. Reading, J. Moffat, P. Belton and D. Q. Craig

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Abstract

The introduction of local thermal analysis [1] has led to the development of further methods for local analysis [2,3] including photothermal microspectroscopy [4] where the tip is used as a sensor for detecting temperature fluctuations induced by absorbing IR radiation. This technique has been extended to include nanosampling [5], where a small amount of material is taken from the sample surface for analysis by, amongst other methods, IR spectroscopy. More recently we have developed a technique where the tip is coated with a material which is then placed on a surface. Chemical interactions between the coated tip and the surface can then be detected. Applications and potential applications of these techniques will be explored.

References

- 1) Hammiche, A., Reading, M., Pollock, H.M., Song, M. and Hourston, D.J., Localized thermal analysis using a miniaturised resistive probe, *Review of Scientific Instrumentation*, 6712 (1996) 4268-4273.
- 2) Reading M., Price D.M., Grandy D.B., Smith R.M., Bozec L., Conroy M., Hammiche A. and Pollock M. P., Micro-thermal analysis of polymers: current capabilities and future prospects, *Macromol. Symp.*, 167 (2001) 45-62
- 3) Pollock H.M. and Hammiche A., Micro-thermal analysis: techniques and applications, *J. Phys. D: Appl. Phys.*, 34 (2001) R23-R53
- 4) A. Hammiche, L. Bozec, M. J. German, J. M. Chalmers, N. J. Everall, G. Poulter, M. Reading, D. B. Grandy, F. L. Martin and H. M. Pollock, Mid-infrared microspectroscopy of difficult samples using near-field photothermal microspectroscopy, *Spectroscopy*, 2004, 19, 20+
- 5) M. Reading, D. Grandy, A. Hammiche, L. Bozec and H. M. Pollock, Thermally assisted nanosampling and analysis using micro-IR spectroscopy and other analytical methods, *Vibrational Spectroscopy*, 2002, 29, 257-260

Micro/Nano thermal analysis of pharmaceutical dosage forms

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Abstract

The introduction of local thermal analysis [1] has led to the development of versatile array of further methods for local analysis [2]. All of these methods can be used to obtain information on the physical state and chemical composition of surfaces in a spatially resolved way [3]. Spatial resolution is of the order of microns or tens of nanometers [4,5] depending on the mode and probe used. In addition to local thermal analysis hot-tip AFM imaging can also be used [4]. The 'toolbox' of techniques has now been extended to include coating the tip and then studying how the coated tip interacts with a sample surface [5]. Applications of these techniques will be illustrated on pharmaceutical dosage forms.

References

- 1) Hammiche, A., Reading, M., Pollock, H.M., Song, M. and Hourston, D.J., Localized thermal analysis using a miniaturised resistive probe, *Review of Scientific Instrumentation*, 6712 (1996) 4268-4273.
- 2) Reading M., Price D.M., Grandy D.B., Smith R.M., Bozec L., Conroy M., Hammiche A. and Pollock M. P., Micro-thermal analysis of polymers: current capabilities and future prospects, *Macromol. Symp.*, 167 (2001) 45-62
- 3) Pollock H.M. and Hammiche A., Micro-thermal analysis: techniques and applications, *J. Phys. D: Appl. Phys.*, 34 (2001) R23-R53
- 4) Harding L, King W.P., Craig D.Q.M. and Reading M., Nanoscale characterisation and imaging of partially amorphous materials using local thermomechanical analysis and heated tip AFM, *Pharm. Res.* *in press*
- 5) The development of thermally assisted particle manipulation and thermal nanointeraction studies as a means of investigating drug-polymer interactions
L Harding, J Wood, DQM Craig, M Reading
J.Pharm.Sci., **2007** *in press*

Name PROFESSOR READING, MICHAEL

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Date of Birth 20/1/56

Present appointment Professor of Pharmaceutical Characterisation Science (March 2004),
School of Chemical Sciences and Pharmacy

Address **School of Chemical Sciences and Pharmacy**
University of East Anglia
Norwich, NR4 7TJ

Qualifications **BSc in Applied Chemistry 1978, PhD from 1983**

Title of PhD Thesis **A comparative study of thermoanalytical methods and their application
to the study of the decomposition of selected transition metal oxysalts
(January 1983)**

Summary of Research Experience

During the 10 years I spent in industry with ICI, my work was concerned with modelling and characterising the structure and behaviour of polymeric coatings. Out of this came a commercialised computer model for polymerisation and network formation called Dryad (Intelligensys) and two commercialised instruments, the Thin Film Analyser (Rhopoint) and Modulated Temperature DSC, or MTDSC, (TA Instruments). Since leaving ICI, I have been mainly interested in the development of novel nanocharacterisation methods based on near-field thermal techniques. The first of these was local differential scanning calorimetry and thermomechanical analysis (both commercialised as Micro TA now Nano TA with much higher resolution probes). This was followed by local volatilisation-MS and GC-MS and photo

thermal IR micro spectrometry (PTMS). We have applied these methods to a variety of systems including polymers, pharmaceuticals and biological samples. Another interest has been characterising the dynamic mechanical properties of surfaces as a function of temperature (from -70°C to over 300 °C). Special attention has been given to Nanosampling, a technique that enables picogram quantities of material to be taken from a selected point on a sample surface then analysed.

Most recently the focus has been on improving the spatial resolution of these methods to sub micron length scales through a new generation of thermal probes.

Appointments held

Post Doctoral Fellow, CNRS, Centre for Thermodynamics and Calorimetry Marseilles, France (January 1983 to February 1984)

Research Scientist at ICI Paints Research Department, Slough, UK (July 1984 to January 1986)

Team Leader of the Thermal Analysis Group at Stanton Redcroft Research and Consultancy Department, London, UK (January 1986 to October 1987)

Thermal Analysis Group Team Leader and subsequently Characterisation Section Manager at ICI Paints Research Department Slough, UK (October 1987 to April 1997) in charge of 27 people organised in 8 teams covering thermal characterisation, rheology, microscopy, NMR, vibrational spectroscopy, chromatography and mass spectroscopy, wet chemical analysis and bio-analysis. Also senior scientist with an international strategic role as a member of the Corporate ICI Analytical Science Steering Group.

Director of the Advanced Thermal Methods Unit, IPTME, University of Loughborough (April 1997 to February 2004)

Professor, School of Chemical Sciences and Pharmacy, University of East Anglia (March 2004 to present day)

Achievements

- MTDSC has become a highly successful commercial product offered by most manufacturers (where patent considerations permit).
- Special editions of the two leading journals in thermal analysis (Journal of Thermal Analysis and Calorimetry [1998] and Thermochemica Acta, [1997]) have been produced that were devoted entirely to modulated temperature calorimetry.
- International conferences dedicated to MTDSC have been held in Germany, Japan and Canada with numerous local meetings together with a major session at the 1996 International Congress on Thermal Analysis (ICTAC, the only world-wide conference on thermal methods, it is held once every 4 years).
- Micro/nano-TA has become a multi-award winning successful commercial product.
- Five successful international symposia on micro-TA have already been organized: the first in the UK in 1998, the second in the US in 2000, the third in 2003 in Germany and the 4th in Paris on 2004 and as part of NATAS 2007 in the US.
- Editor of 2 books, one on Modulated Temperature DSC (with Prof. D Hourston) and one on thermal analysis applied to pharmaceuticals (with Prof. Duncan Craig)
- Author and co-author of 10 book chapters with 2 more in press.
- Author and co-author of over 60 articles in refereed journals
- Author and co-author of over 30 patents
- Full Professor at a grade 5 department (only a handful of department in the UK have the higher award of 5 star)

Awards

- 1979 - French Government Scholarship to work with J Rouquerol Head of the CNRS Centre for Thermodynamics and Microcalorimetry.
- 1988 - Royal Society of Chemistry Thermal Methods Group Young Scientist Award.
- 1998 - Pittcon Gold Award for best new instrument of 1998 for micro-TA.
- 1998 - R&D 100 Award for micro-TA.
- 1999 - UK Millennium Product Award for micro-TA.
- 2000 - Mettler Award (the highest honour given by the North American Thermal Analysis Society)
- 2007 - R&D 100 Award for nano-TA
- 2007 - Elected a Fellow of the North American Thermal Analysis Society
- 2007 - Winner the GlaxoSmithKline international achievement award (with Prof. D Criag)

Other Positions Held

- Affiliate Professor at the University of Washington, Seattle (1993 -)
- IUPAC Thermophysical Properties Working Party (1994-1998)
- Member of the Polymer Physics Group of the Institute of Physics (1995-1998)
- Editorial board of Thermochemica Acta (2000 -)
- Chairman of Royal Society of Chemistry Thermal Methods Group (2006-)

Solid-state characterisation of pharmaceutical coatings - From nanometers to macroscopic dimensions

Staffan Schantz, AstraZeneca R&D, Mölndal, Sweden

Water-based polymer coatings have found widespread use in pharmaceutical industry, for example in taste masking or improving mechanical stability of tablets. The main driver for waterborne processes has been the environmental concern associated with traditional organic solvent-based coatings. In some more demanding applications such as modified release however, water-based systems have sometimes shown shortcomings when it comes to e.g. process robustness and storage stability. In order to solve these technical problems there is clearly a need for a more fundamental understanding of film formation, for example involving characterisation of the hierarchical structures typical of colloidal polymers giving insight in how structures on different length scales may be relevant for different physical phenomena.

The presentation will illustrate the importance of characterisation at different length scales from the segmental level of copolymers, via the colloidal dimension of dispersion particles, to the macroscopic length scale of formulations. Results from case studies will be given using mainly solid-state NMR, DMTA, and AFM.

References

- 1) S. Schantz, H. Carlsson, A. Motiejauskaite and A. Larsson, *17th Int. Symp. Polymer Anal. Char.*, Heidelberg, Germany, June 6-9, 2004, Conf. abstracts, p.22.
- 2) S. Schantz, H. Carlsson, T. Andersson, S. Erkselius, A. Larsson and O.J. Karlsson, *Langmuir*, **23** (2007) 3590.
- 3) S. Karlsson, A. Rasmuson, I. Niklasson Björn, S. Schantz, *Powder Tech.*, submitted.

Biography

Staffan Schantz

After obtaining a PhD in Physics at Göteborg University in 1990 (Raman and Brillouin scattering), Staffan visited as a post-doc at the University of Trento (low-frequency Raman), and worked 1991-96 as a research associate at Chalmers University of Technology. He became associate professor in Polymer Technology in 1995 (solid-state NMR).

Staffan joined former Astra Hässle in 1996 as Research Scientist in Drug Delivery Research. After the merger to AstraZeneca he became Associate Principal Scientist in 2001 (Product Development), and was appointed Principal Scientist in 2003. Staffan is currently holding a global position as Principal Scientist in Materials Science in Pharmaceutical & Analytical R&D (GPAR&D), AstraZeneca.

Staffan achieved AstraZeneca GPAR&D Innovation Awards in 2001 (solid-state NMR applications) and 2003 (film formation). He has published more than 30 articles and co-authored 3 patent applications in the areas of polymer electrolytes, electron conducting polymers, polymer blends and interphases, water-based polymer films, colloids, amorphous materials, and pharmaceuticals.

The combination of X-ray photoelectron spectroscopy, XPS, and X-ray absorption spectroscopy, XAS provides information on the local molecular and crystallographic structure of materials as well as the chemical state of the individual atoms and the nature of functional groups contained in a material. Especially XAS is an incisive probe because it can provide bond distances and angles without any requirement of long range order. XAS is in this sense complementary to X-ray diffraction and scattering techniques, which require long-range order. Both XPS and XAS offer information on both bulk and surface of a material. These features make a combination of XPS and XAS a potentially powerful tool for the analysis of amorphous systems, for the characterisation of thin coatings and surfaces, and for the detection of minority surface phases and species. However, their application for the characterisation of pharmaceutical systems has long been held back by the fact that the characterisation of these materials requires 'soft' X-rays (i.e., X-ray photons with energies below 1000 eV), which were not compatible with existing environmental chamber technologies. These limitations have been overcome by work over the last few years. I will summarise recent progress in the development of environmental cells and detectors that has facilitated the application of soft XAS to pharmaceutical [1] and other solid molecular materials. Even studies of liquid solutions and suspensions are now almost routinely possible using purpose-designed flow cells. To demonstrate the considerable analytical possibilities of soft X-ray spectroscopies, but also some of its limitations, I will present a number of examples from recent studies by my research group, addressing a variety of nanostructured systems relevant for formulation, solid state characterisation, and drug delivery.

[1] A.M. Booth, S. Braun, T. Lonsborough, J. Purton, S. Patel, S. L. M. Schroeder, **American Institute of Physics Proceedings**, 882 (2007) 325-327.

Sven Schroeder

Sven studied Chemistry (with experimental atomic physics and analytical philosophy) at the [Freie Universität Berlin](#) from 1986 to 1991. He finished his degree with a 9-month full-time research project in the [Surface Science group of Klaus Christmann](#). From 1988 to 1991 he also held a teaching assistantship in Physical Chemistry, and concurrently a full undergraduate scholarship by the [German National Academic Foundation](#).

After completing his Chemistry degree (Dipl-Chem) he took up a 1-year visiting scholarship at [Stanford University](#), funded jointly by the [German National Academic Foundation](#) and Stanford University. He worked with [Robert J. Madix](#) in the Department of Chemical Engineering, studying gas adsorption dynamics on noble metal surfaces by means of molecular beam techniques.

In 1992 he started PhD studies on the development of *in situ* electron-yield X-ray absorption spectroscopy for the characterisation of reactions under the supervision of [Trevor Rayment](#) and [Richard M. Lambert](#) in the Department of Chemistry at the [University of Cambridge](#).

From 1995 to 1996 he held a one-year postdoctoral fellowship with [Robert Schloegl](#) at the [Fritz-Haber-Institut](#) in Berlin, working on the selectivity of oxidation reactions over Cu catalysts.

In 1996 he was awarded the Oppenheimer Research Fellowship in Colloid and Surface Science at the [University of Cambridge](#), but after holding this position for 9 months he accepted a 5-year research and lecturing position at the [Freie Universität Berlin](#).

In August 2002 he took up a joint Lectureship in the Departments of Chemical Engineering and Chemistry at UMIST.

In 2005, right after the formation of The University of Manchester from UMIST and VUM, he was promoted to Senior Lecturer.

In 2007 he was promoted to Reader.

Personal Data

Name: Katsuhide Terada

Present Address: Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510 Japan

Position: Professor, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences

Education:

Graduated School of Pharmacy, Chiba University, March, 1975

Obtained Master degree (Pharmacy), Chiba University , March, 1977

Received Ph. D. (Pharmacy), The University of Tokyo, 1983

Major subjects: Physical pharmacy and Pharmaceutical Technology

Position held since graduation:

1977 - 1986 : Assistant Prof. Chiba University (Faculty of Pharmaceutical Sciences)

1986 - 1990 : Associate Prof. Toho University (Faculty of Pharmaceutical Sciences)

1991 - 1996 : Chugai Pharmaceutical Co. Ltd.

Manager of Formulation Technology Division and Analytical Division

1996 - present Professor of Toho University (Faculty of Pharmaceutical Sciences)

Membership: President of Society of Pharmaceutical Machinery and Engineering of Japan

President of PDA Japan Chapter

Senior Director of ISPE Japan

Representative of Pharmaceutical Society of Japan

Council of The Academy of Pharmaceutical Sciences and Technology, Japan.

Council of Japan Society of Calorimetry and Thermal Analysis

Editor of Asian Journal of Pharmaceutical Sciences.

etc.

Publications: More than 110 research papers, 30 reviews, 25 technical books are published.

On being an Expert Witness

Terry Threlfall,

University of Southampton, U.K.

Abstract

Experiences are presented of acting as a visible expert witness in some high-profile pharmaceutical patent litigation cases, as well as remaining invisible behind the scenes in many more litigation and opposition proceedings. Some personal comments on the patent system are also presented.

Abstract. DSC is widely used, but it is not always understood how much information DSC traces can provide. With the help of the Burger-Ramberger and Lian Yu Rules, supplemented by solubility or slurring data, phase diagrams can be derived. The errors inherent in the van Hoff extrapolation or in Urakami's procedure need to be appreciated, but rough phase diagrams are often sufficient. Accurate diagrams can be derived with considerably more effort.

Degrees in Chemistry and in Law, and PhD in Synthetic Organic Chemistry, all from the University of London. Post-doc at the ETH, Zuerich (Eschenmoser). 30 years in the pharmaceutical industry (spectroscopy, microscopy, analysis, process research, technical management, patent maintainance). Appointed Industrial liaison executive at the University of York in 1990. Since 2003 Research Fellow in the Crystallography group at Southampton University, (crystallisation and polymorphism studies).

C.J. Coles, T. Horton, M.B. Hursthouse, S. Huth, G. Tizzard and T.L. Threlfall
University of Southampton, U.K.

Abstract. Single crystal structures usually, and polymorph prediction nearly always, relate to low temperatures. By contrast, nearly all analytical results and all useful behavioural measurements (stability, solubility) are concerned with temperatures above zero degrees C, particularly room temperature and 37 degrees C. Analysis of the CDB, after removal of many errors, suggests that the average thermal expansion is about 0.012% per degree, although substantial anisotropic lattice expansion is very common.

Carbohydrates in Amorphous States: Molecular packing, nanostructure and interaction with water

Job Ubbink

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Amorphous carbohydrates and carbohydrate polymers are widely used in foods and pharmaceuticals for the encapsulation of nutrients and drugs. In these applications, the interaction with water is critical as it is a strong plasticizer of amorphous carbohydrates. However, the sorption of water by carbohydrates and the effects of absorbed water on molecular mobility including plasticization, matrix rearrangements, crystallization and diffusion are still relatively poorly understood, mainly because molecular and structural analyses of the amorphous state are lacking. In the lecture, I will report on the results of our study with the University of Bristol (UK) on the molecular packing and nanostructure of amorphous carbohydrates and the plasticizing effects of water. In this study, we have combined Positron Annihilation Lifetime Spectroscopy (PALS) with Molecular Dynamics (MD) simulations and thermodynamic analysis. I will discuss four different cases:

1. The effect of water on the molecular structure of amorphous carbohydrate matrices and molecular mobility [1, 2];
2. The impact of low-molecular weight carbohydrates on the molecular packing of carbohydrate polymers [2-4];
3. The physics of the sorption of water by bidisperse mixtures of amorphous carbohydrates [5];
4. The organization of water in amorphous and crystalline trehalose and the implications for anhydrobiosis and biostabilization [6].

1. Kilburn, D.; Claude, J.; Mezzenga, R.; Dlubek, G.; Alam, A.; Ubbink, J. Water in Glassy Carbohydrates: Opening It Up at the Nanolevel. *J. Phys. Chem. B.* **2004**, *108*, 12436.
2. Limbach, H.-J.; Ubbink, J. Conformations and Molecular Packing of Maltooligomers in Carbohydrate-Water Systems: A Molecular Dynamics Study. *Soft Matter* (submitted, 2008).
3. Kilburn, D.; Claude, J.; Schweizer, T.; Alam, A.; Ubbink, J. Carbohydrate Polymers in Amorphous States: an integrated thermodynamic and nanostructural investigation. *Biomacromolecules* **2005**, *6*, 864.
4. Townrow, S.; Kilburn, D.; Alam, A.; Ubbink, J. Molecular Packing in Amorphous Carbohydrate Matrixes. *J. Phys. Chem. B.* **2007**, *111*, 12643.
5. Ubbink, J.; Giardiello, M.-I.; Limbach, H.-J. Sorption of Water by Bidisperse Mixtures of Carbohydrates in Glassy and Rubbery States. *Biomacromolecules* **2007**, *8*, 2862.
6. Kilburn, D.; Townrow, S.; Meunier, V.; Richardson, R.; Alam, A.; Ubbink, J. Organization and mobility of water in amorphous and crystalline trehalose. *Nature Materials* **2006**, *5*, 632.



Job Ubbink studied physical chemistry at the University of Leiden, and obtained his PhD at Delft University of Technology on a study of the statistical mechanics of DNA. After stints as Visiting Scientist at the University of Bristol and Moscow State University, he joined industry, first at Givaudan and since 1999 at the Nestlé Research Center. His research interests include glassy materials, carbohydrate physics, microbial biophysics and the delivery of bioactive ingredients in food.

Short Biography

Dr. Peter van Hoof graduated in 1993 at the University of Nijmegen, the Netherlands his main subject was Solid State Chemistry. For this he studied with Prof. Dr. Bennema in Nijmegen and with Prof. Dr. Kern in Marseille, France. Subsequently he obtained his PhD in 1998 at the Solid State Chemistry group of Prof. Bennema, the title of his thesis is “Growth and Morphology of n-Paraffin Crystals”. Since then he is working in the pharmaceutical industry with Organon which became part of Schering-Plough since 2007. He started working as a research fellow on Polymorphism and crystallization and later as a section leader in the field of spectroscopy and API identification. In 2003 he started to setup a solid state characterization laboratory within the same company. This laboratory includes techniques such as X-Ray Powder Diffraction, solid state NMR, Infrared spectroscopy, FT-Raman spectroscopy, optical microscopy, thermal analysis, microcalorimetry and particle size determination. He holds more than 40 publications and oral presentations on crystal growth, polymorphism and solid state characterization.

Presentation title:

High resolution real time tracking of modified release dosage form in the gastrointestinal tract

Abstract

Modern imaging methods based on magnetic measurements like Magnetic Marker Monitoring (MMM) and Magnetic Resonance Imaging (MRI) provide detailed insights into the behavior of dosage forms in the GI tract. MMM is based on the labeling of dosage forms as a magnetic dipole. After ingestion the magnetic dipole field is measured using extremely sensitive measurement equipment with high three dimensional resolution in real time. Data on esophageal transport, gastric residence, small intestinal transit and colon transport will be presented and discussed. Special focus will be given to food induced mechanisms like gastric retention, gastro-colonic and gastro-ileocecal reflexes.

Werner Weitschies studied Pharmacy and received his Ph.D. in Pharmaceutical Sciences in 1990. From 1990 to 1995 he worked as a scientist in the research laboratories of Schering AG in Berlin in the field of nano- and microparticulate contrast agents. From 1996 to 1998 he was head of a research department in the field of magnetic nanoparticle relaxation measurements at the Institute for Diagnostic Research of the Free University of Berlin. Since 1999 he is Professor of Biopharmaceutics and Pharmaceutical Technology at the Institute of Pharmacy in Greifswald. His main research areas are the investigation of the behavior of dosage forms in the gastrointestinal tract, and the development of nanoparticle based techniques for molecular imaging and physical therapy.

Short CV – Dr Rob Whittock.

Rob Whittock undertook a PhD in Physical Organic Chemistry with Professor Harry Heller at Cardiff University. During this time he synthesised a number of complex organic molecules, which required the use of single crystal X-ray diffraction to unambiguously determine the structural isomer that had been obtained. This started his interest in crystallisation and the growth of single crystals, which subsequently led him to take up a position within AstraZeneca in Oct 2000, investigating the solid-state chemistry of new candidate drugs during both the discovery and development phases of drug development.

In addition to his interest in solid-state chemistry, he has a strong interest in intellectual property law and thus he studied on a part-time basis, whilst at AstraZeneca, to complete a graduate diploma in law (2002-2004) at Nottingham Law School, and the Bar Vocational Course (2004-2006) at BPP Law School, London.

In 2007, he was appointed Associate Director – Materials Characterisation at Molecular Profiles, where his main role was the leadership and technical direction of the materials characterisation team with respect to international patent litigation support for pharmaceutical drugs.

His current position is within the intellectual property law group at one of the top five UK law firms.

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**ORDERING and DISORDERING OF PHARMACEUTICALS
UPON MECHANICAL MILLING:
THE ROLE OF T_g**

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Mechanical milling is a usual process used in the course of drug formulation to reduce the particle size. However this process may also change the physical nature of the end product, leading sometimes to an amorphization and sometimes to a polymorphic transformation. The origin of the duality between these two kinds of transformations is not yet clearly understood and, up to now, only few investigations have been performed to study the correlation between the nature of the transformation and the milling conditions.

We present here a short review of recent results which clarify and rationalize the general pattern of transformations induced by milling in some pharmaceutical compounds. Special attention has been paid to the effect of the milling temperature. In particular, it is shown that amorphizations occur when milling is performed far enough below the glass transition temperature (T_g) of the material while polymorphic transformations occur when milling is performed above T_g. This apparent limit is puzzling since the glass transition itself is basically not a thermodynamical equilibrium event but only the manifestation of the change from an ergodic (above T_g) to a non ergodic (below T_g) situation.

We also present detailed investigations which reveal that some polymorphic transformations are not direct but involve, on the contrary, a transient stage of amorphisation, immediately followed by a recrystallization towards a more or less stable polymorph. This suggests that the structural transformations observed upon milling result from a competition between an amorphization process due to the ballistic shocks and a subsequent recrystallization process which is thermally activated. Since the recrystallization process is directly governed by the molecular mobility in the amorphous state, it prevails over amorphization at rather high temperatures leading to an apparent polymorphic transformation. On the other hand, the recrystallization is inefficient at rather low temperatures so that a complete amorphous state can be reached. The milling itself is thus expected to have an amorphizing character whatever the milling temperature while the latter governs the subsequent evolution of the amorphized fractions between the ballistic shocks. Coherently, the change in the apparent nature of the transformation induced by milling occurs in a narrow temperature range around the

glass transition temperature T_g where the molecular mobility is known to evolve the most rapidly.

Dr J.F. Willart CNRS Researcher since 1991

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Habilitation in Physics at the University of Lille1 (2002)

Doctorate (Ph.D.) at the University of Lille 1 (1991)

Main research field: Physics of out of equilibrium molecular materials

Since a few years, our investigations aim to rationalize the physical transformations (amorphization and polymorphic transformations) of molecular materials induced by mechanical milling and dehydration. We are mainly concerned with sugars (glucose, lactose, trehalose...) polyols (mannitol, sorbitol...) and some drugs (fananserine, indomethacine...). Our main results concern: (i) The formation of molecular alloys by solid state vitrification. (ii) The manipulation and the exploration of the energy landscape of glasses by mechanical milling. (iii) The formation of superheated crystalline phases by dehydration of crystalline hydrates below T_g .

Raman spectroscopy; from pre-formulation to product

Adrian. C. Williams

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“Can a Raman renaissance be expected via the near-infrared Fourier-Transform technique?¹”. The world of Raman spectroscopy has moved at an impressive rate since this question was raised in 1991. Initially driven by the development of Fourier-Transform instruments which brought Raman into the molecular spectroscopy characterisation arena occupied by FT-infrared analysis, Raman spectrometers have now found use in pharmaceutical analyses both within the research and development arena and, increasingly, in the area of in process control and monitoring. Instruments have evolved further with the majority available today using CCD detector technology and numerous lasers ranging from the near infrared (785 nm) to visible (e.g. 633, 532, 488 nm) to deep UV (e.g. 244 nm). This latest generation of instruments allow rapid spectral collection, particularly valuable for process monitoring, numerous sampling accessories such as fibre optic couplings and 2- and 3-dimensional (confocal) mapping of samples.

This presentation shows examples where Raman spectroscopy has been valuable for examining polymorphism, process optimisation during granulation and outlines some areas where technological advances now allow unique capabilities in pharmaceutical research and manufacture. Real time polymorph conversions of carbamazepine during heating were followed using FT-Raman spectroscopy² whilst dispersive Raman at 488, 514, 633 and 785 nm was used to monitor solvent mediated crystallisation of piracetam polymorphs. We have also employed Raman spectroscopy to examine the effects of granulation conditions during tablet manufacture and storage of a crystalline drug, which could dissociate into an amorphous free base³. Despite the spectral similarities between the two drug forms, low levels of API dissociation could be quantified in the tablets; the technique allowed discrimination of ~ 4% of the API content as the amorphous free base (i.e. less than 1% of the tablet compression weight). More recent advances, such as the use of Raman microscopic imaging, allow micron-scale spatial resolution of chemical species in tablets.

Clearly the technology underpinning Raman spectroscopy has moved rapidly since the 1990's and the capabilities are yet to be fully exploited beyond the research laboratory. To answer the question posed at the beginning: yes, the Fourier Transform technique provided impetus and acted as a catalyst for a renaissance of Raman spectroscopy and we have moved beyond FT- with more rapid data collection, ease of use and flexibility in sampling. The next step appears to be moving Raman spectroscopy from the Renaissance to the Industrial Age.

1. Schrader, B., Hoffmann, A., Simon, A., Sawatzki, J. “Can a Raman renaissance be expected via the near-infrared Fourier-Transform technique?” *Vibrational Spectroscopy*, **1**: 239-250, 1991.
2. O'Brien, L.E., Timmins, P., Williams, A.C., York, P. “Use of in situ FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs. *J. Pharm. Biopharmaceut. Anal.*, **36**: 335-340, 2004
3. Williams A.C., Cooper V.B., Thomas L., Griffith L.J., Petts C.R., Booth S.W., “Evaluation of drug physical form during granulation, tableting and storage. *Int. J. Pharm.*, **275**: 29-39, 2004.

Brief Curriculum Vitae: Professor Adrian Williams

Employment

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Appointments

1990-2004: School of Pharmacy, University of Bradford (Lecturer, Senior Lecturer, Reader, Professor of Biophysical Pharmaceutics).

2004 to present: Professor of Pharmaceutics & Director of Research, School of Pharmacy, University of Reading

Membership of Learned Societies

Fellow, Royal Society of Chemistry.

Member of the American Association of Pharmaceutical Scientists.

Member of Academic Pharmacy Group, RPSGB.

Member Academy of Pharmaceutical Scientists

External Appointments

Expert witness for Merseyside Police Serious Crime Squad.

Appointed as a Specialist in the field of Polymorphism and Raman Spectroscopy by European Pharmacopoeia Commission.

Member of EPSRC Peer Review College.

Member of Editorial Boards: Journal of Pharmacy and Pharmacology, Journal of Pharmaceutical Sciences, Current Drug Delivery.

Member of the Board of Pharmaceutics for International Society of Skin Pharmacology and Physiology.

Higher Degrees

Supervised 32 higher degree students. Externally examined 15 PhD's

Grant Income

>£850,000 from research councils (EPSRC, BBSRC), University funds, external bodies (Finance South East) and companies (including Stiefel laboratories, Bristol-Myers Squibb, GSK, Merck Sharp and Dohme, AZ)

Conference presentations

15 invited international presentations including Gordon Research Conferences (USA), CRS meeting in Istanbul and Association de Pharmacie Galenique Industrielle meeting, Paris.

45 invited national presentations.

Other presentations made at a total of 71 national and international meetings, and articles in the press (Yorkshire on Sunday, BBC news).

Summary of drug delivery/controlled release activities at School of Pharmacy at University of Reading.

Pharmaceutical polymers and dendrimers:

We are investigating a range of novel formulations for improving and controlling the dissolution rates of therapeutic agents, and in particular poorly water-soluble drugs. Examples of strategies being explored include:

- Solid dispersions in polymers and sugars.
- Polymeric carriers, and drug release from polymeric devices.
- Amorphous drug forms stabilized by processing and excipients.
- Responsive polymers for site-specific delivery.

Transdermal and topical drug delivery:

Controlled and targeted delivery of topically applied therapeutic agents for local and systemic effects, from delivery vector design to in vivo bioactivity:

- Vesicles and nano-particles for small organic and macro-molecule delivery.
- Bio-responsive delivery systems for targeting to diseased sites.
- Delivery of bioactive agents from traditional remedies.

Delivery of peptides, proteins and genes:

Some of the delivery vectors described are also used to delivery peptides, proteins and genes to tissues. In addition, research considers:

- Protein crystal engineering.
- Protein absorption and structure at interfaces.

Pharmaceutical materials characterisation:

We use numerous characterisation tools for the above projects, including.

- Raman spectroscopy for transdermal permeation monitoring
- In process control and optimisation (Raman)
- NMR characterisation of novel polymers and their interactions with API's

In addition, 2 members of pharmaceuticals staff have responsibility for thermal and spectroscopic equipment to be purchased as part of a £4.5M commitment from the University to build a Chemical Analysis Facility (from Easter 2008); this will house 700 & 500 MHz NMRs, powder & small angle XRD to compliment existing single crystal kit, 3 new mass spectrometers, FT- and dispersive Raman spectrometers (with deep UV laser), FT- and imaging IR spectroscopy, UV, fluorescence and CD equipment and thermal analysis instruments (DSC, TGA, ITC, hot-stage microscope).

Publications

1 book, 71 peer reviewed research papers, 7 review articles in journals, 26 book chapters, 2 patents.

Authored books

1. **Williams, A.C.** "Transdermal and Topical Drug Delivery; from theory to clinical practice". Pharmaceutical Press, London. 2003.

Recent refereed research papers published in journals

1. Khutoryanskaya, O.V., Williams, A.C. and **Khutoryanskiy, V.V.**, "pH-Mediated interactions between poly(acrylic acid) and methylcellulose in the formation of ultrathin multilayered hydrogels and spherical nanoparticles", *Macromolecules*, 2007, 40 (21), 7707-7713.
2. Rawlinson, C.F., **Williams, A.C.**, Timmins, P.T. and Grimsey, I., "Polymer-mediated disruption of drug crystallinity", *Int. J. Pharm.*, 2007, 336, 42-48.
3. DeMatos, L.L., **Williams, A.C.**, Booth, S.W., Petts C.R. and Blagden, N. "Solvent influences on metastable polymorph lifetimes: Real-time interconversions using energy dispersive X-ray diffractometry", *J. Pharm. Sci.*, 2007, 96, 1069-1078.
4. El Maghraby, G.M.M., Williams, A.C. and **Barry, B.W.** "Can drug-bearing liposomes penetrate intact skin?" *J. Pharm. Pharmacol.*, 2006, 58, 415-429.
5. Tekko, I.A., Bonner M.C., Bowen, R.D. and **Williams A.C.**, "Permeation of bioactive constituents from *Arnica montana* preparations through human skin in vitro." *J. Pharm. Pharmacol.*, 2006, 58, 1167-1176.
6. Tekko, I.A., Bonner M.C. and **Williams A.C.**, "An optimised reverse-phase high performance liquid chromatographic method for evaluating percutaneous absorption of glucosamine hydrochloride", *J. Pharm. Biomed. Anal.*, 2006, 41, 385-392.
7. **Williams, A.C.**, Edwards, H.G.M., Lawson, E.E. and Barry, B.W., "Molecular interactions between the penetration enhancer 1,8-cineole and human skin"., *J. Raman Spectrosc.*, 2006, 37, 361-366.
8. El Maghraby, G.M.M., Williams, A.C. and **Barry, B.W.**, "Drug interaction and location in liposomes: correlation with polar surface area", *Int. J. Pharm.* 2005, 292, 179-185.

9. Lu, M., **Williams, A.C.**, Timmins, P and Forbes, R.T., "Disorder and dissolution enhancement: deposition of ibuprofen onto insoluble carriers", *Eur. J. Pharm. Sci.*, 2005, 26, 288-294.
10. Ahmed, A, Barry, B.W., **Williams, A.C.** and Davis, A.F., "Penciclovir solubility in Eudragit films; a comparison of X-ray, thermal, microscopic and release rate techniques", *J. Pharm. Biomed. Anal.*, 2004, 34, 945-956.
11. **Williams, A.C.**, Cooper, V.B., Thomas, L., Griffith, L.J., Petts, C.R. and Booth, S.W., "Evaluation of drug physical form during granulation, tableting and storage", *Int. J. Pharm.*, 2004, 275, 29-39.
12. El Maghraby, G.M.M., Williams, A.C. and **Barry, B.W.**, "Interactions of surfactants (edge activators) and skin penetration enhancers with liposomes", *Int. J. Pharm.* 2004, 276, 143-161.
13. O'Brien, L.E., Timmins, P, **Williams, A.C.** and York, P., "Use of in situ FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs", *J. Pharm. Biomed. Anal.*, 2004, 36, 335-340.