

TOTAL SOLUTIONS FOR THE PHARMACEUTICAL INDUSTRY

CSMA



Modern methods of surface chemical characterisation play an important role in the study and development of pharmaceutical products. X-ray photoelectron spectroscopy (XPS) and time-of-flight secondary ion mass spectrometry (ToF-SIMS) are two of the most important surface analysis techniques, with the following features:

XPS

- Elemental and chemical state information.
- Quantitative analysis.

ToF-SIMS

- Detailed and highly specific chemical information (elements, chemical groups, polymer structures, molecules).
- Highly sensitive (trace detection limits).
- Imaging with high spatial resolution (<200 nanometres).

These capabilities are demonstrated in the pharmaceutical case studies in this brochure.

BENEFITS TO CUSTOMER

- Cost - effective evaluation of the critical interactions between products, plant equipment and packaging throughout the manufacturing process and the entire product life cycle.
- Cleanliness assessment of products, process equipment and materials, and product packaging.
- Rapid identification of contamination, its source and cause.
- Evaluation of product and packaging stability (and product - packaging compatibility).
- Assessment of sterilisation effects on products and packaging.
- Optimisation and acceleration of new product development.
- Reverse engineering of products taken directly from the pharmacy shelf.

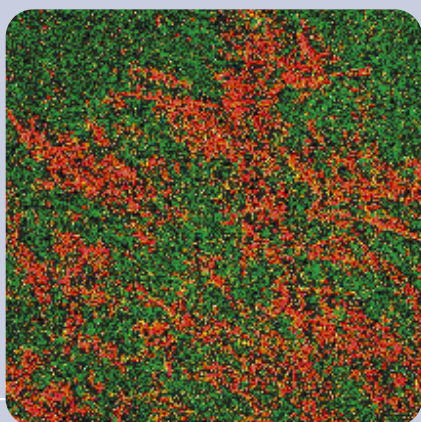
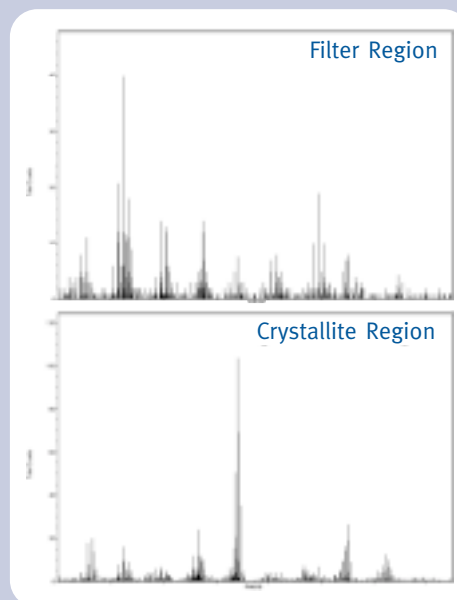


Crystallite Contamination in a Drug Formulation

ToF-SIMS was used to identify a foreign crystalline material which appeared in a drug solution after storage. Only a microscopic amount of crystallite was present, insufficient for bulk analytical techniques. The material was collected on a fine filter and a small clump of crystallites on the filter surface was analysed.

The measurements involved the latest technology whereby RAW data were acquired from an area containing some of the crystallites of interest. Retrospectively, mass spectra were created for *blank filter* and *crystallite* regions providing, by comparison, the *mass spectral fingerprint* for the crystallite. This is illustrated right where the same partial mass range is plotted *off* and *on* the crystalline material.

The information was enhanced by retrospective chemical mapping which clearly showed the crystallites (red; using a peak from the *mass spectral fingerprint*) on top of the filter (green; using a signal which is filter-specific). This work indicated that a polymer additive had leached out of a bottle stopper, into the drug solution and crystallised.



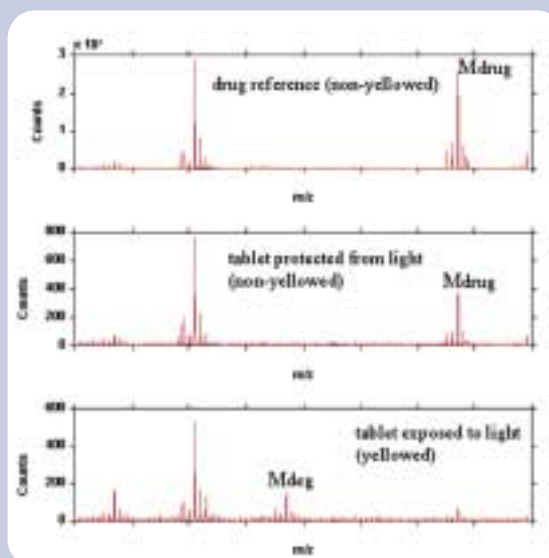
RAW data: A selected area on a sample is scanned and a mass spectrum is acquired and stored at every pixel point. Retrospectively, the following operations can be performed:

- Region-of-Interest (ROI) analysis: For defined regions (any shape and size) within the selected analysis area, it is possible to sum the mass spectra at all of the pixel points within each defined region thus generating area-specific mass spectra.
- Imaging analysis : For the selected analysis area, it is possible to generate chemical maps (images) for any of the spectral peaks. For very weak signals, where there is not enough individual peak intensity to produce meaningful images, it is also possible to add peak intensities thereby improving image statistics.



Surface Yellowing of a Drug Tablet upon Light Exposure

ToF-SIMS was used to investigate the problem of yellow discolouration of white drug tablets upon light exposure. The data showed that selective degradation of the drug molecule had taken place where an acetic acid group was converted to an aldehyde group (mass difference = 30). This resulted in the formation of a new molecule (Mdeg) with a mass of 30 less than the pristine molecule (Mdrug) where M = molecular mass. Conjugation of this aldehyde group with an aromatic ring resulted in a shift in the light absorption from the ultra-violet region of the electromagnetic spectrum into, at least partially, the blue region of the visible spectrum, resulting in the yellow discolouration.



CASE STUDY THREE

SIMS Imaging of a Dry Inhalant Formulation

The SIMS image shows the distribution of 0.5 - 2 micron active drug particles (green) at the surface of a 50 micron carrier granule (red) for a commercial inhalant. In combination with XPS, quantification of the surface drug loading leads to a correlation of the drug coverage with in-vivo performance.

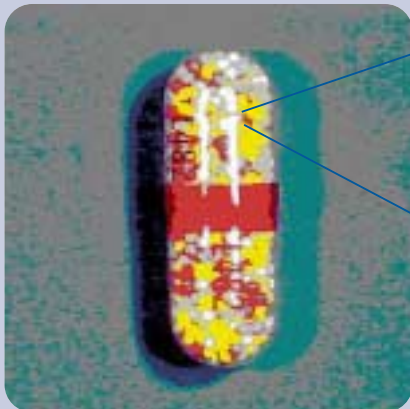


CASE STUDY FOUR

ToF-SIMS Imaging of Coated Drug Beads

State-of-the-art ToF-SIMS has now become an important analytical tool for the research and development of controlled-release drug delivery systems. One approach is to encapsulate a drug bead within a multi-layer polymer coating where the properties of the latter control the rate of drug release. Since the production of this type of multi-component system is difficult, analysis of the final product is vital. As a mass spectrometry, ToF-SIMS is ideally suited for this task and can provide an assessment of the thickness and uniformity of the coating layers as well as the distribution of the drug and other excipients within the bead. This is illustrated by the ToF-SIMS images below for a drug used in heart medication, where the beads were cross-sectioned to facilitate the analysis (data courtesy of Physical Electronics, Eden Prairie, U.S.A).

OPTICAL MICROGRAPH OF DRUG CAPSULE



Optical Micrograph of a single pellet cross-section

RGB OVERLAY OF TOF SIMS IMAGES



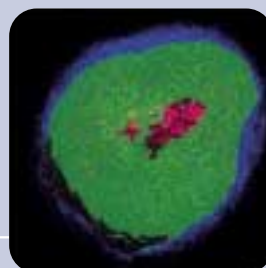
Silica Core
Si⁺



Drug
Molecular Ion
[M+H]⁺
m/z 268



Ethylcellulose
C₃H₅O⁺

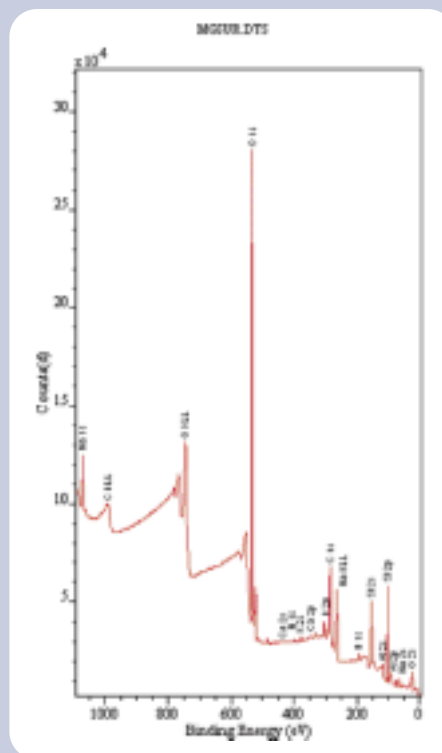


Overlay



Packaging and Storage

Product/package interactions are amongst the most critical in pharmaceutical production. The interaction of the packaging wall with the active substance and/or the carrier can adjust, positively or negatively, the effective dose. Detrimental contamination of the product can also occur from species associated with the package material. The following data show how XPS was used to determine the surface composition of a glass bottle used for drug storage and how the surface composition can vary across the internal surface which is in contact with the product (as well as varying from bottle to bottle). In cases where there is a high affinity of the active substance for the package wall, even small variations in wall surface composition can have a significant effect upon the effective concentration of the active substance.



SURFACE COMPOSITIONS (IN ATOMIC %) BY XPS

Element	Neck	Base	Side Wall
Silicon	21.8	23.2	24.9
Oxygen	49.4	52.7	55.4
Carbon	19.3	13.3	8.6
Sodium	3.6	3.9	4.5
Aluminium	2.1	2.1	2.2
Boron	2.8	3.5	3.8
Nitrogen	0.3	0.3	Not detected
Calcium	0.3	0.2	0.2
Potassium	0.6	0.8	0.5

CSMA provides a complete surface analysis service to industry to accommodate every level of demand:

- rapid turnaround analysis (24 hours)
- problem solving and failure analysis
- litigation and expert witnesses
- training courses
- reverse engineering and competitor analysis
- materials and product development
- patent registration / infringement

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