

Organic and molecular imaging by ToF-SIMS—at the cutting edge

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Introduction

Time-of-flight secondary ion mass spectrometry (ToF-SIMS) is a routine analytical tool for the characterisation of materials, particularly surfaces. It provides detailed chemical structure information (i.e. elements, functional groups, polymer constituents, molecules) with very high sensitivity. Its imaging capability, however, has been greatly limited until now, with the advent of new polyatomic primary ion sources using gold, bismuth and even buckminsterfullerene.

Principles

A pulsed primary ion beam impacts a sample surface, resulting in the emission of particles (secondary ions), which are then mass analysed by their flight times to a time-sensitive detector. In the *static* mode of analysis, samples, including delicate organic materials, are effectively undamaged in the experiment. In this mode, the technique is also very surface sensitive, sampling only the outermost couple of nanometres. It may be used for the analysis of near/sub-surface and bulk regions of materials when coupled with appropriate sample preparation to expose the regions of interest.

In its spectroscopic mode of operation, ToF-SIMS simply provides mass spectra (e.g. see Figure 1). Chemical imaging, however, can be carried out by rastering a micro-focused primary ion beam over the sample surface and collecting a mass spectrum at every pixel point (where, say, a 256 × 256 pixel array is used to define an area). Retrospectively, for any peak in the mass spectrum, an image can be generated. Thus, it is possible to map

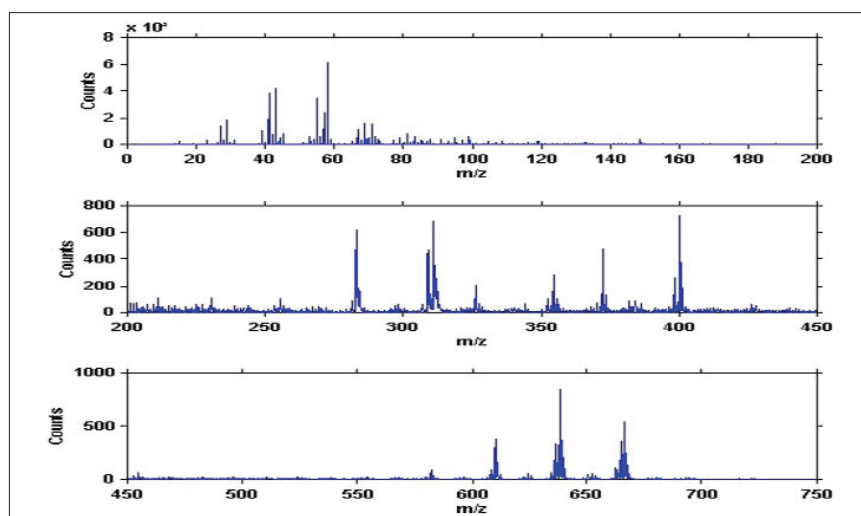


Figure 1. Positive-ion ToF-SIMS spectrum plotted in three segments where, within each mass segment, the intensity is scaled to the most intense peak in the range.

the distribution of species (elements, functional groups, polymer constituents, molecules) providing that each species has one or more diagnostic peaks in the mass spectrum.

As an organic imaging technique, ToF-SIMS has previously been limited by the intensities of those signals that are, structurally, the most significant, i.e. polyatomic clusters including molecular ions. The mass spectra for most organic/polymeric materials are dominated by fragments (e.g. $C_xH_y^{+/-}$), at relatively low mass ($< m/z$ 100, e.g. see Figure 1). Many of these low mass signals can originate from more than one component. As such, despite their high intensities, many of these signals are not sufficiently diagnostic for organic imaging purposes.

With increasing mass, larger polyatomic fragments are observed along with intact molecular and quasi-molecular ions (e.g. see Figure 1, $> m/z$ 200). Each of these

higher mass cluster/molecular signals is structurally more specific and often unique, for one particular component, and, as such, can be used for chemical mapping of that component. With the more established ion sources such as gallium (Ga^+), the intensities of these higher mass cluster/molecular signals are often too weak for chemical imaging. This is due to insufficient yields of these higher mass species under atomic primary bombardment. This problem has recently been overcome by the use of polyatomic primary sources such as gold (Au_n^+), bismuth (Bi_n^+) and C_{60}^+ (buckminsterfullerene), which has resulted in dramatic increases (up to a hundred-fold) in the secondary ion yields of the higher mass species. The yields of these structurally significant species are sufficiently enhanced such that organic and molecular imaging, with sub-micrometre spatial resolution, is now a reality with a

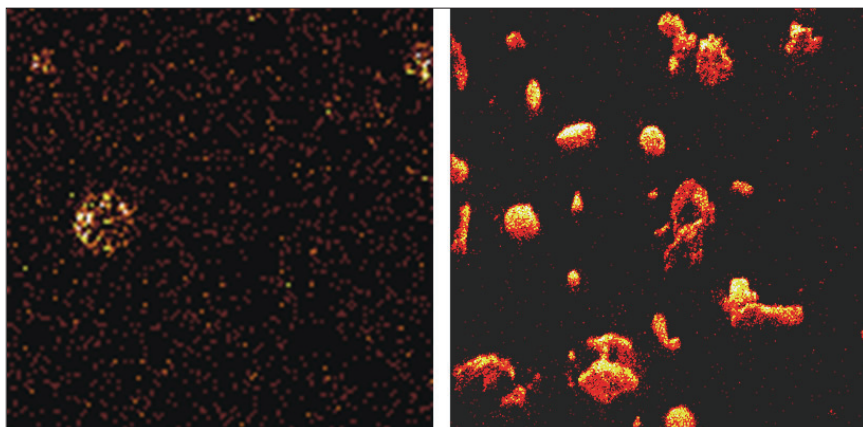


Figure 2. Chemical imaging of pharmaceuticals. Drug molecule images of 1–10 μm drug-loaded particles using gallium (Ga^+ , left image) and bismuth (Bi_3^+ , right image). Data courtesy of ION-TOF GmbH.

capability that far exceeds that obtained in the past.

This superior imaging capability is demonstrated for a pharmaceutical product, comprising a drug on small sugar beads. Figure 2 compares the drug molecular ion images obtained for the particles using both gallium (Ga^+) and bismuth (Bi_3^+) primary ion sources. Using gallium, the drug particles are barely observable, reflecting the low intensity of the molecular ion peak of the drug using this atomic primary source. This contrasts with the drug molecular ion image obtained using Bi_3^+ bombardment where the drug distribution is easily observed.

Applications

The new ToF-SIMS imaging capability can be exploited in a wide range of industries. In the pharmaceutical industry, from the example above, drug loadings and distributions on the surface of carrier particles (e.g. inhalants) can be directly assessed. Tablet formulations may also be studied, where the distributions of species [drug, excipient(s), lubricant(s)] on the tablet surface and throughout the bulk (exposed by sectioning) can be determined as a function of the manufacturing process. With the appropriate sample preparation, polymer-coated drug beads can be studied, where ToF-SIMS can be used to assess the thickness and uniformity of the coating layers as well as the distributions of the drug and other components within the bead.

Figure 3 shows an example from the electronics industry, where a manufacturer of printed circuit boards (PCBs) was experiencing problems with non-wetting of solder on gold bond pads. The various organic and inorganic contaminants detected by ToF-SIMS, including nickel, were identified as the cause of the problem, originating from a contaminated electroplating bath.

Another important area of application is hair care. Modern hair care products include a wide range of shampoos, conditioners, styling products and colourants. The chemistry of each product is complex, with a variety of components formulated to bring a specific cosmetic effect, e.g. cleansing, shine, lustre, thickening. The development of effective hair treatments relies on a detailed knowledge of the surface chemistry of the hair and the effect of the various ingredients of the formulation on the hair structure. The imaging capability of ToF-SIMS

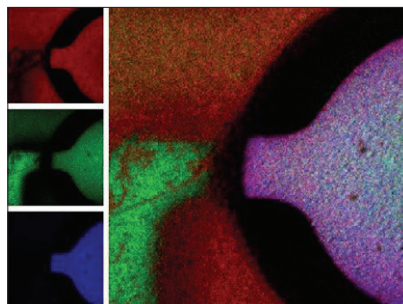


Figure 3. Gold bond pad on a printed circuit board. Evaluation of surface contaminants by imaging ToF-SIMS, using colour overlays; silicon (red), hydrocarbon (green) and nickel (blue). Image area = $500\ \mu\text{m} \times 500\ \mu\text{m}$.

in this area is demonstrated by Figure 4, which shows a human hair. Its mass spectra showed peaks characteristic of protein (from keratin), lipids (e.g. palmitate, 18-methyleicosanoate), calcium, poly-(dimethyl-siloxane) and quaternary alkyl-ammonium compounds (from conditioning agents), and alkyl-sulfates (surfactant). It was possible to image/map selectively each of these species by ToF-SIMS, allowing evaluation of their relative distributions and concentrations across the surface of the hair fibres with treatment. For example, the alkyl-sulfate molecules comprise the structure $\text{C}_n\text{H}_{2n+1}\text{OSO}_3^-$ (where $n=12, 14, 16$ and 18) and are characterised by their intact molecular anion signals at m/z 265⁻, 293⁻, 321⁻ and 349⁻, respectively. These intact molecules were mapped, where Figure 4 shows the distribution of alkyl-sulfate residue (red) on the surface of the hair (cyan, corresponding to the non-specific total ion image). Note, the physical structure of the hair surface is clearly evident.

There is huge scope for imaging ToF-SIMS for the evaluation of surface modifications/coatings on biomedical materials, devices and implants. These are applied to render the materials/devices/implants *biocompatible*, thus preventing any adverse reaction *in vivo* (e.g. thrombosis, inflammation) or *ex vivo* by contact with drawn bodily fluids (e.g. blood). Additionally, the coatings may be *bioactive*, designed to elicit a particular response from the body (e.g. tissue repair and regeneration). The nature, integrity and stability of the surface modifications/coatings

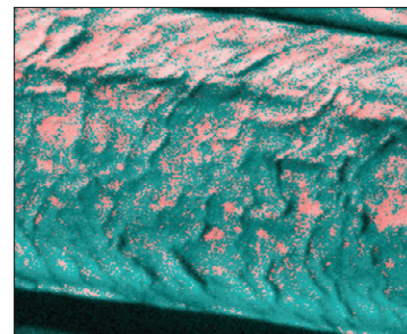


Figure 4. Evaluation of hair treatments. Distribution of the anionic surfactant $\text{C}_n\text{H}_{2n+1}\text{OSO}_3^-$ (red) on the surface of human hair, by imaging ToF-SIMS.

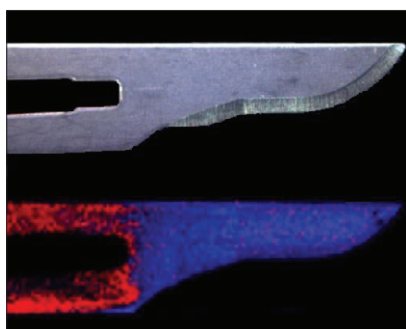


Figure 5. Plasma cleaning of a surgical blade. Optical image (top) and two-colour overlay ToF-SIMS image [bottom; red = protein (non-cleaned area), blue = iron corresponding to the exposed steel substrate (plasma-cleaned area)]. Image width is 18 mm.

are critical to the performance of the material/device/implant, e.g. catheters, vascular grafts, orthopaedic implants, arterial stents, filters, pacemakers, diagnostic sensors. The technique can be extended to biological samples and the localisation of lipids and cholesterol in tissue sections, prepared by cryo-ultramicrotomy, with sub-cellular

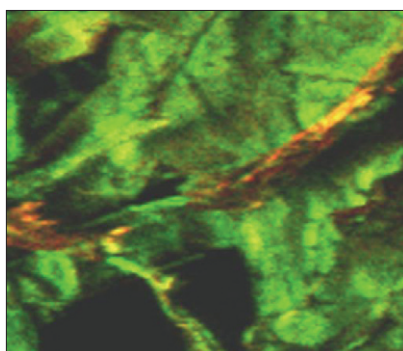


Figure 6. Molecular imaging by ToF-SIMS—coverage of a paper by a wet strength additive. Green (additive, overlying the paper), red (exposed paper). Image area = 200 μm \times 200 μm .

spatial resolution has been reported. More recently, imaging ToF-SIMS has been used to evaluate plasma cleaning of surgical instruments (see Figure 5) for the removal of TSE (transmissible spongiform encephalopathy) infective agents, bacteria and spores. Again, the chemical specificity of this imaging mass spectrometry is exploited

whereby proteinaceous material can be detected and mapped.

The diverse range of industries using paper and textiles is another potentially exciting area of application. For example, imaging ToF-SIMS can be used to assess the integrity of fabric coatings (e.g. water repellent, flame retardant), and the effects of different cleaning treatments/agents or weathering. For example, Figure 6 shows the coverage of a wet strength additive molecule over the surface of a paper towel (where the 3D aspect of this image is quite apparent).

Conclusion

The latest ToF-SIMS imaging capabilities have yet to be widely exploited. The new polyatomic primary ion sources have only recently been developed for routine use in the market and there are relatively few instruments around the world which are equipped with this technology. Nevertheless, the applications to date have demonstrated the potential of ToF-SIMS as a true organic imaging technique.

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