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Time-of-flight secondary-ion mass spectrometry for the surface characterization of solid-state pharmaceuticals

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Abstract

Time-of-flight secondary-ion mass spectrometry (ToF-SIMS) is a highly surface sensitive analytical method for surface chemical identification and surface chemical distribution analysis (mapping). Here we have explored the application of ToF-SIMS for the characterization of solid-state pharmaceuticals and highlight specific case studies concerning the distribution and stability of pharmaceutical actives within solid matrices (pellets and polymeric carriers) and the face-specific properties of pharmaceutical crystals.

Introduction

Physical and chemical characterizations are essential in the development of solid dosage forms of pharmaceutical actives, e.g. powders, tablets, matrices and control-release pellets. Traditionally, the physical properties of pharmaceutical powders have been determined using techniques such as powder X-ray diffraction (XRD) and differential scanning calorimetry (DSC), particularly to characterize the crystalline vs amorphous nature of solid-state pharmaceuticals (Mu & Feng 2001; Rogers et al 2002; Agnihotri & Aminabhavi 2004; Ambike et al 2004; Bergese et al 2005). Techniques such as high-performance liquid chromatography (HPLC) have been used to assess drug concentration and purity (e.g. Liu et al 2005; Xiong et al 2005). Such analysis methods only provide information on the bulk pharmaceutical powder, whereas the behaviour of an active pharmaceutical solid both in-vivo and during processing is largely dependent on its specific surface chemistry. Thus it is highly desirable to utilise techniques with high surface specificity and low detection limits.

Pharmaceutical powders may contain regions that are either crystalline or amorphous in nature. Crystalline particles may exhibit a number of crystal faces, each with its own specific physical and chemical surface properties. The face-specific surface properties of pharmaceutical powders are considered critical in controlling their characteristics and performance during formulation, processing and delivery. For example, it is the surface energetics of a particular crystal face that control interactions with excipient molecules, e.g. polymeric stabilizers or viscosity modifiers (Brittain & Grant 1999; Grant 1999) and particles, e.g. drug particles or particulate binders (Florence & Attwood 1998). These phenomena lead to the observation that the chemical and physical properties of a drug powder are dependent on its polymorphic form (Hazlett 1992). The atomic force microscope (AFM) has been used to provide high resolution images of solid-state pharmaceutical formulations (Ringqvist et al 2003; Mu et al 2005), enabling differentiation of surface crystalline features. However, AFM does not provide any surface chemical information.

There are relatively few reported studies that correlate the specific energetics of pharmaceutical crystals, with their face-specific surface chemistry and the molecular arrangement at the different crystal planes. The surface energy of an active pharmaceutical is commonly characterized in terms of a contact angle, determined using the sessile drop technique. Ideally, this requires access to a single crystal with large, flat faces, a situation not often possible. Compacts of micron-sized pharmaceutical powders are often used to enable sessile drop determination, however this may introduce other variables, e.g. changes in surface energy due to compaction (Buckton 1993), as well as the introduction of surface roughness and porosity (Buckton & Newton 1986). Other methods available for the direct determination of surface energies of pharmaceutical powders include: capillary penetration (Prestidge & Tsatouhas 2000), water adsorption kinetics (Buckton et al 1986; Muster & Prestidge 2005)

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and inverse gas chromatography (IGC) (Tong et al 2001). Good agreement has been reported between the contact angles obtained from both capillary penetration and sessile drop measurements of paracetamol particles (Duncan-Hewitt & Nisman 1993). However, unless the contact angle of each crystal face is determined directly, all the other techniques probe only the average surface energy for a macroscopic sample of the powder, i.e. they provide no insight into crystal face specific properties.

X-ray photoelectron spectroscopy (XPS) has been used to determine the surface energetics and surface chemistry of drug powders. For example, differences in the surface chemistry of a range of morphine sulfate powders have been correlated with differences in their wettability (Prestidge & Tsatouhas 2000), and a linear correlation has been observed between the intensity ratios of X-ray photoelectron signals from hydrophilic and hydrophobic moieties of the morphine ion and the measured particle contact angles. The particle wettability was also shown to be dependent on the aspect ratio of the particles and presumed to relate to the orientation of the morphine ion at different crystal planes. Khoshkhoo & Anwar (1996) related the internal crystal structure of N,N-octyl-D-gluconamide to the crystal face specific contact angles, although they did not address potential differences between the surface and bulk chemistry. Given that XPS has a surface sensitivity of several molecular layers when used for single crystals, it has limited ability to determine the specific arrangement of molecules at the absolute surface. With these thoughts in mind, it is clear that further investigation of the face-specific surface chemistry and structure of pharmaceutical powders is warranted.

Although detailed surface chemical information is available from XPS (John et al 1995; Jonat et al 2004; Mu et al 2005) and to a lesser extent scanning electron microscopy with energy dispersive spectroscopy (SEM EDS) (Chen et al 2004; Bergese et al 2005; Nevsten et al 2005), they are however, restricted to ex-situ applications. In contrast, in-situ surface chemical analysis typically involves techniques such as attenuated total reflection (ATR) infrared spectroscopy (Agnihotri & Aminabhavi 2004; van der Weerd & Kazarian 2004) and Raman spectroscopy (Bugay 2001; Williams et al 2004; Johansson et al 2005; Wartewig & Neubert 2005), which have been used to map the distribution of an active compound within a formulation matrix. Using a combination of both in- and ex-situ techniques provides a significantly enhanced understanding of solid dosage formulations, particularly as hi-resolution XPS instruments become more widely available.

The distribution of an active drug compound within a solid state formulation is of particular interest, since it plays a significant role in controlling solid-state stability and the drug release characteristics i.e. critical in determining dosage form performance and shelf-life. Mapping techniques such as Raman microscopy and EDS have traditionally been applied to ascertain drug distribution within solid matrices; however, both suffer from relatively low levels of surface specificity (i.e. they "see" too much of the bulk material below the surface) and relatively low spatial resolution (see Table 1). Techniques such as XPS and time-of-flight secondary ion mass spectrometry (ToF-SIMS) offer significant improvements in surface sensitivity, although until recently they have not been widely available to the pharmaceutical scientist or formulator. (Other surface specific techniques that can analyse atomic positions with a resolution of 0.1 Å (e.g. low- and high-energy electron diffraction) are applicable for metallic and semi-conducting materials, but not for crystals of non-conducting pharmaceuticals (Woodruff & Delchar 1986)).

ToF-SIMS is increasingly being used for the surface analysis of biomaterial and pharmaceutical products, particularly due to a detection limit, in some cases, in the parts-per-billion range, high spatial resolution and high surface sensitivity (Table 1). These features make it appealing for monitoring the solid state behaviour of pharmaceutical powders and dosage forms, although relatively little exists in published literature. In this article we have reviewed ToF-SIMS instrumentation and methodologies applicable to solid-state pharmaceutical delivery systems. Also, we have reviewed the available literature and have considered three specific case studies of the application of ToF-SIMS to solid-state pharmaceutical delivery systems i.e. face specific crystalline properties of pharmaceuticals; solid-state stability of peptides, proteins and biopolymers; and drug distribution within pharmaceutical matrices.

Instrumentation and methodologies for ToF-SIMS analysis

ToF-SIMS is a variant of so-called static SIMS, in which sub-monolayer surface sensitivity is attained without significant damage to the sample surface. Elemental and molecular information can be gathered from complex surfaces in this way. In the ToF-SIMS experiment, a pulsed primary ion beam is incident on the sample surface and time-of-flight (ToF) secondary ion mass analysis is performed on the ejected positive or negative secondary ions. With the use of multi-stop timing electronics, ToF mass analysis enables the entire mass spectrum derived from each pulse to be collected. Additionally, the pulsed nature of the primary ion beam

Table 1 Performance of time-of-flight secondary-ion mass spectrometry (ToF-SIMS) in comparison with other surface analytical methods and imaging techniques

Imaging technique	Raman	SEM/EDX	XPS	ToF-SIMS
Spatial resolution	>1 μm	100 Å/3–5 μm	~5 μm	0.2 μm
Element detection	Molecular information	B-U	Li-U	H-U plus molecular information
Sensitivity	>1%	>1%	5000 ppm	ppb
Sample limitations	Non-fluorescing	Flat and conducting	Conductors/insulators	Conductors/insulators

allows effective surface charge compensation via electron flooding between pulses and hence the analysis of highly insulating surfaces. Modern instruments also include imaging capability via rastering of the primary ion beam. Most instruments available today are capable of sub-micron ion image resolution with simultaneous high mass resolution.

It should be noted that the main limitation with the SIMS technique is difficulty in quantification of secondary ion yields (Vickerman & Briggs 2001). The ejection processes due to the impact of the primary ion are complex and differ markedly with the type of primary ion employed. Moreover, the secondary ion yield of a particular element or molecular ion is strongly affected by the matrix in which it is bound—the so-called "matrix effect". It is possible to calibrate the secondary ion yield of dilute elements in the same matrix of known concentration. The use of standards becomes problematic when the concentration of the element of interest is high enough to effectively alter the matrix characteristics. Consequently, the majority of ToF-SIMS measurements are comparative rather than quantitative in nature. For a more detailed discussion of quantification using ToF-SIMS, we refer the reader to Vickerman & Briggs (2001), a useful reference on ToF-SIMS.

Primary ion sources typically include Ga^+, Cs^+, In^+ and Au^+, although reactive cluster (e.g. SF_5^+, C_{60}^{p+}, Bi_n^{p+}) species are receiving growing interest, particularly for increasing molecular sensitivity to organic materials (e.g. Mahoney et al 2004a, b, 2005; Touboul et al 2005; Weibel et al 2003). Cluster ions such as SF_5^+ and C_{60} have made possible the depth profiling of organic and polymeric samples due to significant signal enhancement (Mahoney et al 2004b). Single or dual-beam depth profiling capability is an integral part of ToF-SIMS operational modes, including the ability to perform ultra-shallow depth profiles. The latter has seen intense application in the microelectronics industry.

A simplified schematic of a typical ToF-SIMS instrument (based on the Physical Electronics PHI TRIFT II system used in several of the reported case studies) is shown in Figure 1. The time-of-flight spectrometer itself consists of three electrostatic analysers around the flight path providing energy compensation. Flight time differences between secondary ions ejected at the beginning and end of the primary ion pulse are also minimized. Finally, mass separation occurs in the drift tube along to the detector. The ion flight time, t is then given by

$$t = L\sqrt{\frac{m}{z}\cdot\frac{1}{2V}} \qquad (1)$$

where L is the flight distance, m is the secondary ion mass, z the ion charge and V the ion velocity.

By way of example, the instrument used for several of the following case studies was a Physical Electronics PHI TRIFT II ToF-SIMS with a pulsed liquid metal ^{69}Ga ion gun. An accelerating potential of 15 kV was used to optimize for spectral resolution (typically between 3000 and 5000 m/Δm) and 25 kV was used for the optimization of spatial resolution (<1 µm and ~1500–3000 m/Δm). Spectra were typically acquired for ions and molecular fragments up to 2500 amu. Image dimensions depended on sample type and feature size but the maximum image area is limited to ~300 × 300 µm without defocusing, while an electron flood gun was used for charge neutralization. Sample preparation for ToF-SIMS

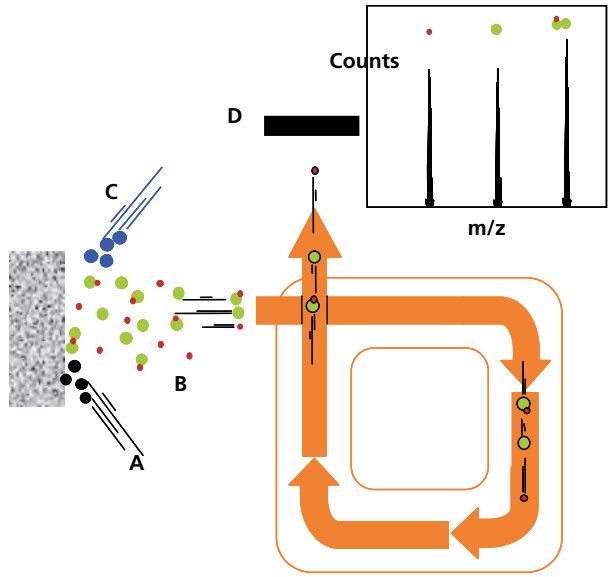


Figure 1 Schematic diagram of Trift time-of-flight secondary-ion mass spectrometry (ToF-SIMS) system, including; primary ion beam (A), ejected secondary ions (B), electron flood gun for charge compensation (C) and mass analyser (D). Courtesy I. Kempson.

measurements depends on the form or geometry of the sample, for example: pharmaceutical powders (e.g. drug crystals, proteins, etc.) are typically mounted on metal foil before loading in the specimen holder; drug pellets are embedded in a suitable resin (normally used for electron microscopy) and sectioned either with a razor blade or microtome.

ToF-SIMS can be used in a range of surface analysis modes, including surface spectroscopy, 2D surface imaging and 3D depth profiling, as depicted schematically in Figure 2. The surface sensitivity and types of information gleaned through static SIMS, and ToF-SIMS in particular, derives from the extremely low effective primary ion fluxes impinging on the sample surface. During the course of a ToF-SIMS experiment, less than one in a thousand surface sites may be disrupted by the beam. The ejected secondary ions comprise charged elemental and molecular clusters, parent ions and neutral species. Charged secondary ions typically comprise less than 5% of the ejected material. However, it is the molecular information – molecular surface spectrometry – provided by ToF-SIMS that makes the technique particularly suited to the study of pharmaceutical materials and systems.

Case studies

Face specific crystalline properties of pharmaceuticals

The surface chemistry of specific crystal faces of two model drugs, *N*,*N*-octyl-D-gluconamide (OGA) and sulfathiazole (polymorphic form III), has been characterized using ToF-SIMS (Muster & Prestidge 2002). The face specific surface chemistry was correlated with the surface energetics as characterized by sessile drop contact angles, surface roughness characterized by AFM and specific molecular orientation at each crystal face determined by molecular modelling.

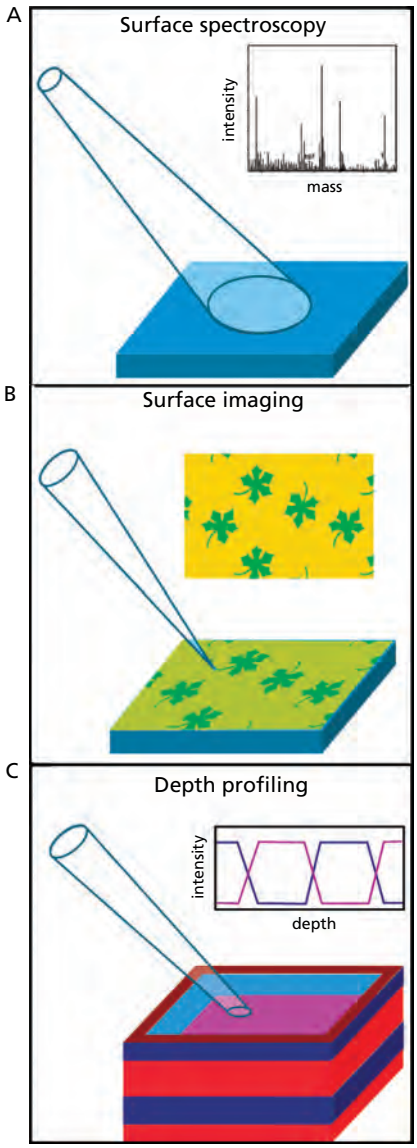


Figure 2 Schematic diagram of time-of-flight secondary-ion mass spectrometry (ToF-SIMS) analysis modes: (A) surface spectroscopy, (B) 2D surface imaging and (C) 3D depth profiling.

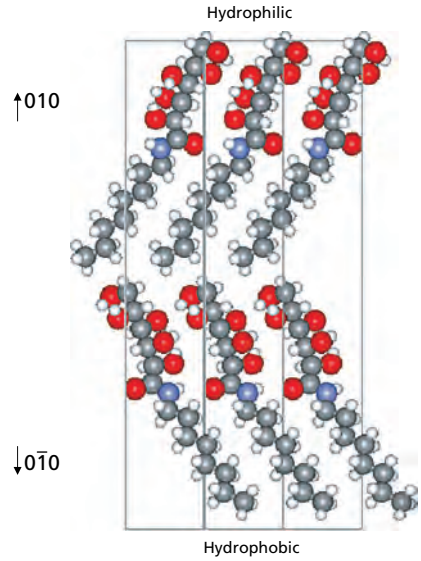


Figure 3 Molecular model of OGA crystal structure, note the molecular orientation of functional groups within the unit cell and the hydrophilic [010] and hydrophobic [0$\bar{1}$0] faces.

Surface ion concentrations for each mass fraction were estimated by normalizing the integrated peak area of interest against both the total ion count (TIC) and the sum of the parent ion and parent ion fragments i.e. the total molecular count (TMC) (Walls 1989). Impurities present on crystal surfaces contributed to less than 15% of the TIC and were due to both trace amounts of salt (NaCl and KCl) incorporated within the crystal and adventitious carbon species. Differentiation between the hydrophilic and hydrophobic crystal faces of OGA and sulfathiazole was possible due to an observed increase in TIC from the positive ion ToF-SIMS spectrum for each sample (Muster & Prestidge 2002).

From the hydrophobic [0$\bar{1}$0] face of OGA (shown in Figure 3), the sum of ion fragments associated with the alkyl chain section of the OGA molecule corresponded to 68% of the total ion count (TIC) emitted (i.e. $\Sigma_{\text{alkyl ions}}/\text{TIC} = 68\%$), whereas from the hydrophilic, [010] crystal face, $\Sigma_{\text{alkyl ions}}/\text{TIC} = 33\%$. This change reflects a difference in the physical arrangement of OGA molecules at the respective crystal faces, where the alkyl chain is exposed at the [0$\bar{1}$0] surface; this is in good correlation with the face specific contact angles obtained from sessile drop measurements ($\theta = 43°$ for the [0$\bar{1}$0] face and 76° for the [0$\bar{1}$0] face). Similarly, Lhoest et al (1998) have reported an orientation dependence for hydrocarbon fragment emission from proteins adsorbed on polystyrene substrates; these differences were considered in terms of variations in the adsorbed conformation.

A crystal face-dependent adsorption behaviour has also been observed for OGA crystals, where a common pharmaceutical polymer excipient, ethyl(hydroxyethyl) cellulose (EHEC), was observed to preferentially adsorb on the hydrophobic [010] OGA face (Muster 2001), in good agreement with a proposed adsorption mechanism (Kapsabelis & Prestidge 2000). These findings highlight the potential for improving understanding in the processing of pharmaceutical excipients using sensitive surface analysis.

Equivalent ToF-SIMS investigations on sulfathiazole crystals (Muster & Prestidge 2002) have identified a significantly greater TIC from the more hydrophobic [102] face than from the more hydrophilic [100] face, as shown in the ToF-SIMS positive ion mass spectra and unit cell molecular models (Figures 4 and 5, respectively). This was attributed to an increase in binding between neighbouring sulfathiazole molecules at the [100] face rather than at the [102] face. This was in good correlation with the molecular orientation of sulfathiazole (Figure 4). Furthermore, a greater concentration of non-fragmented ions were released from the [102] face, where the sulfathiazole molecule was lying perpendicular and had limited direct exposure to the ion beam, than from the

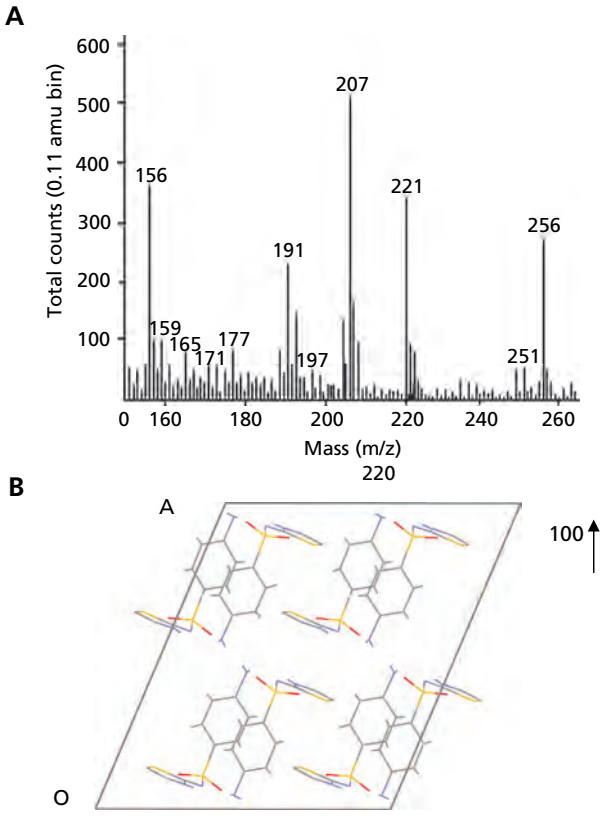


Figure 4 Time-of-flight secondary-ion mass spectrometry (ToF-SIMS) positive ion mass spectra (A) and molecular model (B) for hydrophobic sulfathiazole [102] crystal face.

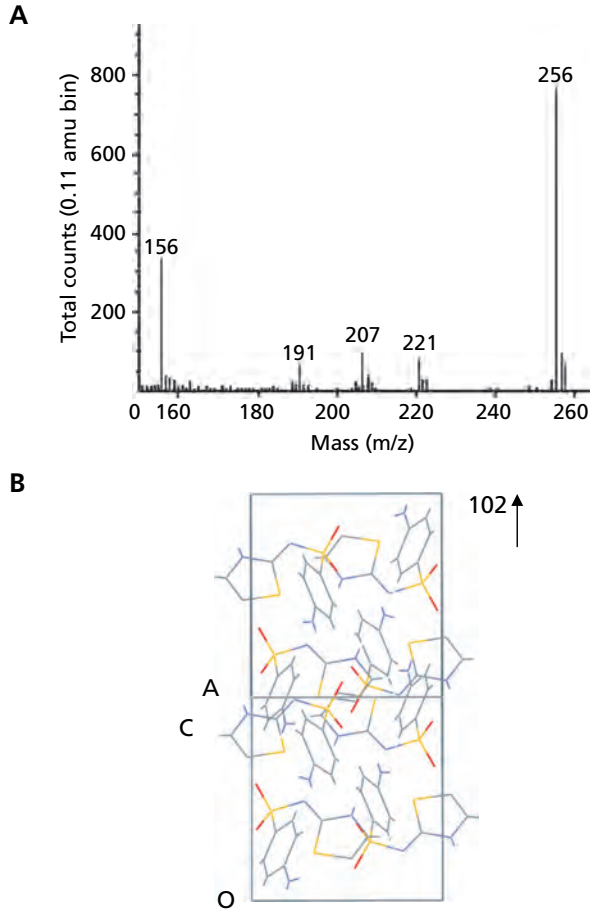


Figure 5 Time-of-flight secondary-ion mass spectrometry (ToF-SIMS) positive ion mass spectra (A) and molecular model (B) for hydrophilic sulfathiazole [100] crystal face.

[100] face. Sulfathiazole molecules that were orientated parallel to the [100] face were more easily fragmented (Lhoest et al 1998) than molecules at the [102] face. With this in mind, fragments of sulfathiazole with molecular masses 92 amu, 140 amu and 156 amu (Table 2) were emitted at a greater relative concentration from the [100] crystal face than from the [102] face. This confirmed that at the [100] face, the orientation of the sulfathiazole molecule was such that the parent molecule was held more tightly within the bulk of the crystal and fragment ions were released in preference to the molecular ion. Complimentary colloid probe AFM adhesion studies (Muster & Prestidge 2002) confirmed the sulfathiazole face specific surface energetics (indicative of wettability) relating to molecular orientation.

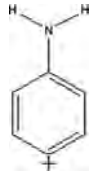
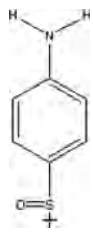
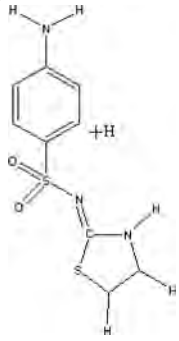
Molecular fragmentation patterns in the ToF-SIMS spectra of OGA and sulfathiazole were strongly crystal face dependent; this concurred with the molecular orientation at crystal faces. For OGA, ion fragments associated with the hydrocarbon component were more prevalent from the more hydrophobic $[0\bar{1}0]$ face. For sulfathiazole, the molecular ion was more prevalent in the SIMS spectrum from the [102] crystal face, whereas fragment-ions were more prevalent from the [100] face. At the [100] face the sulfathiazole molecule was more highly exposed to the ion beam and more strongly associated with adjacent molecular layers in the crystal, as indicated by the relatively low total ion count.

These studies have furthered our understanding of the face-specific properties of pharmaceutical crystals and have implications when considering such processes as tableting, crystallization, excipient interaction, dissolution, etc. and hence influence formulation and delivery characteristics.

Stability of solid state delivery systems containing peptides, proteins and biopolymers

Proteins and peptides are being developed as a new generation of therapeutic agents by the pharmaceutical industry, and their increasing therapeutic use as lyophilized or freeze-dried formulations has intensified interest in their solid-state stability. Methionine, an amino acid present in many peptides and proteins, is particularly susceptible to oxidative degradation to the corresponding sulfoxide. This oxidative degradation may occur at any stage of drug development, from initial peptide synthesis, through product formulation to eventual storage. Sun & Gardella (2000) studied the oxidation of short methionine-containing peptides (methionine enkephalin (ME) and methionine-enkephalin sulfoxide (MEO)), by analysing the negative ion spectra of the deprotonated molecular ion obtained from ToF-SIMS. The apparent oxidation rate constant was

Table 2 Common mass fragments obtained from sulfathiazole [100] and [102] crystal faces

Mass fragment	% TMC	
	[100] (TIC – 74137)	[102] (TIC – 501944)
92 amu 	22.7	11.8
140 amu 	15.9	11.8
152 amu 	31.8	25.5
192 amu 	29.5	50.8

determined by the experimental peak area ratio, $I_{MEO\text{-}H}/I_{ME\text{-}H}$, and it was observed that methionine enkephalin was oxidized to the corresponding sulfoxide derivative under exposure to UV light at a faster rate than when exposed to air.

ToF-SIMS has been used also to study the hydrolytic degradation of biopolymers such as polyglycolic acid, poly(lactic acid) and poly(sebacic acid), commonly used in drug delivery formulations, e.g. as nanoparticles or microparticles. Low molecular weight oligomers were found to be generated upon hydrolytic degradation, by using ToF-SIMS (Chen & Gardella 1999). The progression of polymer erosion upon hydrolytic degradation (pH 7.4 and 10.0) of poly(L-lactic acid) (PLLA) in the presence of a water insoluble model additive (triphenylamine, PH_3N) was studied (Lee & Gardella 2003, 2004; Lee et al 2003). ToF-SIMS spectra were analysed for characteristic positive ions from the degraded PLLA and PH_3N substrates, in particular, the molecular ions $[C_3H_4O]^{\bullet+}$ and $[Ph_3NH]^+$, respectively. It was observed that PLLA degradation at pH 10 was approximately two times faster than at pH 7.4. ToF-SIMS has also been used for the depth profiling of a tri-block copolymer (Pluronic P104) within a polymeric biomaterial (poly(lactic acid)) (Mahoney et al 2005), which showed specific surface segregation of the P104, followed by a depletion layer and finally a uniform bulk composition, consistent with theoretical predictions of polymer segregation in polymer–copolymer blends.

In principle, ToF-SIMS is capable of imaging proteins and other biomaterials with sub-micron resolution; however, it is unable to ionize large molecules such as proteins intact, requiring the identification of peptide specific fragmentation patterns. Further complicating the data analysis is that proteins consist of the same 20 amino acids, which in turn share similar structural features of the biopolymer matrices themselves. A range of multivariate analysis techniques, including principal component analysis (PCA) and linear discriminant analysis (LDA), have been used to analyse ToF-SIMS data to distinguish between protein and biomaterial fragmentation patterns (Aoyagi et al 2004a, b; Rangarajan & Tyler 2004). The usefulness of ToF-SIMS in characterizing peptide and protein delivery systems is evident, particularly degradation processes that can be difficult to observe using conventional techniques.

Drug distribution within pharmaceutical matrices

Numerous controlled-release delivery systems are available for a wide range of active compounds and these have been developed to achieve sustained release and reduced side-effects, for minimizing plasma drug concentrations as well as to increase patient compliance. Typically these formulations consist of a core containing the active compound and a polymeric coating, which may consist of numerous polymer binder layers to provide the required drug release profile. Dissolution studies have traditionally been used to characterize the drug release from such a vehicle; however, they provide no direct information concerning the specific distribution of components within the solid-state product. The controlled-release of an active compound from a biopolymer delivery vehicle is highly desirable. However, the polymer matrix must provide a well characterized drug release rate and this feature will depend particularly on the adequate dispersion of active molecules within the polymer matrix, a feature typically difficult to ascertain experimentally. ToF-SIMS and other sensitive surface imaging approaches offer significant insight in the characterization of drug delivery matrices. A ToF-SIMS image from a typical cross-sectioned drug release pellet is given in Figure 6. The position of the drug molecular ion, which is in two different forms (hydrated and non-hydrated), can be clearly identified (Figure 6c and d). However, this is not obtainable from the equivalent SEM image (Figure 6a). Furthermore, ion signals characteristic of the excipient used in the outer coating can also be identified (Figure 6e).

Using a combination of XPS and ToF-SIMS, John et al (1995) determined the localization of a peptide drug (leuprorelin (leuprolide)) within a solid matrix of hydroxypropylcellulose. ToF-SIMS was used to map the leuprorelin distribution along the cross section of a range of peptide–polymer blends by analysing for immonium and immonium-type ions (from the proline, arginine and tyrosine residues

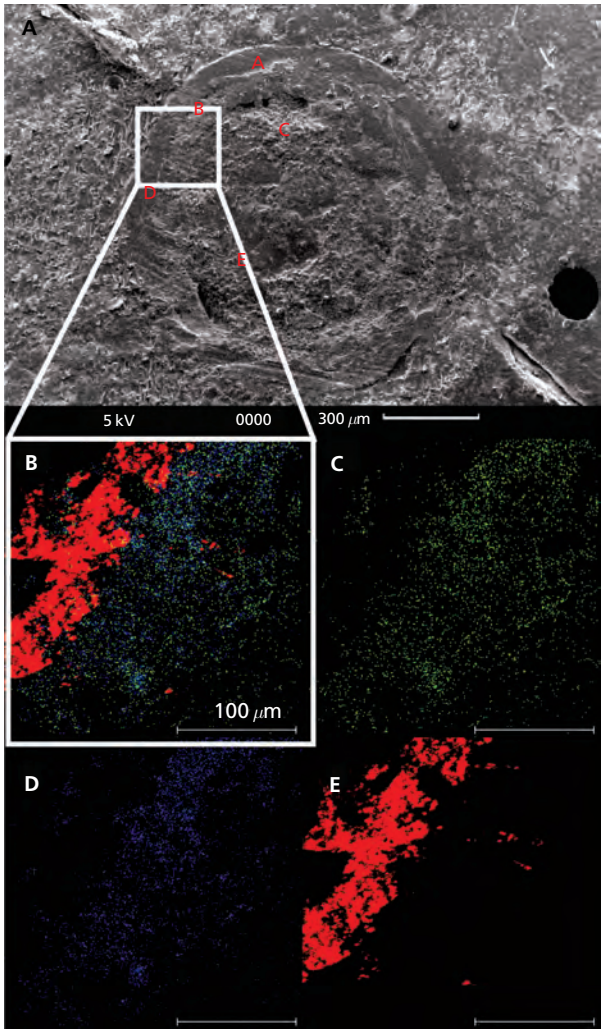


Figure 6 SEM and time-of-flight secondary-ion mass spectrometry (ToF-SIMS) images of a pharmaceutical controlled-release pellet. A, SEM image; B, overlay image; C, drug form I; D, drug form II; and E, coating layer.

within the peptide) and the protonated molecular ion $(M+H)^+$ (John et al 1995). Dispersion of the leuprorelin across the polymer matrix was observed to be non-uniform, with an enhanced concentration of the leuprorelin at the polymer–air interface. The incorporation of 12% oleic acid in the formulation was also found to improve the axial distribution of leuprorelin within the matrix, attributed by the authors to either a reduction in surface free energy of leuprorelin or an increase in degree of solvation within the acidic polymer matrix.

Cross-sections of three different controlled-release pellet formulations (paracetamol, theophylline and prednisone) were studied with ToF-SIMS, in an attempt to characterize the distribution of drug, excipients and coating (Belu et al 2000). Insight into drug distribution within the core was obtained by imaging of the specific parent molecular ion of each drug, with observations ranging from distinct micrometre sized regions to completely homogeneous distributions, highlighting the significant potential for inter-batch variability.

Cluster ion bombardment has successfully been used to obtain depth profiles of 4-acetamidophenol for a range of loading levels (1–50%) within a poly(lactic acid) matrix using dynamic SIMS analysis (Mahoney et al 2004b). In particular, 4-acetamidophenol segregation and domains were observed at 5 and 20% loading levels, however at 50% loading levels a decrease in sputter rate was observed, resulting in an increase in resultant beam-induced damage to the film.

ToF-SIMS provides an invaluable tool for formulation scientists, providing significant insight into drug and excipient distribution within a matrix. This is beneficial given the complex manufacturing processes commonly involved, as well as the impact drug distribution in a matrix has on its release profile.

Future directions

ToF-SIMS is a powerful characterization technique available to pharmaceutical scientists. When used spectroscopically, its high surface sensitivity enables identification of a specific molecule's orientation at individual crystal faces, while the surface chemical imaging capabilities of ToF-SIMS provide new insight into drug distribution within solid dosage forms, offering significant improvements in spatial and elemental resolution over existing technologies. It is highly desirable to correlate solid-state transport processes with release kinetics and use this in the design and optimization of improved controlled-release pellets and matrices. As the imaging resolution of ion beams is further improved it will be possible to achieve ToF-SIMS imaging resolution of a few nanometres, hence drug distribution within pharmaceutical nanoparticles may be achieved. Likewise, the application of principal component analysis (PCA) to ToF-SIMS is further enhancing understanding of the relationship between spectral intensities and molecular orientation and conformation, e.g. for peptide and protein drugs. This enables the quantitative identification of different polymorphic forms or polymorphic mixtures, or crystalline and amorphous regions, as well as imaging them on a surface or cross-section sample. With improvements in instrumentation, potential applications of ToF-SIMS continue to emerge, such as the mapping of drug distribution within biological tissues, and applications are already beginning to be explored.

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