

# Analytical Solutions

May 9, 2007 (Version 2.0)

for BioTechnology

## BN 1410

### TOF-SIMS Chemical Imaging Applications in the Pharmaceutical Industry

#### Discussion

Time-of-flight secondary ion mass spectrometry (TOF-SIMS) combines chemical imaging with the specificity and detection limits characteristic of mass spectrometry, which makes this technique advantageous over chemical imaging via spectroscopy. Pharmaceutical tablets are often imaged to monitor the quality and uniformity of manufactured layers since these layers will affect stability and dissolution profiles. TOF-SIMS is able to monitor atomic and molecular components within tablets and is often used as a Process Analytical Technique (PAT) for root cause investigations.

The results of this work illustrate an example of TOF-SIMS chemical imaging of ibuprofen tablet cross sections. Well-defined image models are easily developed to image specific atomic and molecular components of a system without the use of chemometric data analysis (Table 1). Figure 1 illustrates a model of a tablet cross section which defines the color, filler, and seal coat layers with a core region that encompasses the active pharmaceutical ingredient (API). The remaining figures contain TOF-SIMS chemical images and line scans. A layered system is depicted with filler (e.g. sucrose and cellulose) and color (e.g. silicon from SiO<sub>2</sub>) coat regions observed. The last figure clearly shows ibuprofen (API) in the core region with sucrose and povidone detected in the filler coat region. A thin silicon region (resembling a seal coat) bisects the filler and core areas. Comparing the sucrose line scans, it is clear that the Filler/Core interface is better defined than the Color/Filler interface, where sucrose concentration gradients run 40 and 100 microns across the cross section, respectively.

Imaging tablet cross sections permits layer thicknesses to be measured. The distribution and location of core, filler, and color coating components can also be monitored. These properties are important to monitor since the thickness and integrity of the layers will affect the dissolution and stability properties of tablets. The line scan slopes produced from the chemical images provide a method to monitor and quantify the integrity of the coating interfaces (including layer mixing). The combination of the chemical images and the line scans provides a visual representation to compare tablets from intra- and inter-batches. 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

Component	Polarity	Characteristic Peaks (m/z)
Ibuprofen (API)	Positive	191, 192, 205, 206, 207, and 208
Sucrose	Positive	163, 343, and 365
	Negative	161 and 341
Cellulose/Starch	Positive	161
Povidone	Positive	96, 98, 112, 124, and 138
Silicon	Positive	28
	Negative	28
Sodium	Positive	23
Titanium	Positive	48
Simethicone	Positive	133, 147, 207, 221, and 281
Carnauba/beeswax	Negative	227, 255, 283, 309, and 465
Sulfate	Negative	80, 96, and 97
Lauryl Sulfate	Negative	265 and 293

Table 1. TOF-SIMS image model used for the ibuprofen tablet.

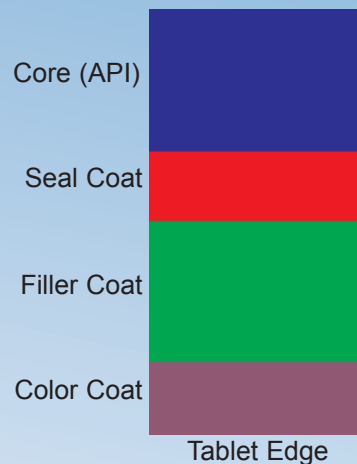


Figure 1: Tablet cross section illustrating the core, seal coat, filler coat, and color coat regions.

sub-micron spatial resolution also allows TOF-SIMS to be used as a powerful tool to reverse engineer products and as a process analytical tool for root cause investigations. The chemical imaging capabilities of TOF-SIMS can easily adapt to the study of stent coatings, catheters, a wide range of delivery systems, and solid mixtures including formulation ingredients.

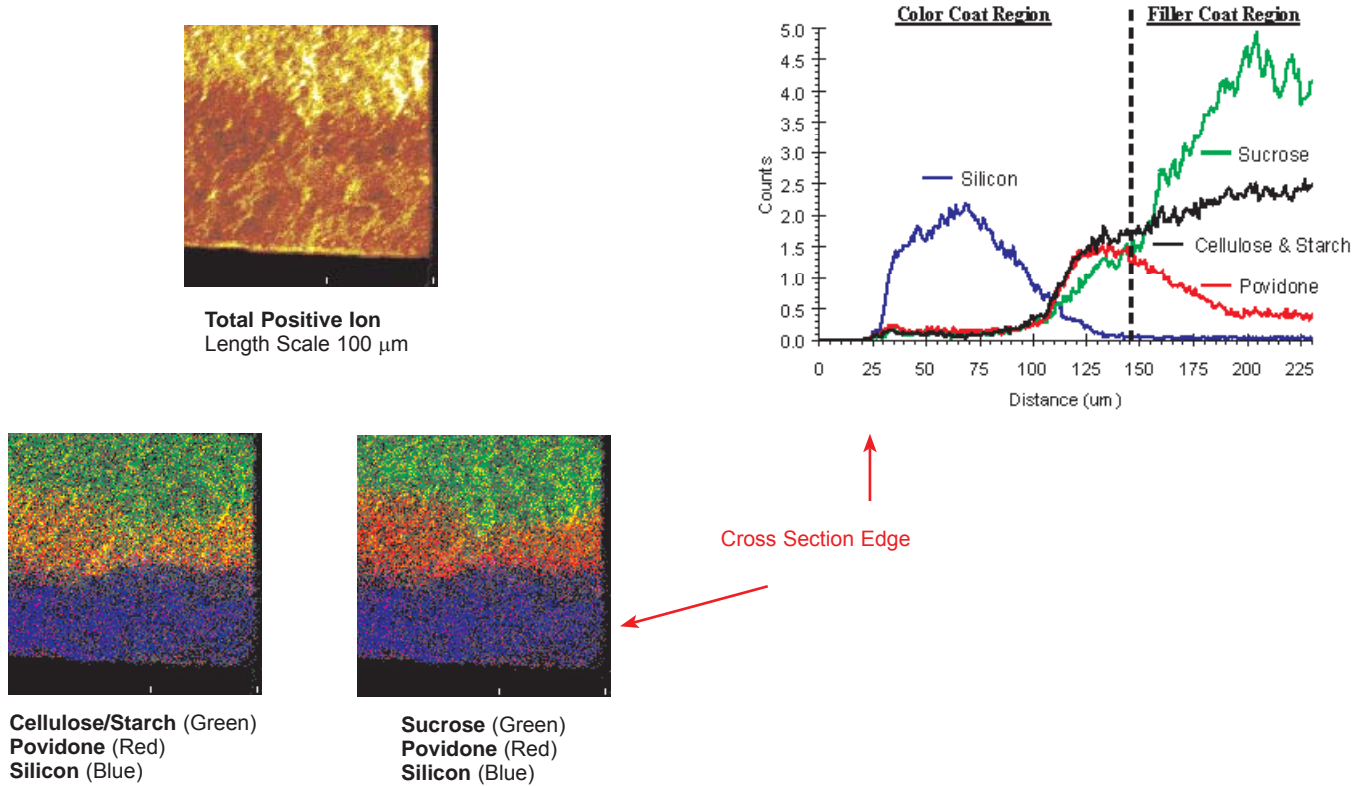
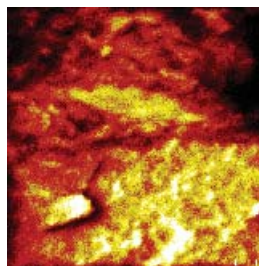
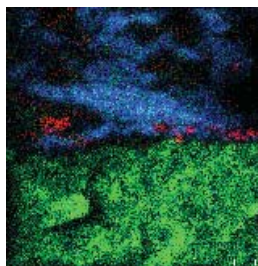


Figure 2. Chemical images and line scans illustrating the complex **Color/Filler** coat interface of the tablet cross section.

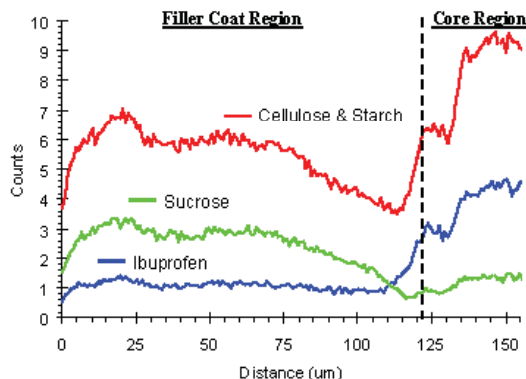
**Core Region**



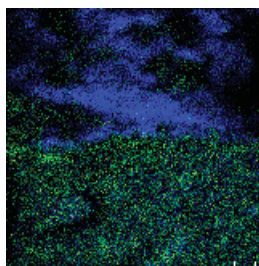
**Total Positive Ion**  
Length Scale 10  $\mu$ m



**Ibuprofen (Blue)**  
**Silicon (Red)**  
**Sucrose (Green)**

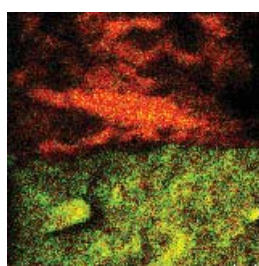


**Core Region**



**Ibuprofen (Blue)**  
**Povidone (Green)**

**Core Region**



**Cellulose/Starch (Red)**  
**Sucrose (Green)**

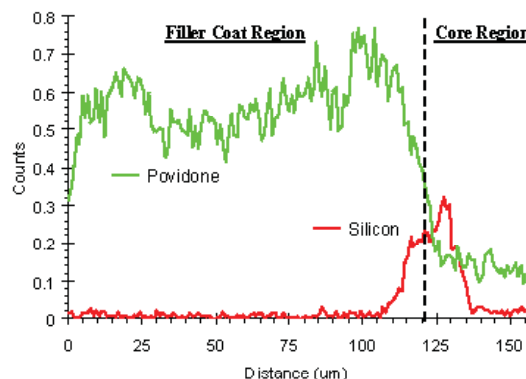
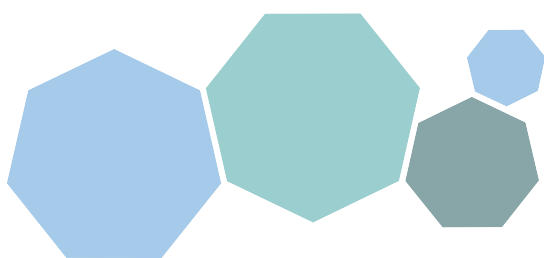


Figure 3. Chemical images and line scans illustrating the sharp **Filler/Core** coat interface of the tablet cross section.



**United States Locations**

Tempe, Arizona  
+1 480 239 0602 info.az@eaglabs.com  
+1 602 470 2655 fax

Sunnyvale, California  
810 Kifer Road  
+1 408 530 3500 info.ca@eaglabs.com  
+1 408 530 3501 fax

1135 E Arques Avenue  
+1 408 738 3033  
+1 408 738 3035 fax

785 Lucerne Drive  
+1 408 737 3892  
+1 408 737 3916 fax

Peabody, Massachusetts  
+1 978 278 9500 info.ma@eaglabs.com  
+1 978 278 9501 fax

Chanhassen, Minnesota  
+1 952 828 6411 info.mn@eaglabs.com  
+1 952 828 6449 fax

East Windsor, New Jersey  
+1 609 371 4800 info.nj@eaglabs.com  
+1 609 371 5666 fax

Syracuse, New York  
+1 315 431 9900 info.ny@eaglabs.com  
+1 315 431 9800 fax

Raleigh, North Carolina  
+1 919 829 7041 info.nc@eaglabs.com  
+1 919 829 5518 fax

Round Rock, Texas  
+1 512 671 9500 info.tx@eaglabs.com  
+1 512 671 9501 fax

**International Locations**

Shanghai, China  
+ 86 21 6879 6088 info.cn@eaglabs.com  
+ 86 21 6879 9086 fax

Tournefeuille, France  
+ 33 5 61 73 15 29 info.fr@eaglabs.com  
+ 33 5 61 73 15 67 fax

Frankfurt, Germany  
+ 49 (0) 693053213 info.de@eaglabs.com  
+ 49 (0) 69307941 fax

Tokyo, Japan  
+ 81 3 5396 0531 info.jp@eaglabs.com  
+ 81 3 5396 1930 fax

HsinChu, Taiwan  
+ 886 3 5632303 info.tw@eaglabs.com  
+ 886 3 5632306 fax

Uxbridge, United Kingdom  
+ 44 (0) 1895 811194 info.uk@eaglabs.com  
+ 44 (0) 1895 810350 fax