PHYSICAL ELECTRONICS

TOF-SIMS IMAGING OF A DRUG PELLET

Cross-Section Using a Bi_3^{2+} Cluster Ion Beam

INTRODUCTION

Pharmacuetical companies have expanded their research into new approaches to enhance the long term storage of pharmaceuticals by identifying new coatings to target the site of drug pellet dissolution in the patient (for example, enteric drug delivery systems). These studies have led to increased product lifetime and drug usefulness, as well as enhanced differentiation with competitors' products. To evaluate these new drug delivery technologies, molecular imaging of the drugs in drug pellet cross-sections is highly desirable.

Figure 1 shows the variation of the molecular weight in over-the-counter (OTC) drugs presently sold in Japan. This data indicates that the largest number of drugs have a molecular weight within the range of 300 to 400 with over 75% of the drug ingredients having a molecular weight under 700, and over 90% of the drug ingredients having a molecular weight under 1000, and over 99% of the drug ingredients having a molecular weight under 2000. This mass range matches the high sensitivity region of Time of Fight Secondary Ion Mass Spectrometry (TOF - SIMS) equipped with newly-developed cluster metal primary ion sources. These primary ion sources

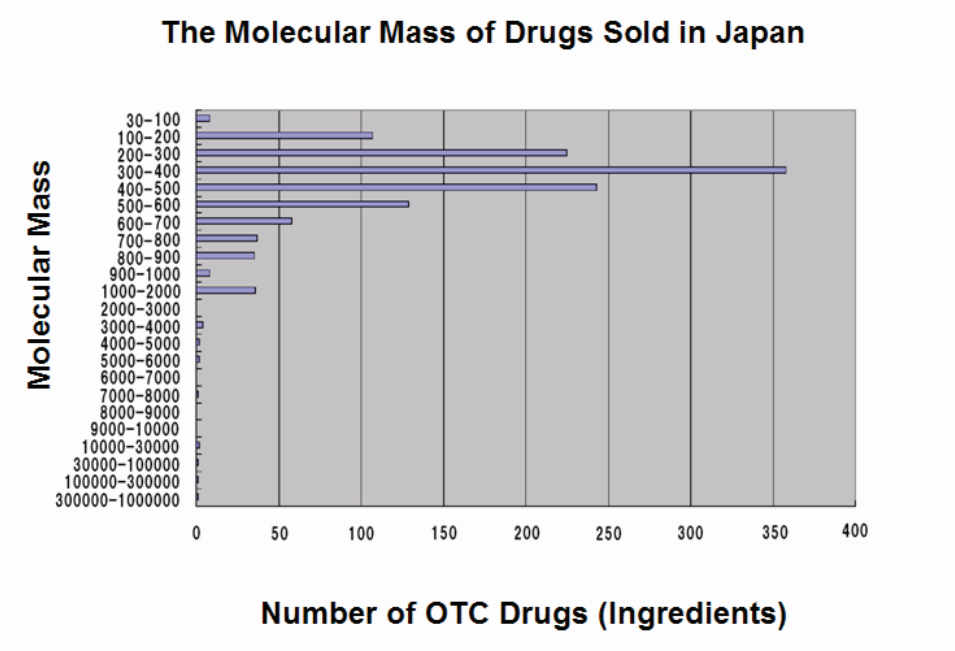

Figure 1: The distribution of molecular mass of over-the counter (OTC) drugs sold in Japan (data obtained from a Japanese Medical Information Center).

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can be rastered over the surface of the drug pellet cross-section to produce molecular ion images with sub-micron spatial resolution.

This application note illustrates the use of TOF-SIMS for analysis of the cross-section of a pellet from a drug capsule intended for the oral treatment of coughs. The TOF-SIMS analysis shows that the internal distributions of the organic materials are not homogeneous. In addition, the localization of some ingredients in the surface layer of the pellets are also identified. This information demonstrates that TOF-SIMS analyses can supply important information for the development of new pharmaceutical technologies related to drug delivery.

EXPERIMENTAL

A commercially available oral fine granule antibiotic drug (molecular weight is approximately 400) formulated in a drug granule was cross-sectioned and mounted for analysis in a PHI TRIFT IV TOF-

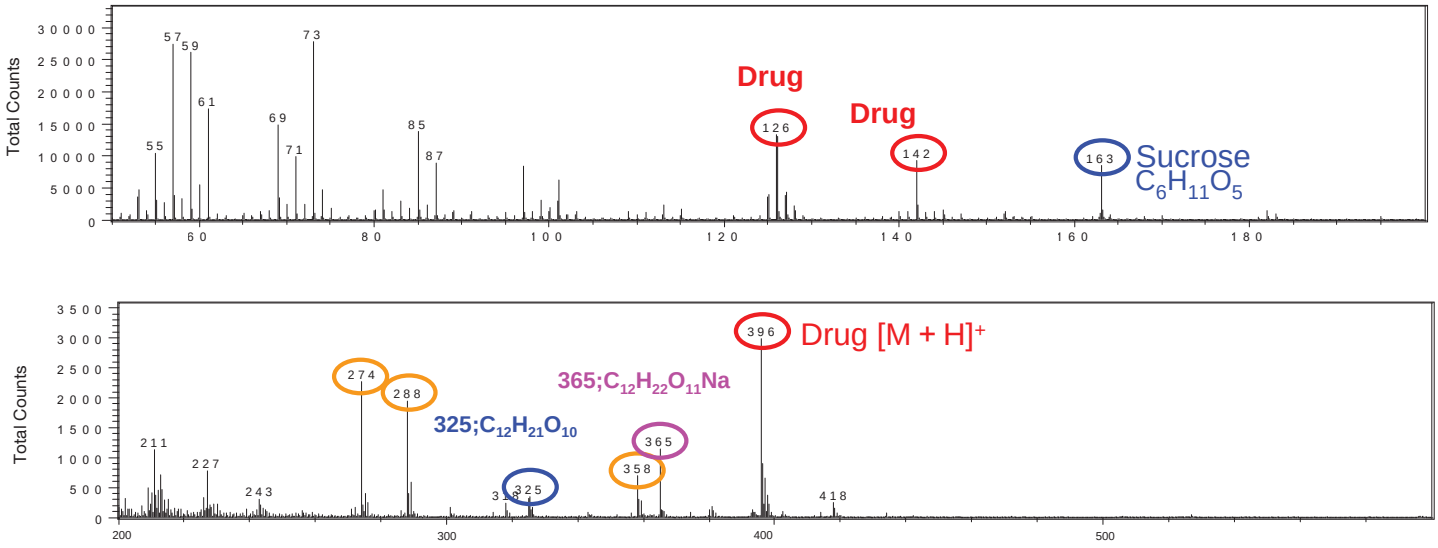

Figure 2: Positive ion TOF-SIMS spectrum of the drug granule cross-section

SIMS instrument. The diameter of the granule was about 300 µm. A pulsed 60 keV Bi_3^{2+} ion source was used for the primary ion beam. The field of view of analyses was either 400 x 400 µm^2 or 50 x 50 µm^2 with each image containing 256 x 256 pixels. Each pixel in the image contains the entire mass spectrum from the pixel area. The analysis time was approximately 30 minutes. Positive and negative secondary ion mass spectra were collected within the imaged area of analysis. A pulsed low energy electron beam was interlaced with the primary ion beam to maintain a constant surface potential for analysis of the insulating sample.

RESULTS

Figure 2 shows the positive ion TOF-SIMS mass spectrum of the drug granule cross-section with several of the peaks from the drug identified on the spectrum. The molecular ion peak of the drug was detected as $[M+H]^+$ at 396 amu. Figure 3 shows several mass selected images from the cross-section analysis. The $[C_6H_{10}O_5]^+$ ion image was identified as sucrose (excipient). In the case of sucrose, the negative molecule ion $[C_{12}H_{22}O_{11}]^-$ was observed with high intensity (not shown in the figure) as well as the displayed positive ion species. The peak and image at 59 amu $[C_3H_7O]^+$ was observed and it was identified as the ion from hydroxypropylcellulose (HPC; binder). A series of fragment ion peaks from $[C_6H_{12}O_6(C_6H_{10}O_5)_nNa]^+$ are observed at 365 amu, 527 amu, 689 amu, 851 amu and 1013 amu. The displayed image at 365 amu is representative of the distribution from the polysaccharide originating from either Arabian gum or starch which is blended with the drug in the granule. The images at 274 amu, 388 amu, and 358 amu cannot be identified from the disclosed ingredients listed for the commercial formulation, but they are associated with the ingredients

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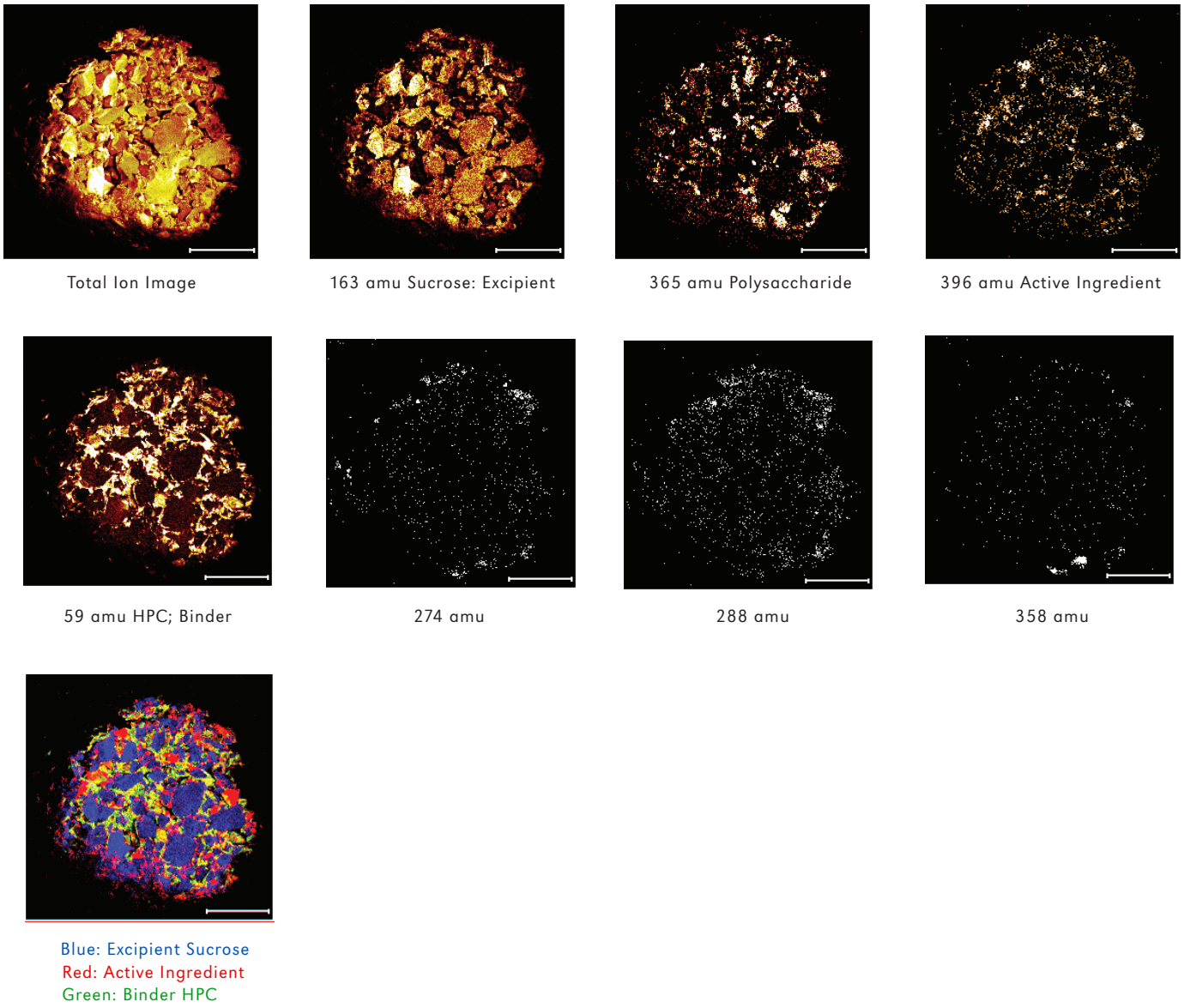

Figure 3: Mass image of the drug granule cross-section (FOV 400 x 400 μm²). The scale bar in the figure is 100 μm.

distributed around the surface (i.e., edges) of the granules.

Figure 4 shows the mass images from a higher magnification field of view of 50 μm by 50 μm. Using a Bi_3^{2+} cluster primary ion source, the intensities for the desired secondary ion peaks are sufficient for very small area imaging. TOF-SIMS analysis indicates that the drug ingredients are localized in micron scale domains. Based on patent information, this drug has low water solubility, suggesting the possibility that in the formulation process, the drug substance is prepared as fine granules of several microns in size and blended into the granules.

CONCLUSION

The sensitivity improvement for higher mass secondary ions resulting from the use of primary cluster ion sources expands the applications of TOF-SIMS to the pharmaceutical industry. In this application note, the distribution of a drug substance of approximately 400 amu in finely dispersed granules was observed. Apart from the distribution of the drug ingredient, unexpected high concentrations of unknown ingredients near the edges of the granule were also observed.

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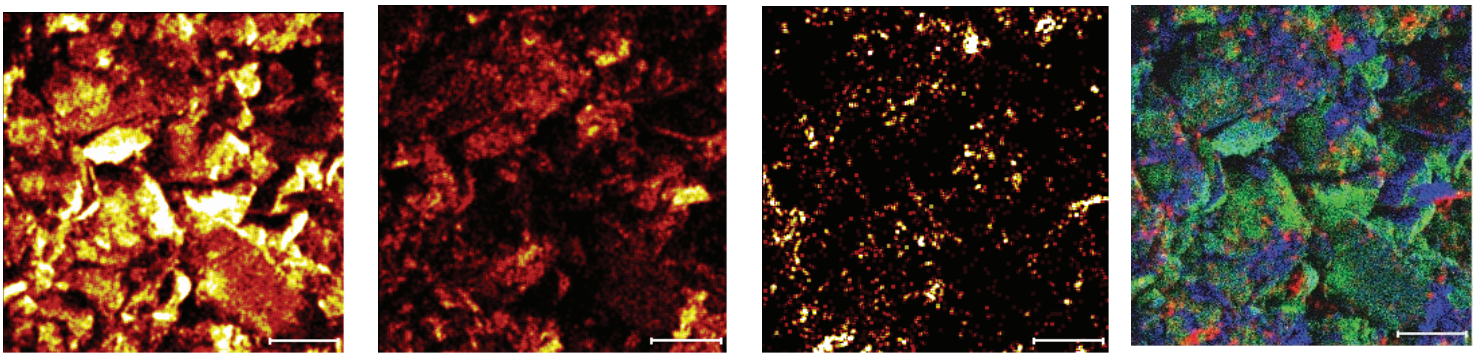

59 amu Binder | 163 amu Excipient | 365 amu Active Ingredient

Blue: Excipient Sucrose
Red: Active Ingredient
Green: Binder HPC

Figure 4: Mass and superimposed image of the drug granule cross section (FOV 50 x 50 μm²). The scale bar in the figure is 10 μm. The distributuion of the active ingredient with spatial domains of several μm is observed.

This data demonstrates sub-micron scale TOF-SIMS mass imaging to cross sections of drug delivery pellets. In addition, the high sensitivity of the TRIFT analyzer for imaging rough surfaces is demonstrated with these drug pellet cross-section samples. It is expected that TOF-SIMS will find a growing role in the evaluation of new drug delivery technologies, improving product quality and product differentiation.

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