



TOF-SIMS Imaging Applications in the Pharmaceutical and Food Industries

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INTRODUCTION

The technique of time-of-flight secondary ion mass spectrometry (TOF-SIMS) combines chemical imaging with the specificity and detection limits characteristic of mass spectrometry. Chemical imaging is readily used to study a wide range of pharmaceutical samples including tablet cross sections. Examples of possible TOF-SIMS applications includes the investigation of coating homogeneity, particle size analysis and distribution, process analytical control, cleaning validation, root cause investigations, and reverse engineering. TOF-SIMS is a technique where low dose primary ions collide with a sample surface thereby producing secondary ions unique to the sample analyzed. Chemical images are obtained by rastering a submicron diameter primary ion beam across a sample to produce secondary ions from small, finite regions on the sample surface. To demonstrate the specificity and imaging capabilities of TOF-SIMS, a cross section of an over-the-counter ibuprofen tablet was imaged. Molecular specificity and ppm detection limits allowed for detailed image models to be easily prepared. Numerous chemical components were identified illustrating well defined core/filler and color/filler coat interfaces. The concentration gradients of components across these interfaces are known to affect dissolution profiles. TOF-SIMS is able to detect and image numerous components within a single system which is advantageous compared to current spectroscopic imaging techniques. Images of M&M candy cross sections are also presented, which illustrates the diversity of samples that can be analyzed by this imaging technique.

Applications for the Pharmaceutical Industry

General Applications

- Quality control
- Cleaning validation
- Root cause investigation

Example:
Contamination studies

Chemical Imaging Applications

- Particle size analysis
- Grain boundaries
- Homogeneity studies

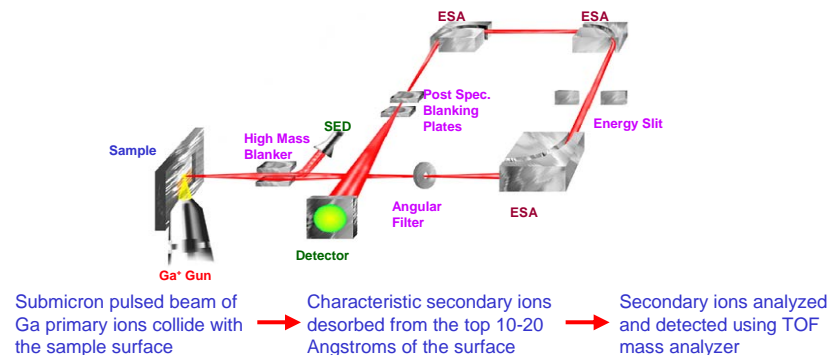
Example:
Formulation ingredients

- Layer integrity of coatings
- Reverse engineering of products

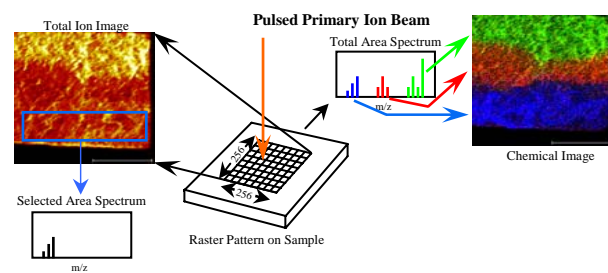
Example:
Capsules and tablets

TOF-SIMS PRINCIPALS

Schematic View of the Physical Electronics™ TRIFT II TOF-SIMS

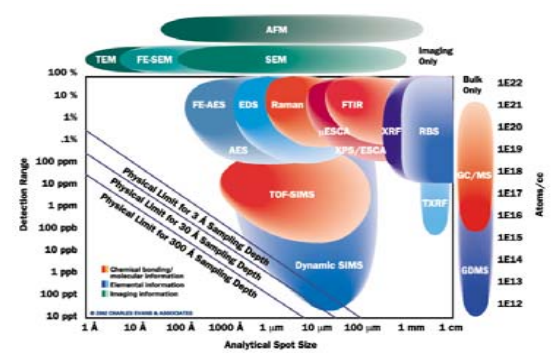


Rastering Primary Ion Gun and Chemical Imaging



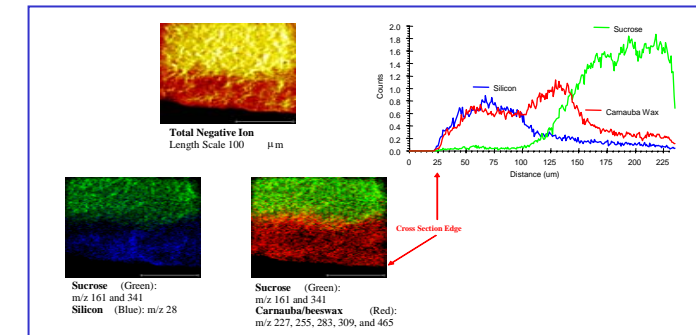
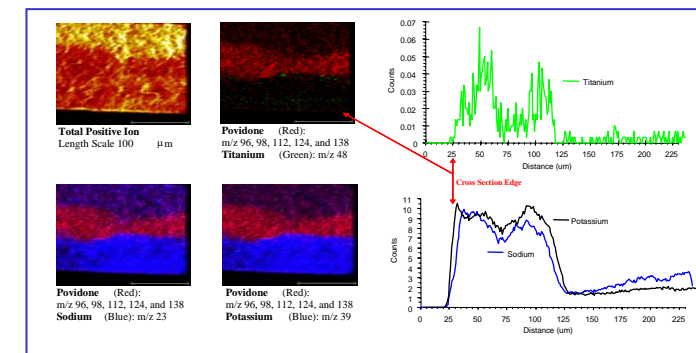
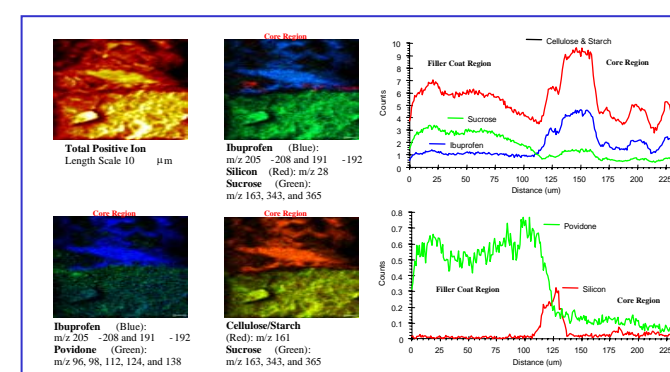
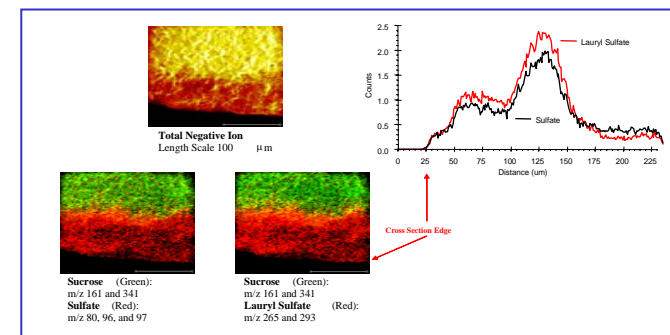
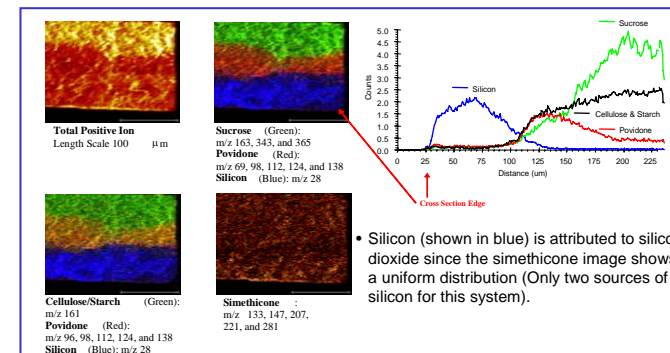
The primary ion source is rastered over a 256 x 256 pixel array. At each pixel, the beam is pulsed and a full mass spectrum is collected. The total ion current at each pixel is displayed as is the cumulative SIMS spectrum. Once the analysis is completed, spectra can be generated from regions of interest within the total ion image and/or images can be generated from peaks within the total area spectrum.

Analytical Resolution Versus Detection Limits



Application 1 – IMAGING IBUPROFEN TABLET CROSS SECTIONS

Color/Filler Coat Interface of Tablet Cross Section



Summary: Ibuprofen Tablet Images

1. Chemical images clearly illustrate the location of atomic and molecular components as well as the extent of layer mixing within the ibuprofen tablet.
2. Tablet coating quality can be monitored by examining image line scan slopes for various component, which provides a visual representation to monitor changes in dissolution profiles.
3. The ability of TOF-SIMS to monitor atomic and molecular components within pharmaceutical systems illustrates a clear advantage over spectroscopy imaging techniques.

Application 2 – M&M CANDY CROSS SECTION

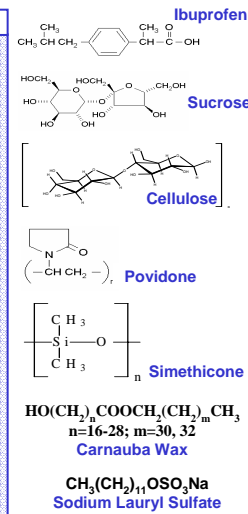
Summary: M&M Candy Images

1. Image models are versatile and can be adapted to a wide range of various samples without the use of chemometrics.
2. The quality of the image models are reinforced using both polarities (positive and negative ion models).
3. As expected, large thickness variations were observed for the color coatings since candy coatings are not controlled to extent of pharmaceutical tablets.

Application 1 – IMAGING IBUPROFEN TABLET CROSS SECTIONS

Tablet Ingredients	
Active ingredient	Purposes
1. Ibuprofen 200mg	Pain reliever / fever reducer
Inactive ingredients	
1. Acetylated monoglyceride	Surfactant
2. Beeswax and/or carnauba wax	Polishing agent
3. Croscarmellose sodium	Dissolution aid / assists water uptake
4. Iron oxides	Coloring agent
5. Lecithin	Surfactant
6. Methylparaben	Preservative
7. Microcrystalline cellulose	Plasticizer
8. Pharmaceutical glaze	Preservative
9. Povidone	Dispersing / suspending agent
10. Propylparaben	Preservative
11. Silicon dioxide	Polishing agent
12. Simethicone	Defoamer
13. Sodium benzoate	Preservative / flavoring agent
14. Sodium lauryl sulfate	Surfactant / wetting agent
15. Starch	Filler
16. Stearic acid	Plasticizer
17. Sucrose	Filler
18. Titanium dioxide	Coloring Agent

TOF-SIMS Image Model for Ibuprofen Tablet		
Component	Polarity	Characteristic Peaks (m/z)
Ibuprofen (API)	Positive	191 (M-CH ₃), 192 (M-CH ₃), 205 (M-H), 206 (M), 207 (M+H), and 208 (M+2H)
Sucrose	Positive	163 (C ₆ H ₁₁ O ₅), 343 (M+H), and 365 (M+Na)
Cellulose/Starch	Negative	161 (C ₆ H ₁₀ O ₅) and 341 (M-H)
Povidone	Positive	96 (M+H-O), 98 (M+H-CH ₃), 112 (M+H), 124 (M+CH), and 138 (M+C ₂ H ₅)
Silicon	Positive	28 (Si)
Sodium	Negative	28 (Si)
Titanium	Positive	23 (Na)
Simethicone	Positive	48 (Ti)
Simethicone	Positive	133, 207, and 281 (CH ₃ SiO(C ₂ H ₅ SiO) _n); 147 and 221 (C ₁₂ H ₂₅ Si(C ₂ H ₅ SiO) ₂)
Carnauba/beeswax	Negative	227 (C ₁₉ H ₃₇ O ₂), 255 (C ₁₉ H ₃₇ O ₂), 283 (C ₁₈ H ₃₅ O ₂), 309 (C ₂₀ H ₃₉ O ₂), and 465 (C ₃₀ H ₅₇ O ₂)
Sulfate	Negative	80 (SO ₃), 96 (SO ₃), and 97 (SO ₃ H)
Lauryl Sulfate	Negative	265 (M) and 293 (M+C ₂ H ₅)



CONCLUSIONS

The specificity of TOF-SIMS allows for the development and utilization of well-defined image models without the use of chemometric data analysis, which is advantageous over spectroscopy imaging systems. The results of this work show two examples of TOF-SIMS chemical imaging, including an application of this technique to analyze pharmaceutical tablet cross sections. Imaging tablet cross sections allows layer thicknesses to be measured as well as monitoring the distribution and location of core and coating components. These properties are important to monitor since the thickness and integrity of the seal and filler coat layers will affect the dissolution properties of the tablet. The line scan slopes observed within the chemical images provides a method to monitor the integrity of the coating interfaces including layer mixing. The imaged M&M candy cross section provide an example of a coating layer with large variations in thickness. The thickness defects in the candy color coat were expected since these layers are only used as a crude preservative barrier. With ppm detection limits and 10 to 20 Angstrom surface sensitivity, TOF-SIMS is a technique that adapts easily to contamination analysis and cleaning validation studies within the pharmaceutical industry. The enhanced specificity coupled with sub-micron spatial resolution allows TOF-SIMS to be used as a powerful tool to reverse engineer products as well as a process analytical tool for root cause investigations. The chemical imaging capabilities of TOF-SIMS easily adapts to the study of stent coatings, catheters, delivery systems, and solid mixtures including formulation ingredients.