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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 SiO2) 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.

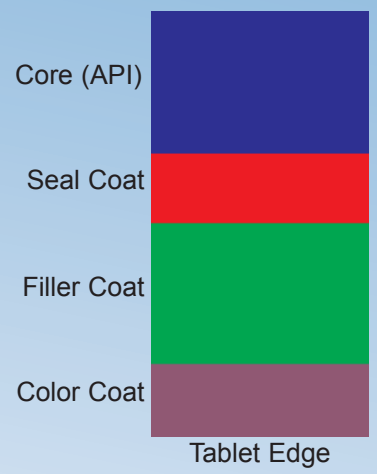

Figure 1: Tablet cross section illustrating the core, seal coat, filler coat, and color coat regions.

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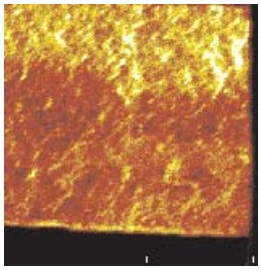
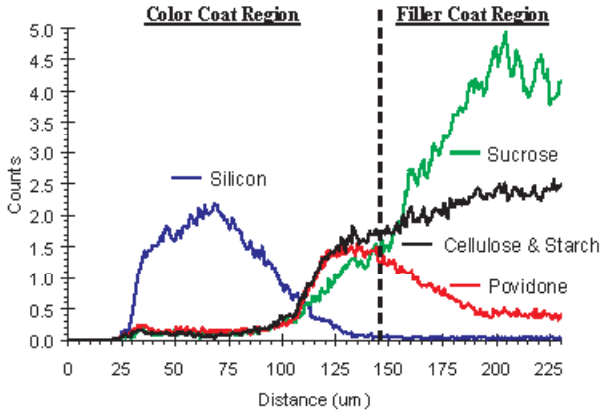
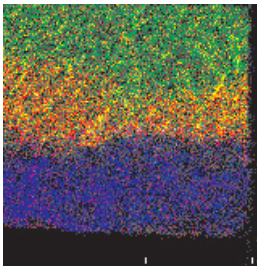
sub-micron spatial resolution also allows TOF-SIMS to be used as a powerful tool to reverse engineer products and as a process analytical tool for root cause investigations. The chemical imaging capabilities of TOF-SIMS can easily adapt to the study of stent coatings, catheters, a wide range of delivery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

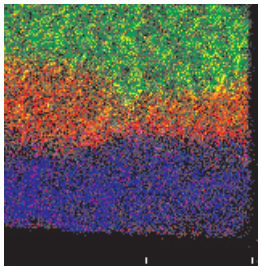


Total Positive Ion
Length Scale 100 μm





Cellulose/Starch (Green)
Povidone (Red)
Silicon (Blue)



Sucrose (Green)
Povidone (Red)
Silicon (Blue)

Cross Section Edge

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

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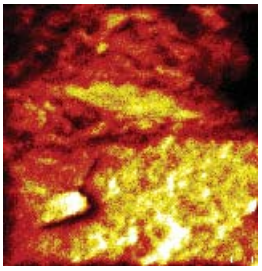
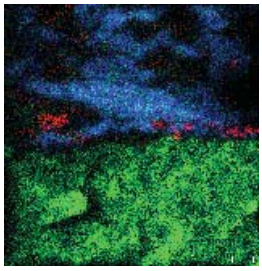
Core Region

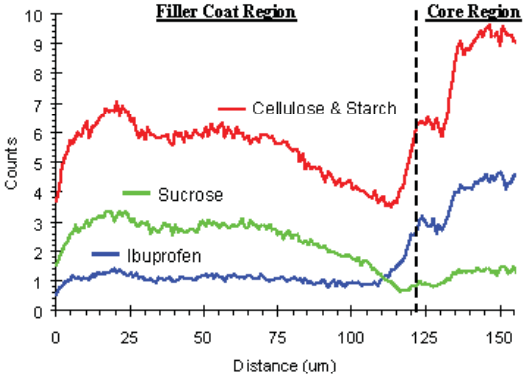


Total Positive Ion
Length Scale 10 µm

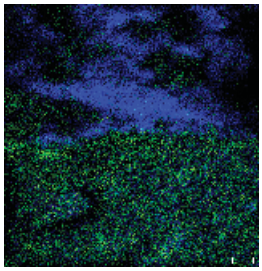
Core Region



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

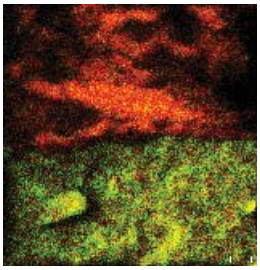


Core Region



Ibuprofen (Blue)
Povidone (Green)

Core Region



Cellulose/Starch (Red)
Sucrose (Green)

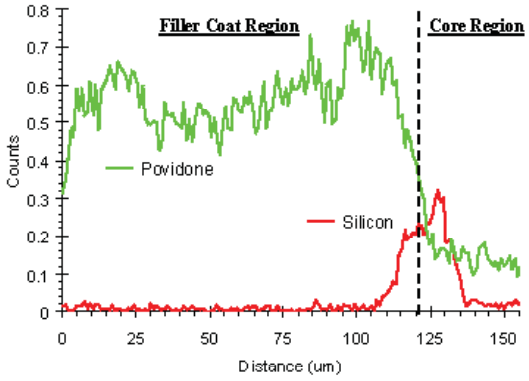


Figure 3. Chemical images and line scans illustrating the sharp **Filler/Core** coat interface of the tablet cross section.

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