Drug Delivery & Formulations

Micro- and Nanothermal Analysis of Pharmaceutical Materials

Microthermal analysis enables the properties of pharmaceutical materials to be determined in the early stages of drug development – offering advantages in both practical and regulatory terms.

By Ljiljana Harding, Mike Reading and Duncan QM Craig at the School of Chemical Sciences and Pharmacy, University of East Anglia, Kevin Kjoller at Anasys Instruments, and Nico Gotzen, Doctoral Fellow of Vrije Universiteit Brussel

Ljiljana Harding is a postgraduate student in the Pharmaceutical Materials Science and Nanoscience Group at the School of Chemical Sciences and Pharmacy, University of East Anglia. Her PhD project, supervised by Professors Mike Reading and Duncan Craig, is aimed at investigating the applications of micro/nanothermal analysis of pharmaceutical materials. She obtained an MPharm at the School of Pharmacy, University of Belgrade (Serbia) and, prior to joining Professor Craig’s group, worked with freeze-dried pharmaceuticals at the pharmaceutical company Hemoform (Serbia).

Mike Reading is Professor of Pharmacy at the University of East Anglia (Norwich, UK) and Chief Scientific Officer at Anasys Instruments (Santa Barbara, CA). He gained a BSc and then a PhD (1983) from the University of Salford (UK) and, after post-doctoral work in France (at the CNRS, Centre for Calorimetry and Thermodynamics, Marseille), worked with ICI until 1997 when he left to join the IPTME (Institute of Polymer Technology and Materials Engineering) at Loughborough University (UK). In 2004 he moved to UEA to take up a chair in pharmaceutical characterisation science. Professor Reading’s current research centres on using scanning probe microscopy to characterise the structure and chemical composition of samples on a small – preferably nano – scale. He has been given the Mettler Award (the highest honour awarded by the North American Thermal Analysis Society) and a Royal Society of Chemistry Thermal Methods Group Young Scientist Award.

Duncan Craig is the Head of Pharmacy and Chair in Pharmaceutics at the School of Chemical Sciences and Pharmacy, University of East Anglia. He obtained a BPharm (Hons) at the University of Bath (1984) and went on to read for a PhD at the University of London (1989) in the area of drug dispersions in water-miscible polymers for drug delivery, with particular interest in developing novel thermal and dielectric techniques for physical characterisation. From 1988 to 1999, he held a range of posts from Teaching and Research Assistant to Reader at the School of Pharmacy, University of London. In 1999 he moved to a Chair in Biophysical Pharmacy, School of Pharmacy, Queen’s University Belfast, before moving to UEA in 2003. His current research interests focus on the development of novel approaches to the characterisation and design of drugs and drug delivery systems; these include polymeric delivery systems, amorphous drugs, lipid-based drug dispersions and microparticulate systems, including taste-masking microspheres.

Kevin Kjoller is Vice President of Research, Engineering and Applications at Anasys Instruments (Santa Barbara, CA). He has been involved with the research and development of Scanning Probe Microscopes (SPMs) since 1987, mostly within Digital Instruments/Veeco (Woodbury, NY), and is regarded within the SPM industry as one of the world’s leading technology and applications experts in the field. At different points throughout his 16-year career with DI/Veeco, he managed all of the applications and research SPM product development — in particular, the product development efforts for the Bioscope II Platform and a couple of generations of the Nanoscope Controller. Mr Kjoller has a BS in Physics from the University of California, Santa Barbara.

Nico Gotzen has been a Doctoral Fellow of the Fund for Scientific Research Flanders (FWO-Vlaanderen) since October 2004. He is working on the characterisation of thermally-induced phase separation in smart polymer layers of polymer blends and diblock polymers using SPM related techniques.

Thermal methods are one of the fundamental tools available to pharmaceutical materials scientists and have been widely used for many years for the characterisation of pharmaceutical materials. Conventional thermal techniques, such as differential scanning calorimetry (DSC) and modulated temperature DSC (MTDSC) are well established and extensively used; however, it should be borne in mind that, as bulk measurement techniques, they provide results that represent the sum of all the constituents in the specimen, with the thermal response often being dominated by the higher concentration material. Furthermore, such methods provide no information on the size, shape or spatial distribution of constituents within a multicomponent system.
Micro/Nano thermal analysis (MTA/nano-TA) overcomes these disadvantages by combining atomic force microscopy (AFM) with thermal methods of analysis. The principle of MTA is based on performing highly localised material property characterisation on a micrometre to a sub-micrometre scale on a sample subjected to a controlled temperature programme using a heated tip.

**MTA INSTRUMENTATION**

As with an AFM, the major component of an MTA system is a cantilever with an integrated tip that is used to scan the surface, its position being controlled in the X, Y and Z directions by means of a piezo-electric scanner. Laser light is used to measure the degree of bending of the cantilever, and thereby the normal force acting between the tip and sample. Instead of standard AFM tips, the instrument uses a thermal probe; these can be of many kinds but we will consider only two here. The first is manufactured from Wollaston process wire (platinum/rhodium core surrounded by a silver sheath), forming a loop attached to the cantilever; the second is the more recently introduced silicon nanoprobe which has much higher spatial resolution.

At the end of the Wollaston probe, the silver is etched away to leave a platinum/rhodium thermal tip, which results in a higher resistance at the tip than in the remainder of the wire. An electric current passed through the probe results in Joule heating of the exposed tip. The thermal probe acts not only as a source of heat, but also as a near-field temperature detector. The temperature signal can be used to generate a thermal image (by maintaining the temperature of the tip at a constant value), and to perform localised thermal analysis (by ramping the temperature of the tip). As with an AFM, the height of the probe is used to build up topography images, which are created independently of temperature measurements.

The sample can also be heated in a controlled manner – an approach known as localised thermal analysis (LTA). For this, the tip is placed on a chosen location on the sample surface (commonly using previously acquired topographical and/or thermal images as a guide) and a heating signal is applied at a specific rate, with both the variation of power supplied to the tip and the deflection of the cantilever measured as a function of temperature to yield a localised differential thermal analysis signal (L-DTA) and localised thermomechanical analysis signal (L-TMA), respectively. In this manner, both the dimensional changes and thermal transitions associated with the sample are measured as a function of temperature. Melting, glass transition, crystallisation, physical collapse and other phenomena can be detected using this method.

Although the name MTA was originally given to the combination of LTA with near-field microscopy, in its wider sense MTA includes any form of localised characterisation or analysis with near-field thermal probes in combination with microscopy (1). The technique can be used in combination with dynamic mechanical analysis, infrared spectroscopy or analytical pyrolysis with gas chromatography-mass spectrometry. Hybrid instrumentation is being developed to enable chemical fingerprinting of materials on a small scale (1).

**PHARMACEUTICAL APPLICATIONS**

Since its commercialisation in 1998, MTA has found applications in numerous fields, including polymer, biological and microelectronics science. The method has also attracted considerable interest within the pharmaceutical sciences (2), although the use of MTA is still in comparative infancy in this field.

The most important advantage of the technique for pharmaceutical applications is the ability to perform thermal analysis studies on specific regions of a multicomponent sample; this makes it possible to distinguish between different components or physical forms within a dosage form. Standard thermal techniques often require only a few milligrams of sample to be placed in an instrument, which necessitates breaking the dosage form or analysing the individual components of the final delivery system. In MTA, it is possible to analyse the dosage form in situ and, as modification of the sample is not necessary, the possibility of physically altering the sample during preparation is avoided.

The analysis performed is highly localised, and the rest of the sample is preserved in its original unheated state, avoiding the risk of irreversibly altering the whole sample. The heating rates used in LTA are high (up to 100°C/sec) using Anasys Instruments hardware/software technology, which is two orders of magnitude higher than rates used in conventional DSC measurements (5-500°C/min). LTA is quick and multiple runs can be carried out on samples available in a very limited quantity. An average LTA analysis lasts approximately one minute, which gives the possibility of the instrument being used in batch monitoring, as a part of process analytical technology.

LTA and scanning thermal microscopy (SThM) have been shown to be able to distinguish between components within pharmaceutical tablets (3), solid dispersions (4) and drug-loaded polymeric microspheres (5). These early works were aimed at attempting to distinguish between the drug substance and excipient in a dosage form. Crystalline polymorphs of a drug could be identified within a tablet sample using LTA (6). Furthermore, the analysis of a tablet coating was successfully performed in situ (7). The composition and morphology of pharmaceutical powder particles have been studied by MTA in a work by Murphy et al. (8). With the recent
advent of new high resolution thermal probes, this can now be achieved on a scale well below 1 micrometre.

THREE-DIMENSIONAL IMAGING
At present, there exists a paucity of techniques whereby materials can be characterised in a spatially resolved manner, especially in terms of providing sub-surface, three-dimensional information. MTA has recently been used as a three-dimensional imaging tool for the analysis of pharmaceutical compacts (9). This novel imaging technique was tested on HPMC (hydroxypropyl methylcellulose)-paracetamol compacts, using a grid of L-TMA measurements to obtain three-dimensional information (Figure 1). This technique allows the study of transition temperatures across the surface of the sample as well as analysis of the distribution of materials below the surface of the material by having the probe penetrate the sample surface. The technique is believed to have potential for broader use, particularly in the study of multicomponent systems where information on the sub-surface distribution or surface migration of the components may be an issue.

NANOTHERMAL ANALYSIS PROBES
The major disadvantage of the MTA technique has been the relatively low spatial resolution both in SThM and LTA mode; the reason for this is the size of the Wollaston thermal probe, which is much less sharp than the conventional AFM probe. Efforts are being made to overcome this. The new generation of micromachined thermal probes can achieve a spatial resolution for imaging and LTA that is 100x better than with conventional Wollaston probes; the products (supplied by Anasys Instruments) are named nanothermal analysis probes (nano-TA probes). Nanoprobes are manufactured using doped silicon that renders the probes electrically conductive (Figure 2). The free end of the cantilever is doped with a lower implant level than the legs (10) and hence has a higher electrical resistance than the legs. An electrical current running through the cantilever causes resistive heating at the tip end.

Nano-TA probes offer several advantages over conventional Wollaston probes. The probes are capable of imaging in a range of AFM modes (contact and intermittent contact mode) with a spatial resolution comparable with conventional AFM probes. This is illustrated in Figure 3 which shows an image of a rubber blend sample where the domains of the two components, with sizes of ~50nm, are clearly resolved. Furthermore, they show excellent characteristics for local thermal analysis: excellent repeatability can be achieved and the temperature drift is very low.

Zhang et al. (11) demonstrated that nano-TA probes can be used to map and determine the morphology of a phase-separated HPMC/EC (ethylcellulose) blend – a candidate for coating drug delivery products (Figure 2). High resolution images show a structure with an occluded phase, and L-TMA identified that the continuous matrix corresponded to HPMC while the occluded phase was predominantly the EC component, suggesting incompatibility between the two polymers.

ANALYSIS OF BIAXIALLY ORIENTED POLYPROPYLENE FILMS
Biaxially oriented polypropylene films are extensively used in the packaging of pharmaceutical dosage forms. These films are typically multi-layered. Van Asche et al. (12) studied a three-layer structure – a thick layer of polypropylene homopolymer sandwiched between two thin layers that are about 1µm thick. The core layer provides the mechanical properties of the film, while the skin layers provide sealing and/or surface properties. Thermal analysis was performed in cross-section by embedding the film in epoxy resin and sectioning, Figure 4 shows a topographic
image, obtained in contact mode, in which the 1µm skin layer can be clearly seen. In the same figure, we see the results for LTA which clearly distinguish between the transition temperatures of the different materials. Using these measurements, parameters such as the degree of crystallinity and the effects of processing on the individual layers can be studied directly.

CONCLUSIONS AND FUTURE PROSPECTS

The pharmaceutical community is becoming increasingly concerned about the need to anticipate product behaviour at an early stage of the drug development cycle, for both practical and legislative reasons. MTA appears to have a potential for both two- and three-dimensional imaging of multicomponent samples which may aid product characterisation. Novel nano-TA probes have greatly improved the spatial resolution for this technique. A particularly powerful aspect of the new probes is the ability to provide the crucial link between fundamental physicochemical characterisation (thermal analysis) and spatial mapping of specific sample properties (PFM-AFM, pulsed-force-mode atomic force microscopy).

It can be concluded that MTA offers a unique insight into the structure and properties of complex materials in a spatially resolved manner. The technique lends itself to being used as a powerful tool for predicting product behaviour at the early stages of the drug development, which is important in both practical and regulatory terms. The intensive research in this field will undoubtedly continue, bringing even more sensitive probes and even greater interfacing of MTA with other analytical techniques; this will enable the approach to yield yet more specific information on the structure and properties of materials in pharmaceutical and other scientific fields.

The authors can be contacted at kevin@anasysinstruments.com

References


Figure 4: Images of a multilayer packaging film with local thermal analysis showing analysis of the 1 micron layer.