AN INNOVATIVE EDXRD VERIFICATION PROBE
Charles M. Dozier and Noureddine Anibou
*XStream Systems, Inc.*
*Sebastian, FL*

**ABSTRACT**

Verification of materials is an increasingly important need in pharmaceutical distribution. XStream Systems, Inc has developed an Energy Dispersive X-ray Diffraction (EDXRD) system which can quickly verify crystalline pharmaceuticals in the distribution cycle. Materials may be in solid or powder form, and the technique is non-destructive. Unlike Angular X-ray Diffraction (AXRD), a “white” x-ray beam between 20 and 80 keV is used. This energetic beam can penetrate through relatively thick materials, diffracting from crystallites within the samples. Materials can be observed even when they are located within opaque, sealed containers. That is, for most cases the drugs can be examined in their sealed, packaged vials without any sample preparation.

The tabletop unit uses a confocal geometry to maximize the x-ray intensity from a relatively low-powered, air-cooled x-ray source. The beam is collimated by a circular slit assembly before the sample. A similar slit assembly after the sample collimates the diffracted beam. A single, state-of-the-art, CdTe solid-state detector with a multichannel analyzer is used to process the diffracted signal. This collimation system interrogates a doughnut-shaped volume within the sample under test.

One of the design goals was to develop a unit that is capable of performing quick verification or detection of complex materials and mixtures at a number of points along the distribution paths yet can be operated by personnel with minimal scientific knowledge. Rapid identification of unknowns is possible using neural network search algorithms or pattern matching techniques. The Material Recognition Software Engine (MRSE) utilizes a localized SQL database to store and process the raw spectra data. The MRSE takes the sample data and determines if it matches any known patterns within its database. This engine has demonstrated that it can verify a number of drugs within 30 sec with better than 97 percent accuracy.

**INTRODUCTION**

Although most medicines are safe in the United States, the rate of growth of counterfeit products is increasing rapidly. Monitoring the distribution system to ensure that these drugs are found before they are dispensed to innocent victims has become an important issue for drug manufacturers and distributors.

X-ray technologies can play an important role in this monitoring if they can be applied in a manner that allows for rapid detection of these counterfeits. Radiography allows one to examine shapes and densities of objects but cannot make unique identification of specific
This document was presented at the Denver X-ray Conference (DXC) on Applications of X-ray Analysis.

Sponsored by the International Centre for Diffraction Data (ICDD).

This document is provided by ICDD in cooperation with the authors and presenters of the DXC for the express purpose of educating the scientific community.

*All copyrights for the document are retained by ICDD.*

Usage is restricted for the purposes of education and scientific research.

DXC Website – [www.dxcicdd.com](http://www.dxcicdd.com)

ICDD Website - [www.icdd.com](http://www.icdd.com)
drugs. X-ray fluorescence can identify components of materials. Yet in many cases, knowledge of the elemental composition is not sufficient to verify a drug’s composition. X-ray diffraction does have the ability to identify drugs that are made from crystalline materials based on their unique crystalline diffraction patterns. For typical angular dispersive techniques, this requires sample preparation and prevents this method from being a rapid analysis technique. However, energy dispersive x-ray diffraction has advantages that allow it to be used to make such comparisons. Not only does this technique allow one to observe the crystalline behavior, but since more energetic x-rays are used, one can make these measurements within the sealed, opaque containers that most medications are packaged.

In this paper, we will present an instrument that can verify many pharmaceutical drugs in their original vials. Designed to be used in the distribution chain, the instrument can be operated by most workers to determine if drugs have been replaced by counterfeits or altered in other ways. The system compares the “fingerprints” of drugs with known “fingerprints” of these drugs. Tests have shown that authentification or verification can be done in times less than 5 minutes and with accuracies better than 98% in most cases

ANGULAR DIFFRACTION VS ENERGY DISPERSIVE DIFFRACTION

In a standard diffractometer, utilizing a monochromatic source of x-rays, atomic planes of various inter-planar spacings \( d \), in crystalline material reflect a single wavelength at various \( 2\theta \) angles. The diffracted x-ray pattern is observed by moving a detector sequentially to each position and measuring the intensity of the diffracted beam. This configuration is called angular dispersive diffractometry and is illustrated in Figure 1.

![Figure 1: (Left) An angular x-ray diffraction set up. (Right) An example of ADXRD spectra showing diffracted intensity as function of angle 2-0.](image)

If the incident beam consists of polychromatic, white radiation, and the angle \( \theta \), is fixed for all the planes, the different sets of planes will reflect a different set of wavelengths, \( \lambda \), into a detector set at a fixed \( 2\theta \) angle (Figure 2). If the detector has the capability of energy resolution, and it is connected to an electronic device for displaying the
horizontal scale as energy, the sorted wavelengths, can be displayed on the basis of their energies. This configuration is called **energy dispersive diffractometry**.

Bragg's law states that $n\lambda=2dsin\theta$. In angular diffraction, $\lambda$ is held constant and as the angle $\theta$ is varied, the observed $d$ spacing changes correspondingly. It can be shown that energy dispersive x-ray diffraction is really just a different representation of Bragg’s law. It is appropriate to write this law in terms of quantum energy, $E$. Thus; $E=\hbar v=\frac{hc}{2dsin\theta}$, where $h$ is Planks constant and $v$ is the frequency. For $E$ in keV and $d$ in Å, Bragg’s law becomes $E=\frac{6.2}{dsin\theta}$. When $\theta$ is held constant, then $E$ changes as $d$ changes.

**THE XT250 VERIFICATION PROBE**

The XT250 system uses the advantageous confocal design shown in Figure 3. The ability to control the depth of focus, the elimination or reduction of the background information, and the ability to collect optical slices through the thickness of the specimen are some of the advantages of such x-ray optical system over the more conventional focusing optical systems. The confocal design requires a high flux density emerging from a small focal spot on the order of 50 micrometer. An air-cooled 40 watts x-ray source was used for this purpose. The incident beam is collimated by a series of 4 slots, set in a circular pattern and centered about the center of the primary axis of the diffractometer. The consequence of this arrangement being that a hollow cone of radiation comprising a small angular range of the off axis component of radiation emerges from the focal spot. One can imagine the cone of radiation as being similar to an ice cream cone. The apex of the cone corresponds to the source of radiation. The base of the cone describes the centroid of the scattering volume or **Voxel**. This volume is defined as the intersection of irradiating and scattered cones. The scattered beam is collimated via a similar slit collimator and directed toward the CdTe solid state detector which has an energy resolution of 850 eV at 122 keV, ($^{57}$Co), and is connected to a multichannel analyzer. The XT250 combination of angle ($2\theta=2.562^\circ$) and x-ray tube energy range (10-80 kV) allows us to monitor a $d$-spacing range between 3.38 and 27.7Å.
THE MATERIAL RECOGNITION SOFTWARE ENGINE

Since one of the compromises in the design that permitted rapid detection is loss of some of the resolution, advanced signal detection algorithms are applied to identify the materials being verified. These approaches are called our Material Recognition Software Engine (MRSE).

It is not possible in the scope of this paper to detail the engine in full. The following illustration shows how the engine works. Up to 50 features in each spectrum are identified. In this multi-dimensional feature space, unique identifications are possible.

As an example, let us use the position and height of two prominent peaks as one feature to be identified. In Figure 4, two peaks have been identified in three different spectra. When the positions of the peaks are plotted in a feature space, the regions in which these peaks are found tend to separate. Boundaries around these features can be constructed. If data from another unidentified sample of one of these three materials was tested, one could quickly identify which spectra one was observing by comparing in which region the two most prominent peaks were located. Obviously, the problem is much more complex than this simple example, but feature extraction such as shown here provide clues which allow us to verify materials when stored in bottles or vials, mixed with excipients, etc.
APPLICATION TO PHARMACEUTICALS

Figure 5 shows examples of data collected from aspirin and ibuprofen, two over the counter drugs, in their original bottles. As one might notice, the two spectra are different. In simple cases such as Aspirin, where a single crystalline phase exists, 2 peaks at energies 24.42 and 48.56 keV are evident and can be respectively identified as (100) and (002) reflections. In these simple cases, lines can be identified. In more complex cases, the line shapes are smeared out because of the relatively low instrument resolution and existence of amorphous or crystalline excipients in addition to the API. In the case of ibuprofen, only the (100) reflection near 21 keV can be identified. At this point one must rely on the power of the MRSE algorithms to extract spectral characteristics and then identify such material. The success rate is high since basic information is there.

Figure 5: Aspirin and ibuprofen spectra collected in 5mins. The (100) and (002) reflections of aspirin are indicated. The ibuprofen (100) reflection near 21 keV is the only identifiable peak in the spectrum.

Figure 6 shows a spectrum of ibuprofen where the sample size, detector aperture, and other parameters that could be adjusted were changed to maximize the resolution of the instrument. When this is done, one can begin to see the various d-spacings, (100), (200), and (210) for ibuprofen appear. However, the time it took to generate this spectrum was over an hour, whereas the spectrum we use to identify ibuprofen required only 5 minutes or less.

Figure 6: A high resolution spectrum of ibuprofen
OTHER APPLICATIONS

The XT250 has been used to examine non-crystalline materials as well. One example has been a series of golf ball cores. Like pharmaceutical drugs in sealed containers, once a golf ball has been fabricated, one must use a penetrating radiation to examine the cores. Figure 7a shows spectra of six different golf ball types. One can see that the cores of these balls produce rather different spectra. Interestingly, the two cores that look quite similar, Type B and C from the second manufacturer are sold with different brand names. These cores appear to be quite similar, if not the same. Also while testing different brands of balls, an anomalous ball was found. Figure 7b shows the difference between the anomalous ball and the remainder of the balls of this brand tested. Whether or not this ball was simply mislabeled, a bad batch of core material, or a counterfeit, we were not sure. However, when the balls were cut open, the cores appeared to be different. This difference was confirmed with x-ray fluorescence measurements. The important point is that the difference in the core material was initially determined without having to disturb the integrity of the ball.

![Figure 7: (a) Spectra showing the differences in core materials of six different ball types from two manufacturers. (b) Spectra of an anomalous golf ball core compared to the spectra of other balls with the same brand labeling.](image)

SUMMARY

The XT250 verification probe provides a new and novel approach to authenticating crystalline pharmaceutical drugs. Of importance is that it can provide this verification capability without having to open sealed, and opaque, containers in which the drugs may be packaged. The time necessary to verify the drugs is less than five minutes, often in as little as 30 seconds. Accuracy of these verifications has been found to be better than 98% for the drugs that we have tested. The system has been designed to be used by non-scientific operators which one may encounter in a distribution warehouse setting.
REFERENCES

1. For example see http://www.pfizer.com/products/counterfeit_and_importation/counterfeit_importation.jsp, or http://www.pfizer.com/products/counterfeit_and_importation/counterfeit_qa.jsp