

New Developments in Wavelength-Dispersive XRF and XRD for the Analysis of Foodstuffs and Pharmaceutical Materials

This article discusses the benefits of X-ray fluorescence (XRF) for the determination of elemental nutrients in foodstuffs and X-ray diffraction (XRD) for the measurement and characterization of different compounds used in the pharmaceuticals industry. In particular, it will show how wavelength-dispersive XRF has simplified the analysis of milk powders and plant material, especially for the determination of lighter elements such as Na, Mg, and N, which have traditionally been difficult by XRF. The study also presents new developments in XRD for the identification and quantitation of specific crystalline polymorphic forms of drug compounds. The suitability of this technique also is shown for troubleshooting pharmaceutical manufacturing problems to better understand the stability of drug formulations and for the quantification of fillers used in the pharmaceutical manufacturing process.

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Over the past 30 years, X-ray fluorescence (XRF) has become the elemental technique of choice for the determination of parts-per-million to percentage concentration levels in many solid materials including metals, ores, rocks, glasses, powders, plastics, ceramics, and foodstuffs (1). The principles of XRF spectrometry are well-documented in the literature (2). A sample is irradiated with a beam of high-energy X-rays. As the excited electrons in the sample fall back to a ground state, they emit X-rays that are characteristic of those elements present in the sample. The individual X-ray wavelengths are then separated and measured via a system of crystals, optics, and detectors. Elemental concentrations in unknown samples are quantified by comparing the X-ray intensities against known calibration standards. The major benefit of XRF over arc or spark emission techniques is that it can analyze both conducting and nonconducting materials as well as inorganic and organic matrices with minimal sample preparation (3,4).

X-Ray Fluorescence

The technique is available in two separate configurations — energy-dispersive (ED) and wavelength-dispersive (WD) XRF. The ED approach measures the intensity of the photon energy of the individual X-rays generated, whereas in WD spectrometry, the polychromatic beam emerging from a sample surface is dispersed into its monochromatic components or wavelengths with an analyzing crystal. A specific wavelength is then calculated from knowledge of the crystal and the diffraction angle (5).

It is generally recognized that WDXRF has several advantages over EDXRF, including better spectral resolution (up to 10 times better for some elements), superior performance for light elements (B to Cl), and the ability to determine major concentrations of elements without risking saturation of the detectors. Figure 1 shows the periodic table, indicating all the elements that can be determined by WDXRF.

The quality of the accuracy and precision of the data gen-

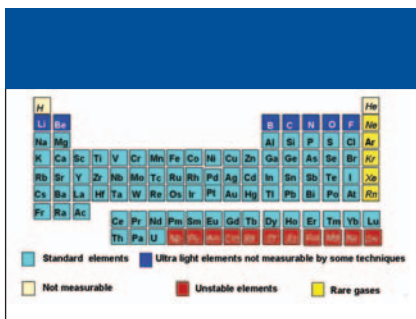


Figure 1: Elements that can be determined by WDXRF.

erated by WDXRF can very well be compared with that of traditional wet chemical methods, but with the clear advantage of faster analysis times. This translates into a significant reduction in the overall cost of analysis, as no complex, labor-intensive wet chemistry procedures are required. The other major benefit of the WDXRF technique is that in addition to conventional quantitative analysis using suitable calibration standards, the technique is able to analyze various types of materials in which no matching standards are available, or where the calibration procedures are time-consuming and expensive. This feature has become possible thanks to the development of powerful “standard-less” analysis software programs using stored calibration graphs. It is generally accepted that the higher performance and better capabilities of WDXRF are helping to push the analytical boundaries traditionally associated with the XRF technique.

X-Ray Diffraction

On the other hand, X-ray diffraction (XRD) is an analytical technique that looks at the X-ray scattering from crystalline or polymorphic materials. Each material produces a unique X-ray “fingerprint” of X-ray intensity versus scattering angle that is characteristic of its crystalline atomic structure. Qualitative analysis is possible by comparing the XRD pattern of an unknown material with a library of known patterns. Although its principles are different, XRD can be considered complementary to XRF. For example, XRF can tell you that a material is composed of iron and sulfur, but XRD can tell you that both iron sulfide (FeS) and elemental

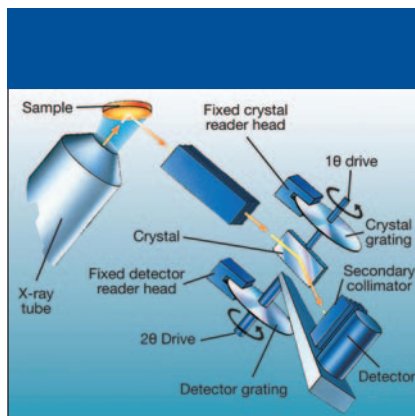


Figure 2: Schematic of the WDXRF instrument used in this study.

iron (Fe) are present. Furthermore, because XRD works with any crystalline solid, there is almost no limit to the types of materials that can be studied (6). Some of the materials that are typically characterized by XRD include chemicals, environmental dusts, rocks, minerals, metals, cements, pigments, and forensic samples.

One of the major applications of XRD is to identify and quantify specific compounds or phases in materials

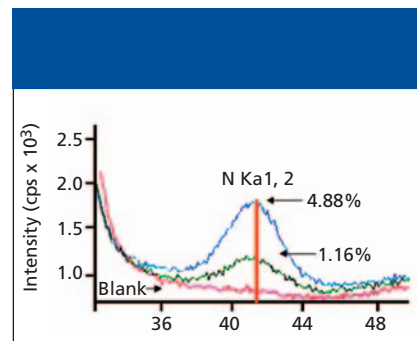


Figure 3: A spectral scan of nitrogen in plant material obtained using a high-power WDXRF system.

that are organic in nature, such as foodstuffs or pharmaceutical compounds. These kinds of applications have evolved over the last few years mainly because of a new generation of solid-state detectors, higher quality optics, and the availability of sampling attachments. These technological improvements have led to both higher sensitivity, which is needed for the detection of minor and trace levels of crystalline compounds in pharmaceutical compounds, and higher resolu-

Table I: Comparison of limits of detection (LODs) of a high (up to 4.2 kW), medium (1.2 kW), and low (50 W) power WDXRF system for the analysis of pelletized milk powders (t = measurement/integration time; NM = not measured) (Note: All precision and LOD data are ppm)

Elem.	Conc. Range in Milk Powder	Advant'x (High Power)	Advant'x (Medium Power)	Optim'x (Low Power)			Conc. Level of Sample Used for Precision Test
		Sequential LOD (t=30s)	Sequential LOD (t=30s)	Sequential LOD (t=60s)	Simultaneous LOD(t=120s)	Precision in 6 runs of Same Pellet (t=60s)	
Ca	0 - 0.16%	4	6.6	10	NM	33	3860
Cl	0 - 0.48%	3	4.3	10	NM	NM	NM
Cu	0 - 0.012%	0.3	0.6	0.6	NM	0.2	5
Fe	0 - 0.33%	1	1.7	2.1	NM	2	60
K	0 - 1%	3.5	6.2	2	NM	44	60,000
Mg	0 - 0.12%	7.2	13.5	NM	22	11 (240s)	600
Mn	0 - 0.0023%	0.3	0.5	1.2	NM	NM	NM
Na	0 - 0.03%	9.3	15	NM	42	28 (240s)	2400
P	0 - 1.1%	1.2	2.2	4.4	NM	18	2600
Se	0 - 3.4 ppm	0.06	0.1	0.24	NM	NM	NM
Zn	0 - 0.2%	0.9	1.6	2	NM	0.7	50

tion for improved spectral specificity in the presence of interfering species.

To demonstrate the benefits of both the WDXRF and XRD techniques, let us take a closer look at some of the more challenging applications that are being carried out today in the pharmaceutical and food industries.

Application of WDXRF to the Analysis of Foodstuffs

WDXRF has been widely used for the chemical analysis of foodstuffs, pharmaceutical raw materials, and agricultural crops (7,8). Standard element coverage is from sodium (Na) to uranium (U), with typical concentration levels from sub-part-per-million levels up to 100%. However, lighter elements (Be to O) can be determined in certain matrices with the use of synthetic multilayer crystals. Sample preparation is very simple. Sometimes, the sample can be analyzed as it is received, or the more common procedure is to dry the sample, grind it into a powder, and then press it into a pellet or tablet. The XRF data shown in this study were generated either on the low-powered (50-W) ARL OPTIM'X or the medium-powered (1.2-kW and 2.5-kW) ADVANT'X, (Thermo Electron SA, Ecublens, Switzerland) WD-XRF spectrometers. They both have been described in the open literature (9). A schematic of the ADVANT'X showing

the principles of sequential operation is shown in Figure 2.

Analysis of Milk Powders

The analysis of infant cereals and milk powders is becoming an increasingly important application for XRF (7). However, one of its greatest challenges has been to determine the low-level nutrients like Se, Mn, Fe, and Zn with good precision and accuracy. For that reason, a comparison of the limits of detection (LOD) in ppm was made on a series of pelletized milk powders using three different excitation sources. This comparison is shown in Table I. The quantitative detection limits are similar for all three approaches, but there is a definite trend toward lower detection limits as the power is increased. Typical measurement precision values (ppm) for six separate analyses of the same pellet (using low power) are shown in the last two columns of the table. However, it is important to emphasize that even though this kind of precision is considered typical for low-level XRF work, the accuracy of the measurements depends on many other factors, including operator experience, sample preparation, calibration standards, and whether appropriate background correction is used.

Nitrogen in Plant Material

Another example of the progress made in the capability of XRF to detect very

low atomic numbers is shown in Figure 3, which shows a spectral scan of nitrogen in plant material. Ten years ago, nitrogen belonged to the list of the elements that could not be determined by WDXRF. Advances in multilayer crystal technology, the thickness and material of detector windows, and instrument sensitivity now allow nitrogen to be included in the list of elements that can be determined by XRF.

This is exemplified in Figure 4, which shows the nitrogen calibration curve obtained for various plant materials (tomato, hay, cabbage, lettuce, wheat, grass, leaves) using the same instrument.

Application of X-Ray Diffraction to the Analysis of Pharmaceutical Materials

Let us now turn our attention to X-ray diffraction. The new generation of X-ray diffractometers has stimulated the

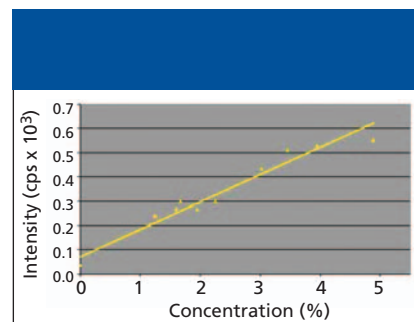


Figure 4: Calibration of nitrogen using various plant materials.

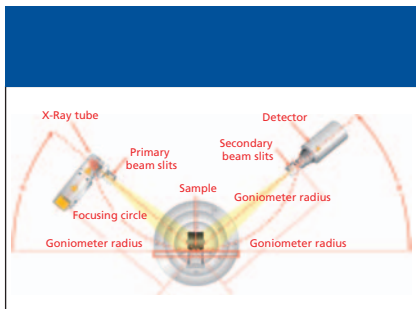


Figure 5: Schematic of the X-ray diffractometers used in this study showing the Θ - Θ geometry.

growth of the technique in the pharmaceutical and food industries both for research and development purposes and for routine quality control testing (10). For example, crystallographic, structural, and phase analysis can give pharmaceutical companies more complete characterization of new materials. However, in such applications, it is absolutely critical that the instrument offers high sensitivity combined with extremely good resolution down to low angles.

Stability of pharmaceutical formulations as a function of relative humidity also can be tested using specially designed environmental chambers. To ensure that formulations will be stable under all possible storage conditions, it is important to know how the material reacts to changes in temperature. In particular, it is possible to know whether thermal expansion is isotropic (identical in all directions) or not (anisotropic). If a given formulation has preferred orientation and anisotropic thermal expansion, changes in storage temperature can result in tablet breakage or other formulation problems. For these kinds of

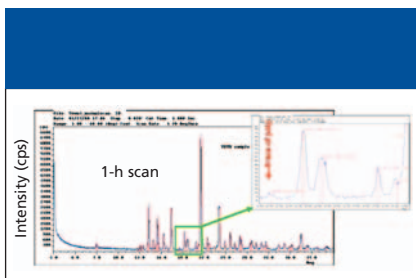


Figure 6: Detection of a polymorphic compound present at trace levels (<1%) using XRD, showing the expanded view of a secondary phase.

manufacturing quality control applications, it is therefore important that in addition to high performance, the instrument also is fitted with suitable sampling accessories.

With that in mind, let us look at some typical XRD applications that are being carried out in the pharmaceutical industry. The XRD data shown in this study were generated using an ARL X'TRA powder X-ray diffractometer (Thermo Electron SA) (11). A schematic of the instrument's geometry is shown in Figure 5.

Measurement of Crystalline Phases

The design of this instrument makes it very suitable for the identification of polymorphic (crystalline) and pseudo-polymorphic compounds generally encountered in pharmaceutical and food compounds (12). Thanks to its high sensitivity, low concentration levels of polymorphic phases can be detected more easily. This can be seen in Figure 6, which shows a 1-h diffraction scan of X-ray intensity against scattering angle of a drug compound. The boxed area in green has been

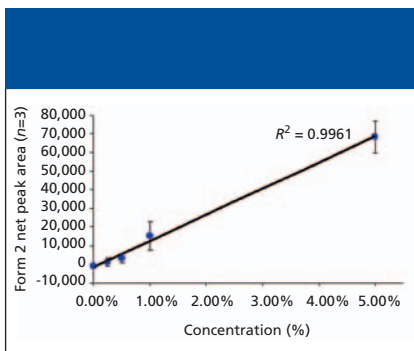


Figure 7: Calibration and quantitation of a secondary phase of the drug compound (ranitidine hydrochloride) shown in Figure 6.

expanded to show the detection of trace levels of a secondary phase of the polymorph. This phase of the compound (ranitidine hydrochloride) was then quantified by standard calibration methods based on peak area measurements shown in Figure 7.

Troubleshooting the Manufacturing Process

Understanding production processes is also crucial in the pharmaceutical industry. Two production plants were using slightly different procedures to produce the same pharmaceutical compound but did not get the same results. XRD with a high-temperature sampling accessory showed that the material produced at one facility was in fact the high-temperature form of the material produced at the other facility. This is illustrated in Figure 8, which shows room-temperature XRD scans (solvates A and B) of the materials manufactured

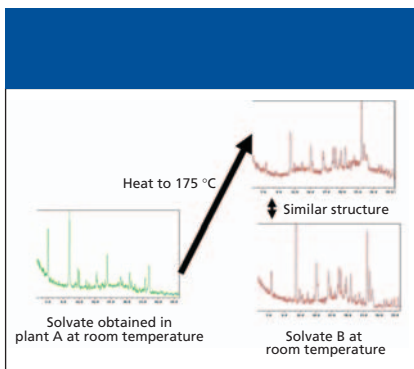


Figure 8: Polymorphic structures (solvates A and B) were produced at two manufacturing plants. High-temperature, XRD experiments helped to better understand the manufacturing process failure.

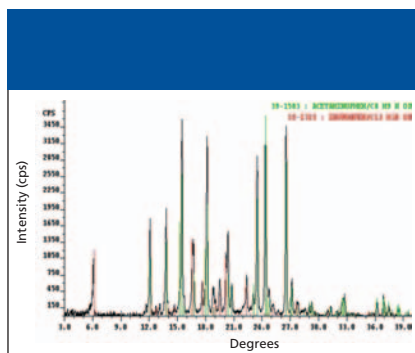


Figure 9: Identification of a mixture of acetaminophen (green scan) and ibuprofen (red scan) using search and match XRD spectral pattern recognition.

at plants A and B, together with a scan performed at 175 °C. It emphasizes how elevating the temperature can lead to different polymorphic phases of the same compound.

Identification of Unknown Phases of a Mixture

Using powerful “search and match” software algorithms, X-ray diffraction pattern databases such as the ICDD (International Centre for Diffraction Data) can be used to identify unknown phases of a mixture. An example of this capability is highlighted in Figure 9, which shows the identification of a mixture of acetaminophen and ibuprofen using pattern recognition.

Stability Testing

Stability of pharmaceutical formulations as a function of relative humidity can be tested using specially designed

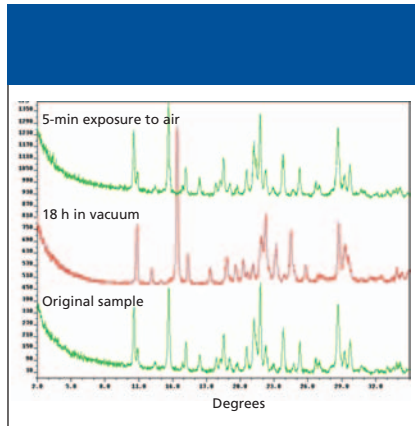


Figure 10: Testing the stability of humidity-sensitive pharmaceutical compound materials using an environmental chamber.

environmental chambers. To ensure that formulations will be stable under all possible storage conditions, it is important to know how the material reacts to changes in humidity as well as to temperature. Figure 10 shows an XRD scan of a compound known to be sensitive to moisture, which was first placed in the environmental sample chamber and measured (bottom green scan). The chamber was then evacuated for 18 h and the sample was measured again. The spectral scan, which indicates that it had been converted to a different form, is shown by the red middle scan. Finally, the stage was opened to the ambient atmosphere and the sample measured again. The sample absorbed moisture from the air and reconverted to its original form in 5 min, which is shown by the top green scan.

Measurement of Fillers

Pharmaceutical excipients or fillers are usually either microcrystalline or amorphous materials. The overall concentration of crystalline to amorphous material often is used as a quality assurance–quality control tool and is an important factor in the solubility and biological uptake of pharmaceutical agents. One relatively quick way to estimate the concentration of crystalline phases is to divide the sum of crystalline peak intensities by the total X-ray diffraction intensity above the background level. The advantage of this approach is that it is not important to know the identity of the different filler phases present in the sample. This approach is exemplified in Figure 11, which shows the individual crystalline peaks in red and the total XRD spectral intensity in green.

Conclusions

A new generation of WDXRF and XRD instruments has been designed that integrates the latest developments in X-ray excitation, optics, and detection methods. In particular, sequential WDXRF has realized a significant increase in sensitivity, allowing high-power systems to be applicable for the analysis of trace and sub-part-per-million levels required by many demanding applications. And where analytical requirements are less demanding, mid-power or even low-

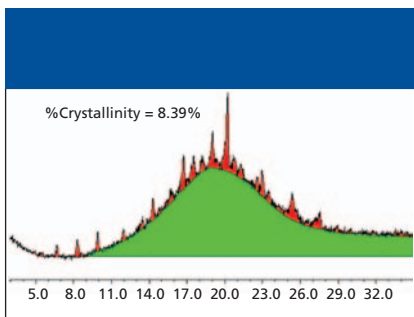


Figure 11: Characterization of crystallinity using XRD can be used to measure the amount of fillers present in a pharmaceutical compound.

power instruments can now adequately carry out the work. Given the ease of operation and inherent advantages of modern XRF, WDXRF has become the preferred technique in a multitude of industries, replacing wet chemical methods and, in many cases, other spectroscopic techniques.

XRD offers an effective and quick method for solving a broad range of application problems related to the varied demands of the pharmaceutical industry. Qualitative, quantitative, and kinetic analyses can be carried out

on just about any type of sample, including polymorphic phases, active drugs, and fillers. In addition, the technique offers a high degree of flexibility, due mainly to the seamless implementation of sampling accessories to rapidly switch from one application configuration to another.

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