Laboratory Products Focus

VISUALISING THE STRUCTURE AND CHEMISTRY OF PHARMACEUTICAL FORMULATIONS

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Open any textbook on pharmaceutics and it is readily apparent that the development of a drug substance into a viable product, which can be easily dispensed to the patient, is no simple matter. Administering the drug in the pure state is a rare occurrence and a significant stage in the development of a pharmaceutical product is the drugs incorporation into a delivery system.

> ***"TODAY'S FORMULATIONS ARE EVER-INCREASING IN COMPLEXITY, WITH NANOMETER SIZED DRUG COMPONENTS, INTRICATE DELIVERY SYSTEMS AND MECHANISMS OF DRUG RELEASE"***

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Ask the simple question of why is there the need for a drug delivery system, and the answer returned is always multifaceted. Primary aims include a dosage form that elicits a predictable therapeutic response, maintains quality (such as chemical and physical stability) and can be mass-produced economically. Oral solid dosage formulations for example, tablets and capsules (containing powders and pellets), remain one of the most convenient methods of drug delivery and account for a large proportion of pharmaceutical products. Yet with the necessary bulking agents, processing aids and disintergrants even the simplest of tablets will be a heterogeneous mixture of many components. Solid dosage design can obtain further levels of complexity, for example, through the inclusion of polymer coatings and matrix systems to control the rate of drug delivery or the site of action. The overall level of complexity thus requires the formulator to call on a multidisciplinary approach combining pharmacy with physical chemistry, material science and chemical engineering. In-situ characterisation of the whole formulation can be vital in correlating the physiochemical and material structure to the observed stability and drug release profiles.

Solid-state analysis of the dosage form has been addressed in the past twenty years or so by the advent and application of advanced spectroscopy and surface analytical tools. The most recent developments enable the often complex data to be visualised through spatially resolved mapping and imaging down to nanometer resolution. Combined with suitable sample preparation techniques or using specific techniques non-invasively it is possible to probe both surface and bulk characteristics. *Table 1*, highlights some of the numerous technologies that have been applied to mapping and imaging of pharmaceutical dosage forms, highlighting resolution and detection limits.

Distribution and identification of components in a heterogeneous system is generally achieved through the application of spectroscopy-based techniques, which provide direct chemical information. Spatially resolved data can be achieved through either mapping or more recently, in some cases, imaging of a whole region of interest. In the former mode of operation, more commonly available, the sample is systematically stepped across an analysis region with spectral data obtained at each and every point of analysis. Retrospective analysis is then used to extract the spatial location of specific chemical entities, for example by the conversion of the intensity of a drug spectral peak to a colour specific pixel intensity.

Table 1. Summary of advanced analytical techniques applied to the spatially resolved analysis of pharmaceutical formulations, giving an indication of typical imaging parameters and detection limits.

Technique	Acronym	Chemical Mapping	High-Res Imaging	Typical Lateral Resolution/microns	Typical Analysis depth/micron	Typical Detection Limits
Time-of-Flight Secondary Ion Mass Spectrometry	TOF-SIMS	✓		0.2 – 0.5	0.001 – 0.002	ppm
X-ray Photoelectron Spectroscopy	XPS or ESCA	✓		2 – 4	0.001 – 0.005	0.01 at%
(Micro) – Fourier-Transform Infrared Microscopy – Attenuated Total Reflectance	FTIR-ATR	✓		15	0.1 – 2.5	1%
Near Infrared Spectroscopy	NIR	✓		5	>5	1%
Raman Microscopy	Raman	✓		<0.5	1	1%
Magnetic Resonance Imaging	MRI		✓	1	1	ppm
Micro Computer Tomography	µCT		✓	5	5	0.1%
Scanning Probe Microscopy / Atomic Force Microscopy	SPM / AFM	✓	✓	0.005	0.001 (z resolution)	1%
Scanning Thermal Microscopy	SThM	✓		1	1	1%
Confocal Laser Scanning Microscopy	CLSM	✓	✓	0.25	0.4	1%
Energy Dispersive X-Ray Analysis	EDAX	✓		1	1 - 5	0.1%
Environmental / Field Emission Scanning Electron Microscopy	ESEM / FE-SEM		✓	>0.005		-

One of the highest lateral resolution (<500nm) and sensitive techniques (<ppm from the outer 1nm) available is time-of-flight secondary ion mass spectrometry (TOF-SIMS). With the improvements in instrumentation during the 1980s and 90s the application to the study of pharmaceutical formulations has become possible. Belu et al published a detailed account of the technique and application of TOF-SIMS to pharmaceutical products in 2000 [1]. In *Figure 1(A)*, an example chemical map is given from our research; where the relative distribution of three components, drug (prednisolone metasulfobenzoate), excipient (lactose) and polymer (ethylcellulose) in a controlled release system has been determined [2]. *Figure 2*, gives a second chemical mapping example where changes in the drug distribution as a function of stability testing have been imaged using TOF-SIMS.

Whilst the sensitivity and resolution are the main advantages for TOF-SIMS the major limitations are the lack of quantitative data and the difficulty in determining secondary structural information. Other chemical spectroscopy tools can address these limitations at the expense of detection limits, depth of analysis and often lateral resolution. Arguably the most commonly applied techniques are the vibrational spectroscopies of mid-infrared,

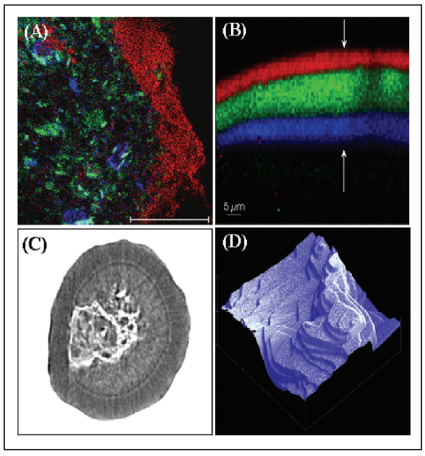

Figure 1. (A) TOF-SIMS overlay image of component distribution in a controlled release pellet ethyl cellulose (red, m/z 59), lactose (green, m/z 365) and prednisolone drug (blue, m/z 589). (B) Raman mapping of a pharmaceutical polymer layered structure (courtesy of Witech). (C) Slice through the centre of a layered pellet, imaged non-invasively by x-ray µ-CT (courtesy of Skyscan). (D) AFM 3-D imaging of the surface of a single drug crystal of paracetamol, each step in the order of one molecular dimension of the drug.

near infrared (NIR) and Raman. Based on the measurement of the interaction of incident radiation on the vibrational modes of specific functional groups, the complementary techniques are used as chemical and structural probes. Additionally, through the use of chemometric packages quantitative data can be extracted down to 0.1% detection limits in the solid state. Instrumental developments are continually emerging in the area of spatially resolved spectroscopy and industrial groups such as Fiona Clarke and Don Clark at Pfizer are applying these advances to practical pharmaceutical analysis [3,4]. Most recent additions include, Confocal optics allowing non-invasive Raman analysis, improved lateral resolution to below 1µm (~ 350nm) and focal plane array detector systems giving the ability to image heterogeneity of whole regions simultaneously and rapidly. Chemical mapping has also seen a significant increase in speed of acquisition for example Witech's CRM200 Raman microscope. *Figure 1(B)*, gives a Raman map obtained in less than 2 hours for a multilayered pharmaceutical polymer system (courtesy of Witech).

Today's formulations are ever-increasing in complexity, with nanometer sized drug components, intricate delivery systems and mechanisms of drug release. To fully understand this complexity high-resolution imaging techniques offering unparalleled resolution (to the nm scale) are used concurrently with spectroscopic analysis. Additionally they often add a new analytical dimension through the ability to study dynamic processes or probe a complete sample non-invasively. For example X-ray microcomputer tomography, first available in the late 1990s, enables

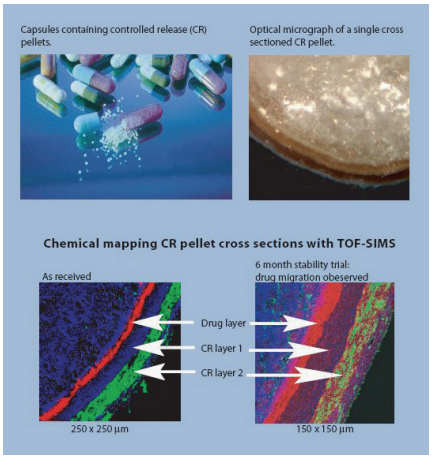

Figure 2. Comparison of controlled release formulations before and after stability testing; by cross-sectional preparation and chemical mapping by TOF-SIMS.

the 3-dimensional structure of a whole dosage form to be generated non-invasively. Based on density differences, the current resolution of the technique for pharmaceuticals is just less than 1µm. A cross-sectional image obtained non-invasively for a multilayered pellet is given in *Figure 1(C)* highlighting regions of high density due to the intact coatings and low density in the core due to porosity (courtesy of Skyscan). A second example is given in *Figure 3*, which shows the inherent cracking occurring within a tablet core after coating, postulated to be an example of tabletting relaxation. Additionally with complete 3D analysis obtained, image reconstruction can be used to quantify parameters such as porosity, coating thickness and content uniformity.

To reach optimum imaging resolution, techniques such as confocal laser scanning microscopy, electron microscopy and atomic force microscopy, need to be utilised. The latter developed by Binnig and coworkers, in 1986, allows imaging of both insulating and conductive substrates down to atomic resolution.

Based on the measurement of forces of interaction experienced by a sharp probe as it is raster scanned across a sample, a 3-dimensional morphological image of the sample surface can be obtained. During the 1990s, differing modes of operation have become available enabling differences in material and thermal properties to also be characterised and imaged. Naturally this has resulted in significant academic research for the potential application to pharmaceutical formulations with the general resolution for these systems between 1 – 5 nm (lateral) and <1 nm (vertical).

The technique is now regularly used to probe material properties of the active product ingredient, such as particle roughness, shape, surface energy, cohesiveness and elastic modulus. *Figure 1 (D)* gives an AFM image of a single

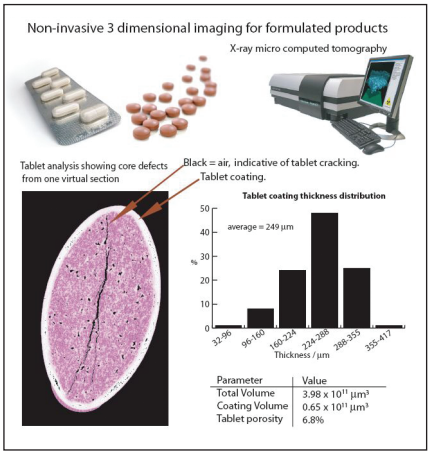

Figure 3. Non-invasive 3-D microscopy imaging revealing the physical structure of formulations and through image analysis quantitative properties.

crystal of paracetamol with each step height the order of the molecular dimension of the drug. Under the flexible imaging environment (air, solution or at elevated temperature and humidity), this is one of the high-resolution techniques allowing the in-situ assessment of the effects of drug processing on areas such as dissolution or crystallisation.

The development of a viable drug delivery system involves the incorporation of many ingredients and often seemingly similar formulations exhibit varied performance.

The advanced spectroscopy and imaging tools available to the formulator offers a new dimension in analysis enabling the visualisation of otherwise complex data in which chemical, physical and material properties can be resolved to nanometer resolution.

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