

## Multiple Characterizations of a Blister Pack Using the XGT-9000



Application Note  
Pharmaceuticals  
XGT20

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**Abstract:** The XGT-9000 is HORIBA's new X-ray microscope. Its analytical versatility allows, multiple characterizations to be performed on a blister pack, from mapping of the full pack to particle size measurements of the capsule content.

**Keywords:**  $\mu$ -XRF, pharmacy, blister, X-ray mappings, transmission mapping

### Introduction

Quality control (QC) is a key aspect in the pharmaceutical industry. Drugs must be marketed as safe and with active formulations whose performance is consistent and predictable. However, QC cannot focus only on the drug itself, but must cover also the packaging material, as it can affect the quality stability and the identification of the drug product. Indeed, packaging must provide protection, minimize the loss of constituents and should have no physical or chemical interaction which could alter the quality or present a toxicity risk.

For instance, in a single run multiple characterizations of a full blister pack can be performed. The mapping of the full product allows to detect defects on the packaging and to check that all capsules are present. Additionally, the capsules can be scanned to evaluate the homogeneity of the coloring elements or to search for foreign material which could have been trapped. Finally, the granulates contained in each capsule can be counted, measured and analyzed.

### Instrument description and methodology

The principle of the X-ray fluorescence is schematically represented in Figure 2. When materials are exposed to X-rays (Primary X-rays in Figure 2) the ejection of one or more electrons from the inner shell of the atom may occur. The removal of an electron makes the electronic structure unstable and in order to re-establish the neutrality, electrons



Figure 1. The new XGT-9000 microscope

With its high degree of versatility, the **XGT-9000** (Figure 1), HORIBA's new X-ray microscope, is the perfect tool for the pharmaceutical industry as it can be easily applied within industrial settings, as well as R&D.

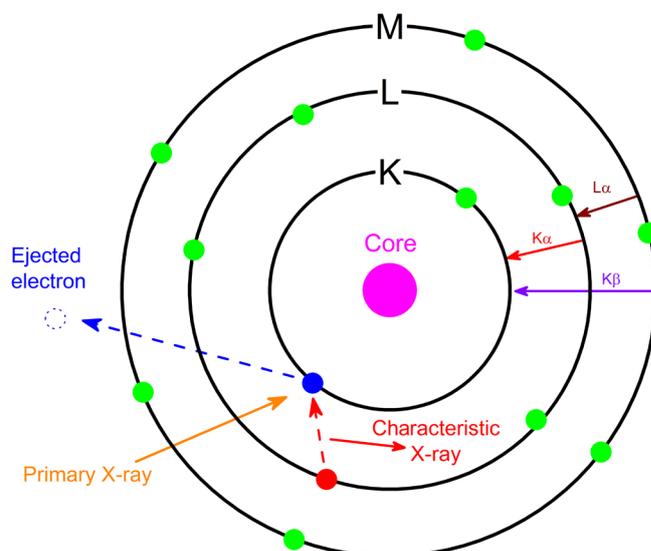


Figure 2. Schematic representation of the X-ray Fluorescence phenomenon.

in the outer shells «fall» into the lower ones to fill the hole left behind. In falling, energy is released in the form of a characteristic X-ray photon, the energy of which is equal to the energy difference of the two orbitals involved ( $K\alpha$ ,  $K\beta$ ,  $L\alpha$ , etc, in Figure 2). Thus, the material emits radiation with an energy characteristic of the atoms present.

In the **XGT-9000** the characteristic X-rays are detected with an energy dispersive silicon drift detector that combines high count rate with good resolution. Furthermore, no liquid nitrogen is needed since thermo-electric Peltier cooling is used.

The advantage of the micro-XRF is the XY sample stage, which provides the possibility to acquire a pixel-by-pixel spectrum from which X-ray elemental images can be reconstructed. In addition, the new **XGT-9000** software is equipped with a functionality to locate and count single particles. For instance, the mappings (X-ray fluorescence, transmitted X-rays or combined) can be processed through this function for particle detection. Then, the average size can be measured, and a size distribution obtained.

The instrument can be run in full or partial vacuum. When working in partial vacuum it is possible to analyse liquids, biological samples or hydrated ones without any damage, as the samples are kept at atmospheric pressure. This unique feature allows characterization of a full blister pack as well as an individual capsule without dealing with the typical deformation induced by vacuum.

## Measurements and results

A commercial blister pack (Figure 3) was used to demonstrate the ability of the **XGT-9000** to provide maximum information within a single analysis.

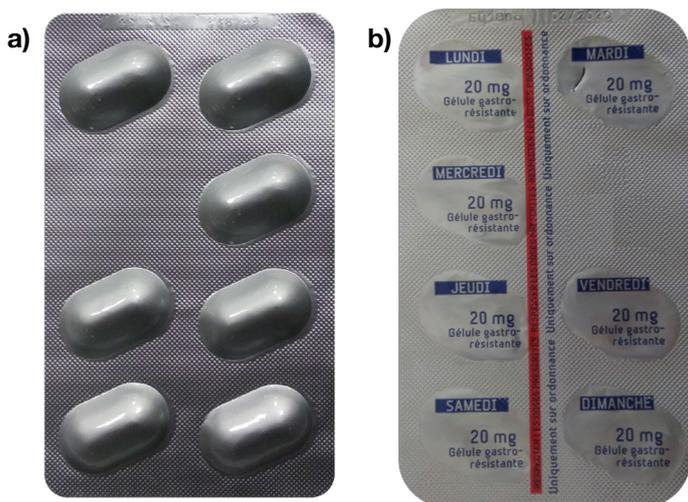


Figure 3. Photo of the analysed commercial blister, showing (a) Side A and (b) the side B.

The large mapping area (maximum 10x10 cm) possible with the instrument and its ability to work at partial vacuum, with the sample kept at atmospheric pressure, has made it possible to fully image in a single run the blister B side (Figure 4).

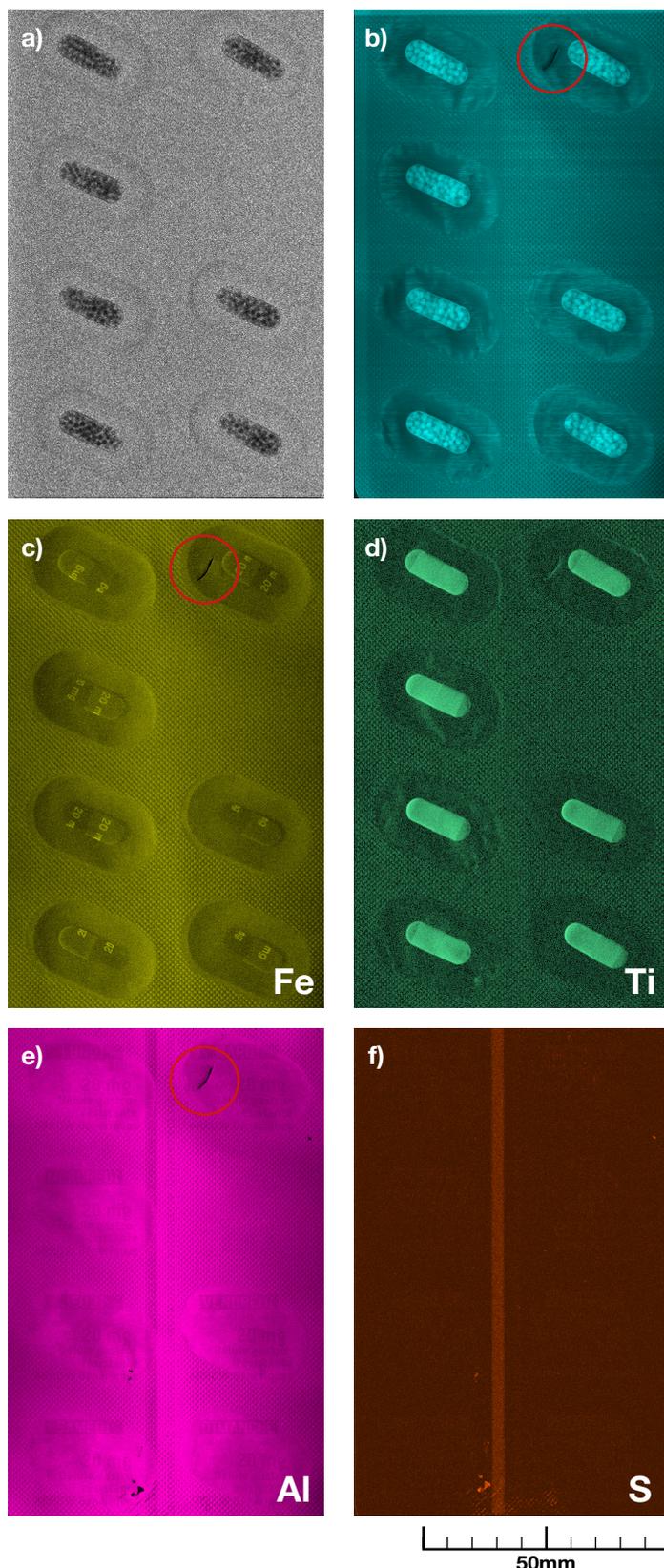


Figure 4. Mapping of the side B of the full blister. (a) transmission image; (b) full spectrum image; (c) Fe image; (d) Ti image; (e) Al image and (f) S image.

The transmission image (Figure 4a) is representative of the X-rays absorption through the sample and clearly shows the presence of capsules filled with granulates. Nevertheless, with analysis of the full X-ray spectrum image (Figure 4b) it is possible to identify the capsules, as well as the granulates inside and even the pattern of the metallic foil. The Fe and Ti images, Figure 4c and 4d respectively, are characteristic

of the colorants used in the capsules, whereas Al (Figure 4e) and S (Figure 4f) come from the packaging, the first being the metallic foil of the blister and the latter used for the coloured warning band. Finally, another useful capability is the possibility to detect a tear in the sealing film (area circled on full spectrum, Fe and Al images)

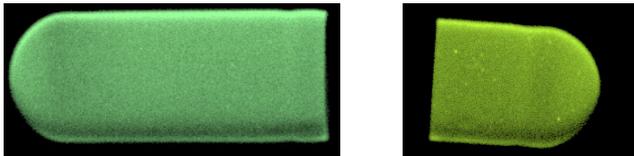
In a second step, we have removed a capsule from the blister and opened it for more detailed analysis: first the parts of the capsule, then the granulates.

In Figure 5 we show the elemental maps of the opened capsules, where the main detected elements are S, Fe, Ti and K. Sulfur and titanium are present in both parts of the capsule, but while the S content is homogeneous, the yellow side of the capsule shows localized spots with a higher Ti content. In addition, some heterogeneities are also observed on the K image (both sides of the capsule). It is worth noting that the iron mapping reveals not only that the yellow side of capsules contains some Fe, but also the ink used for the text.

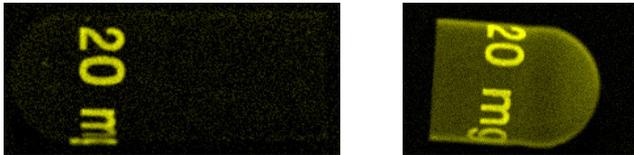
**a) optical**



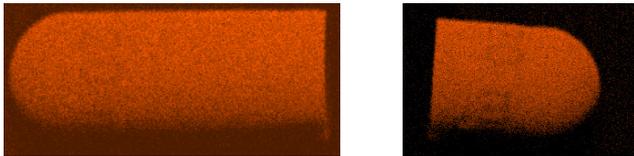
**b) Ti**



**c) Fe**



**d) S**



**e) K**

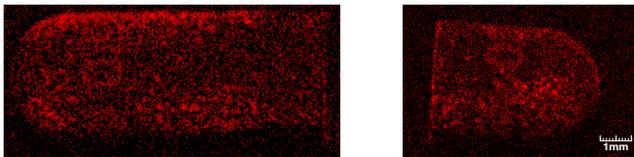


Figure 5: (a) optical image of the two capsules sides; X-rays mappings of the two capsule sides (b) Ti, (c) Fe, (d) S and (e) K.

Figure 6 shows the results of the analysis of the granulates contained inside the capsule. Granulates were stuck of the XY table support using Kapton tape and then analysed directly, outside their shell. Sulfur is the main detected element and is

shown to be homogeneous at the granulate scale. However, some other elements (i.e. Si and Mg) are also present but with a high degree of heterogeneity.

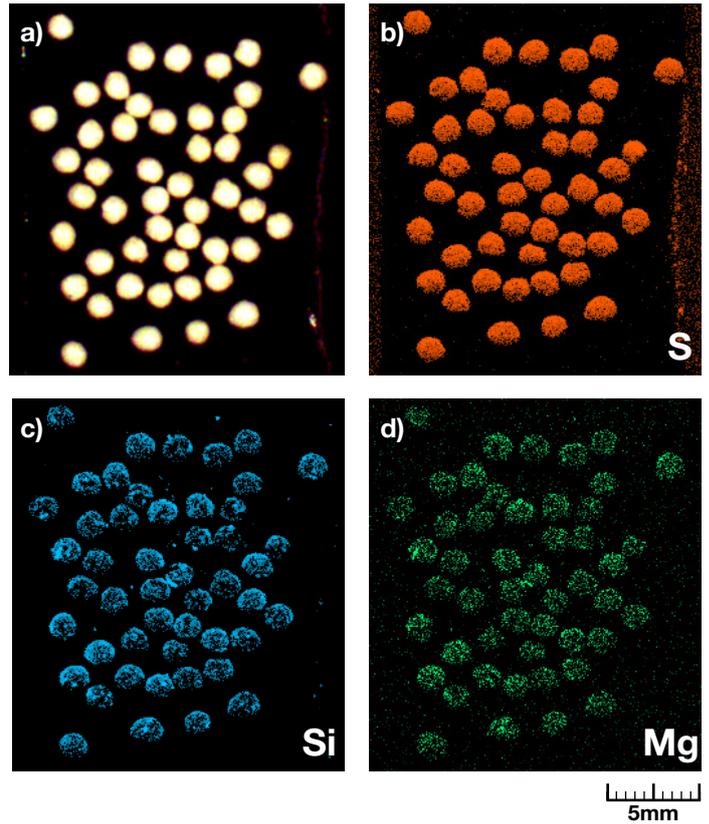


Figure 6: (a) optical image of the granulates; X-ray map of the granulates. (b) S, (c) Si and (d) Mg.

The particle detection function can be used to count and measure the equivalent diameter of individual granulates, obtaining a size distribution chart (Figure 8). In addition, a position file is provided and can be used to perform automatic point analysis of each particle.

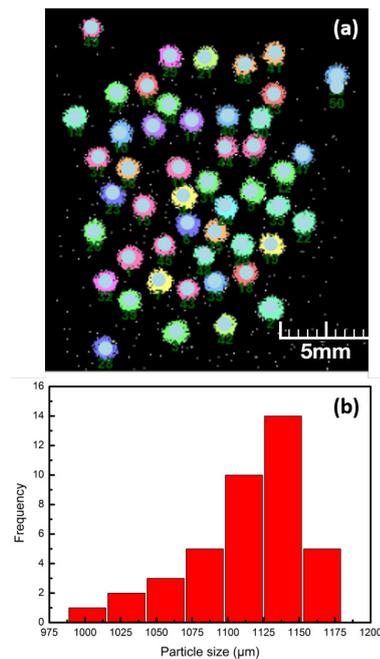


Figure 7. (a) Detected particles and (b) Equivalent circumference diameter distribution.

Finally, in order to show the ability of the **XGT-9000** to detect foreign object we have inserted a metallic shard inside a capsule and performed an X-ray mapping (Figure 8). The transmission image shows the presence of the granulates, proving that the drug is correctly filled, but also the dark spot of the shard.

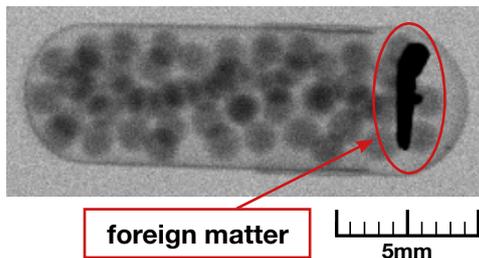


Figure 8. X-ray transmission image of capsule with foreign matter

In addition, the characteristic X-ray image provide complementary information and are shown in Figure 9.

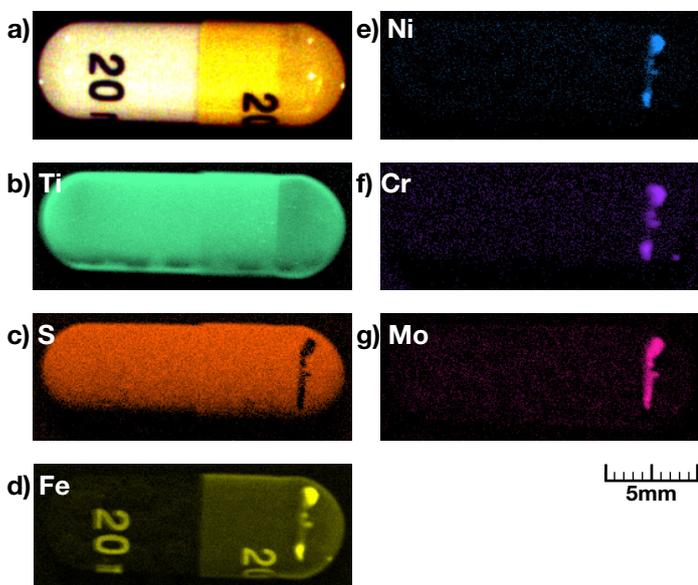


Figure 9. (a) optical image of the capsule; X-Ray map of. (b) S, (c) Ti, (d) Fe, (e) Ni, (f) Cr and (g) Mo.

First of all, the Ti mapping (Figure 10b) shows that the white side of the capsule has a higher Ti content, than the yellow one. Then, the Fe, Ni, Cr and Mo mappings show that these are the primary elements of the metallic foreign object, which can be assumed to be a stainless-steel shard. However, we can notice that the presence of this object modifies the S image, while having no influence on the Ti one. While the Ti signal comes primarily from the capsule, which is above the metallic shard, the S characteristic X-rays are generated not only by the capsule, but also from the granulates (as

shown in Figure 6). However, the presence of the metallic shard alters the contribution to the S signal by absorbing the characteristic S X-rays emitted by the granulates and creating the inhomogeneity observed in the X-ray image (Figure 9c).

## Conclusion

In this application note we have shown that XRF is not only an easy and non-destructive technique, but it is also characterized by a high versatility which could benefit the pharmaceutical industry.

First, with the large mapping area of the **XGT-9000** and the possibility of working in partial vacuum, we have shown that a full blister pack can be imaged, providing information from the surface (X-ray images) and also from the inside of the sample (transmission image). Then, we showed that a single capsule could be studied, showing inhomogeneities in the Ti, K and Fe content, and also that the granulates could be analysed outside of their shell. The particle detection function was used to count and measure the size of individual particles. Finally, a foreign object was inserted inside the capsule, and we proved the ability of the **XGT-9000** to detect and characterize foreign matters.

The **XGT-9000** is a versatile tool allowing information on different elements of a blister pack to be obtained. Its complementarity with other techniques like Raman microscopy can help pharmaceutical laboratories solve production problems as well as gain insight into fundamental research.

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