ToF-SIMS – A Chemical Microscope, Surface Mass Spectrometry for the Biomedical Industry

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ABSTRACT

The need for chemical characterization of surfaces and thin layers has risen in order to support the increasing use of coating and vacuum processing techniques in the medical devices and pharmaceutical industry. Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) has been established over the last years as a powerful surface analytical technique. In particular, the simultaneous detection of atomic as well as molecular ions and the ability to obtain this information with high lateral and in-depth resolution makes ToF-SIMS well suited for the analysis of structured molecular surfaces.

In this contribution, the fundamental principles of ToF-SIMS will be explained first, with special emphasis on the use of polyatomic primary ions, which allow molecular imaging with sub-µm lateral resolutions. In the second part typical applications will be presented.

INTRODUCTION

The composition and structure of surfaces play an important role in the medical devices and pharmaceutical industry. Properties like cleanliness, wettability, biocompatibility etc. are defined by the surface. For example, the chemical composition of the surface of an implant controls how the host will react to it. Also, surface modifications and functionalization on the molecular level are becoming more common, because they allow one to specifically tailor a product to its use, e. g. cardiovascular stents with a drug-loaded polymer coating. Surfaces are not only of importance for the devices themselves, but also for packaging materials or tools like scalpels. For example the interaction with the packaging wall can affect a drug with all its possible consequences ranging from aesthetics (discoloration of a tablet in a blister package) to even changing the active ingredient. Vacuum processes and coatings allow one to actively control the structure and chemistry of surfaces and are therefore of increasing importance.

In order to understand and support these processes, powerful analytical techniques for the identification, as well as the localization and quantification of substances on a surface or at the interface between different layers are of increasing importance. Surface analysis is meanwhile used routinely in research and development (e. g. methods of surface modification on the molecular level), for fast and efficient failure analysis (e. g. defects in coatings) as well as in production and quality control such as the evaluation of cleaning procedures.

Secondary Ion Mass Spectrometry (SIMS), especially in combination with a Time-of-Flight mass analyzer (ToF-SIMS), is one of the most powerful surface analytical techniques available today. It has become well established over the last decade for many industrial and research applications [1]. This article will give an overview of the principle and instrumentation behind ToF-SIMS. Special emphasis will be laid upon the use of polyatomic primary ions, which allow molecular imaging with sub-micron lateral resolution. Three examples will demonstrate which kind of information about the surface chemistry of a sample can be achieved.

PRINCIPLE OF SECONDARY ION MASS SPECTROMETRY

In SIMS, a sample surface is bombarded with a high energy primary ion beam. The primary ion energy is transferred to target atoms via atomic collisions resulting in a so-called collision cascade [2]. Part of the energy is carried back to the surface and subsequently atomic and molecular particles are emitted from the outer layers. Some of the sputtered particles are electrically charged. These secondary ions are extracted by an electric field into a mass spectrometer, where their mass and thus their chemical structure are determined. The emission process of secondary ions is limited to the uppermost one to three monolayers (typically less than a nanometer in thickness) of a solid sample. Secondary ions can be elemental ions, clusters, molecular fragments and whole molecules (up to a mass of approximately 10,000 u) desorbed from the surface. The detection limits are generally in the ppm range. All this makes SIMS a highly sensitive analytical technique delivering information about the chemical composition of a samples surface.

Time-of Flight mass spectrometry (ToF-MS) has the ability to detect all generated ions in parallel. This and an, in principle, unlimited mass range, makes it the optimum spectrometer for surface analysis by SIMS especially for screening of unknown substances. Other types of mass spectrometers (quadrupole, magnetic sector field instrument) also exist in SIMS instrumentation but these are limited as only one or a few preselected ions are monitored at any given time. Modern time-of-flight mass analyzers offer a mass resolution of more

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than 10,000 (defined as the ratio of a mass of a peak divided by the mass difference to the next neighboring peak, which can be distinguished at 50% half width maximum). The parallel detection of a ToF-MS ensures that all of the generated ions (inorganic and organic) are used for the analysis. Thus, it is possible to only consume a minimal part of the surface during analysis leaving the sample effectively undamaged (static SIMS). Alternatively, the surface can be eroded layer by layer (dynamic SIMS) in order to gain information about the in-depth distribution (depth profile) of compounds in near-surface regions.

One challenge in the analysis of organic samples is the limited amount of material available for analysis. This is due to the massive fragmentation of molecules under the influence of a collision cascade, thus leaving layers with a fully destroyed molecular structure behind. For an artifact-free measurement it is mandatory that only data from non-damaged surface areas are collected. This can be statistically achieved by keeping the primary ion dose so low that the probability p to hit an already damaged area is below a certain limit ("static SIMS limit," typically $p < 10\%$). Moreover, exceeding the static limit usually does not help much in improving detection limits for higher mass molecular ions and molecular depth profiling is greatly hampered, because the molecular structure is typically destroyed in deeper layers.

The picture has changed with the advent of cluster ion beams instead of monoatomic ion beams for surface bombardment [3, 4]. Upon impact on the sample surface, these clusters break apart leading to a non-linear overlap of collision cascades with a surface-nearer deposition of the impact energy. It has been demonstrated that the secondary ion yields of most organic compounds can be enhanced by several orders of magnitude. This increase in yield is not accompanied by a likewise increase in surface damage, thus ultimately leaving more material available for analysis [5]. With the commercial availability of cluster (gold or bismuth) liquid metal ions guns, whose beams can be focused down to 100 nm, it is now possible to make use of the increased efficiency for imaging molecular distributions with sub-micron lateral resolution on surfaces.

APPLICATIONS

Surface spectroscopy of plasma-modified polymers

The most universal type of data resulting from a ToF-SIMS analysis is a mass spectrum of secondary ions reflecting the chemistry on the sample surface. While the low mass range, with elemental and small molecular fragment ions, gives valuable information about the surface chemistry, the full strength of ToF-SIMS comes into play when evaluating the higher mass range of a spectrum. Molecules with masses of up to several 1,000 u are often represented in the mass spectrum by their molecular ions or as large characteristic fragments after the loss of a functional group like a hydroxyl-group (OH). Therefore, it is possible to characterize even chemically complex systems on a surface.

One example for surface spectroscopy with ToF-SIMS of a vacuum processed polymeric surface is given in Figure 1. Here, ToF-SIMS has been used to investigate the surface chemistry of plasma-modified polymers [6]. The modification of polymer surfaces by plasma treatment is an important process for tailoring surface properties with respect to their adhesion behavior, their chemical reactivity, and their biocompatibility etc. The spectra were acquired under static conditions. Figure 1 shows details of negative secondary ion spectra of an untreated polycarbonate surface, of Bisphenol A (the main building block of polycarbonate), oxygen-plasma treated polycarbonate, and hydrogen-plasma treated polycarbonate. It can be clearly seen that the plasma treatment changes the chemical structure of the surface. In both spectra

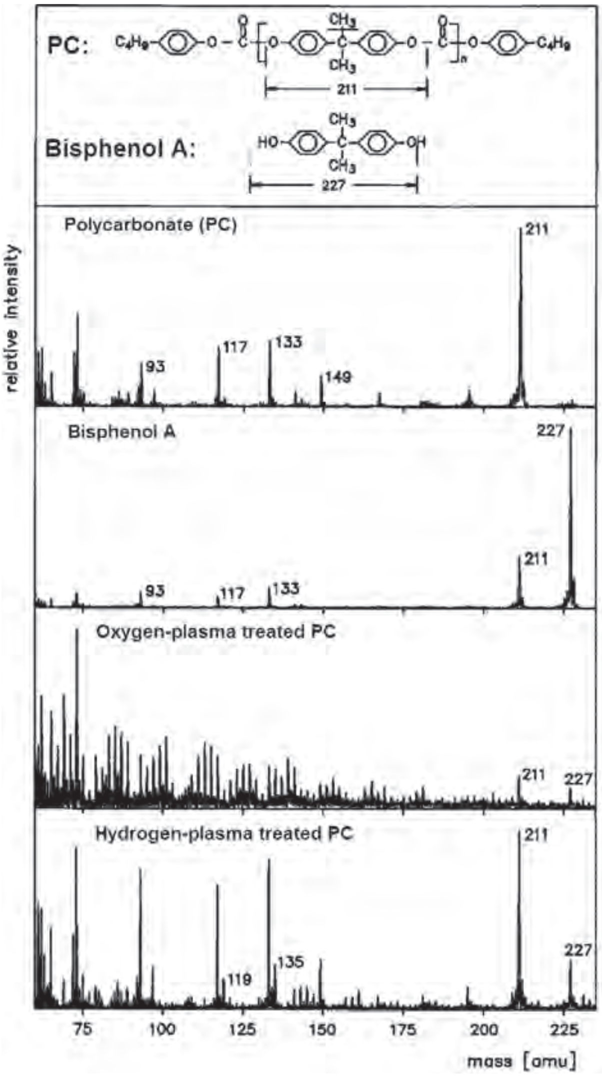

Figure 1: Details of negative secondary ion spectra of polycarbonate, Bisphenol A, oxygen-plasma treated polycarbonate, and hydrogen-plasma treated polycarbonate. (Reflectron-based ToF-MS; primary ion bombardment: 10 keV Ar^+) The structure and some fragmentation pattern of polycarbonate and Bisphenol A are also given.

of the treated polycarbonate a new peak at mass 227 u appears, which corresponds to the deprotonated Bisphenol A, $(M-H)^-$. This indicates chain scission of the polymer at the carbonate group. While the oxygen-plasma oxidizes the surface, as can be seen by the appearance of a variety of new oxygen-containing peaks in the spectrum, the hydrogen-plasma has a reducing effect (new peaks with a mass difference of 2 u in the spectrum). This example demonstrate the outstanding potential of ToF-SIMS for the detection of changes in the molecular surface composition.

Surface imaging of surgical blades

ToF-SIMS analysis is not limited to the spectral characterization of chemical compounds on a surface. By scanning the finely focused primary ion beam over the sample surface it is possible to generate chemical maps (up to 500 x 500 µm^2) showing the lateral distribution of compounds on the surface. Imaging of larger samples (up to 90 x 90 mm^2 or up to 300 mm in diameter for circular samples) is accommodated by scanning the whole sample under the primary ion beam for analysis. During imaging analysis, all ions generated in each pixel are collected by the mass spectrometer and stored in a data file making it possible to display distribution maps for all compounds detected on the sample.

Figure 2 shows secondary ion images of surgical blades from a cleaning and sterilization study. The images were acquired in macro scan mode with a field of view of 25 x 25 mm^2. Cleaning and especially sterilization of surgical tools is of major importance for the success of a procedure. A common method of sterilization for disposable surgical tools is using radiation. The surgical blade on the right is fresh from its package. The blade on the left was used to cut tissue and then irradiated by gamma rays in the upper half only. Figure 2 depicts chemical distribution maps of four different positively charged ions: Fe^+ as a representative of the stainless steel of the blade; $C_4H_{10}N^+$ (Valine) as a typical amino acid fragment of proteins; The phosphocholine-headgroup, $C_5H_{15}NO_4^+$ at mass 184 u, characteristic for phospholipids; and in the fourth map, ions characteristic for diacylglycerol. Note that the diacylglycerol map is a sum of maps of glycerides with different fatty acid chain lengths at masses 551 u (di-palmitoyl-glycerol), 577 u (oleyl-linoleyl-glycerol) and 603 u (di-oleyl-glycerol). The surface coverage of the blade by the tissue residues is mostly less than a monolayer, which can be seen by the rather strong substrate signal (Fe) in most of the area. However, more important to this study, the success of the cleaning can be clearly seen. This example also shows the high efficiency of Bi_3-cluster primary ions in the detection of high-molecular mass ions.

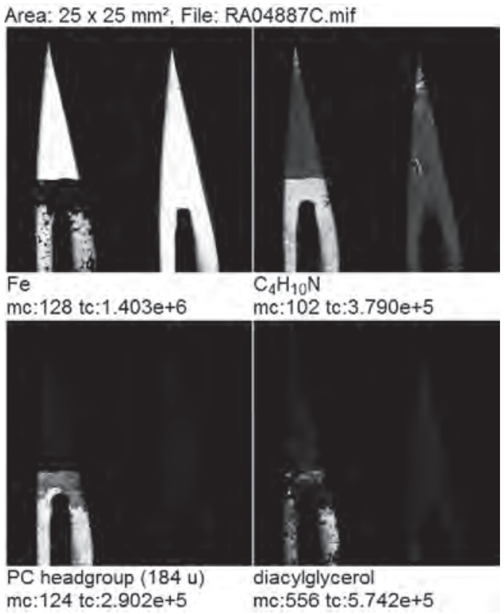

Figure2: Secondary ion images of surgical blades. Right: unused blade; left: used blade, where only the upper part was subsequently sterilized with gamma radiation. (ION-TOF TOF.SIMS 5 instrument; primary ion bombardment: 25 keV Bi_3^+) The subscript of each map gives the ion depicted, the number of counts in the brightest pixel (mc) and the total number of counts (tc). The image is color-coded with a gray-scale. Black corresponds to 0 counts and white corresponds to the brightest pixel.

Depth profiling of molecular coatings on medical devices

ToF-SIMS can be also applied to analyze the in-depth distribution of chemical compounds in near-surface regions and to characterize interfaces between different layers. This is done by using ion bombardment for the controlled erosion of a sample and analyzing the freshly exposed surface in parallel. With the proper selection of the analytical conditions, ToF-SIMS can be used for high performance, ultra-shallow depth profiling with sub-nanometer depth resolution as well as for the analysis of several micrometer thick layers.

One widely used material in the medical device industry is polysiloxane or silicone due to its favorable characteristics such as its ability to withstand a wide range of temperatures, its high degree of compatibility with the human body, its low chemical reactivity and its flexibility. Quite often only the surface of a product is covered with a silicone coating. In those cases it is of importance that the layer is of uniform thickness and homogeneity without defects. ToF-SIMS was used in a quality control study to verify these properties of a silicone layer inside a catheter. Here, the ability to handle even oddly shaped samples (in this case a concave surface with a radius of less then 1 mm) was crucial for the success of the study. Surface images were acquired to verify the homogeneity of the silicone layer. For the determination of the layer thickness, depth profiles were acquired. Figure 3 shows a depth profile on a standard sample, i. e. a glass surface with a silicone coating of a known thickness. Here an additional complication was the fact that both, the coating and the substrate, are silicon-based materials. However, it was possible - even using argon ions for sputter erosion - to distinguish these two materials in a depth profile despite of the heavy fragmentation of molecules (in this case silicone) caused by the ion bombardment. The fragment ion SiC_2H^+ was used as a marker for the silicone.

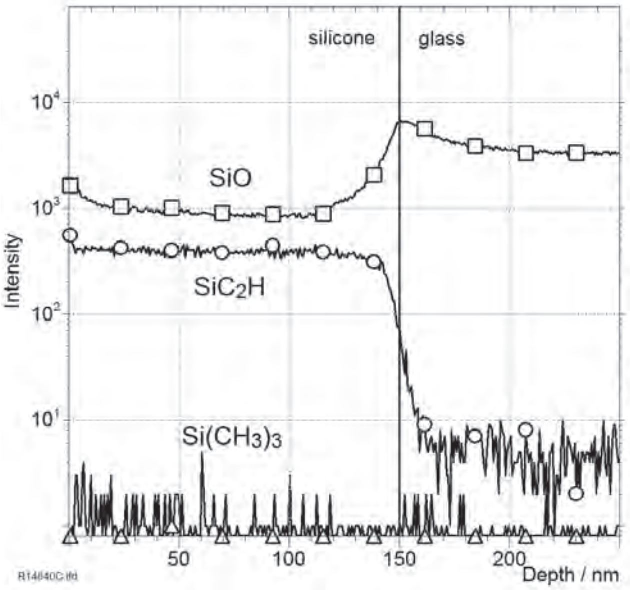

Figure 3: Depth profile through a 150 nm thick silicone layer on a glass surface. (ION-TOF TOF.SIMS 5 instrument; sputter erosion: 2 keV Ar^+; analysis: 25 keV Bi^+)

In recent years with the advent of cluster ion beams like SF_5^+ or C_{60}^+, more and more examples of successful organic depth profiling following molecular ions or large characteristic fragments have been presented [7, 8]. An additional approach to molecular depth profiling has been recently published by N. Mine et al [9]. In contrast to using a cluster beam for sputtering, a low energy (200 eV) cesium ion beam was applied. In principle organic depth profiling is possible on many organic sample systems. The optimum sputter conditions, however, strongly depend on the sample system to be analyzed.

3D-Analysis

By combining depth profiling with imaging analysis, ToF-SIMS can even be used for the three dimensional analysis of small volumes. A complete mass spectrum is saved for every voxel (the volume equivalent of a pixel) in the analyzed volume. It is possible to reconstruct spectra, images and profiles from any region of interest inside the analyzed volume. This possibility of retrospective analysis has been proven to be very efficient, especially for these complex types of analyses. An example of 3D-analysis of animal cells is discussed in the paper of D. Breitenstein et al [10].

SUMMARY

ToF-SIMS is a powerful surface analytical tool suited for all materials compatible with vacuum environment (including powders, insulators and even frozen liquids and biological materials). It can detect all elements (H ... U), is isotope sensitive, and delivers chemical information (molecules, clusters, fragments of several 1,000 u in mass) about the analyzed sample surface with high sensitivity and low detection limit (ppm - ppb). Spatially resolved analysis can be achieved with high lateral resolution (≥ 100 nm) and high depth resolution (≈ 1 nm). One of the many areas, where ToF-SIMS is successfully applied is in the support of the biomedical and pharmaceutical industry and research.

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