X-Ray Powder Diffraction in Pharmaceutical Analysis

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Background

X-Ray Powder Diffraction (XRPD) is an important technique in the testing of Drug Products (DPs) and Active Pharmaceutical Ingredients (APIs) which can be crystalline or amorphous. In crystalline materials, the atoms or molecules are arranged in a highly ordered repeating lattice giving crystalline APIs higher stability. Amorphous materials have no long-range order however give APIs higher solubility.

Polymorphism occurs when a material can exist in more than one crystalline form whilst retaining the same chemical structure. The form is critical in ensuring drug efficacy as forms can interact differently in the body and have varying solubility. It is possible for a substance to interchange between crystalline forms in different environments and so stability is tested at varying timepoints, temperature and humidity.

Figure 1: Diffractograms of Crystalline and Amorphous Materials

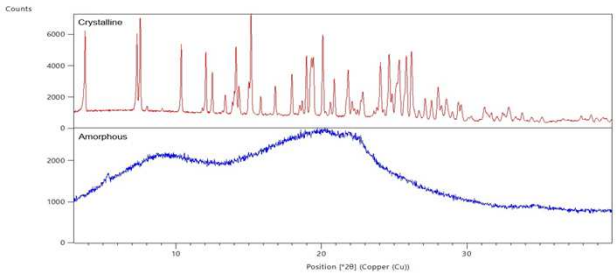


Figure 2: Diffractograms of Polymorphic Forms

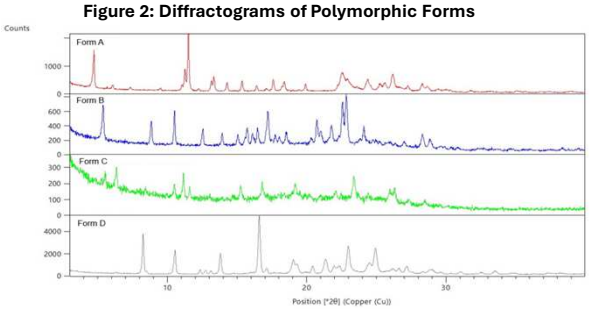
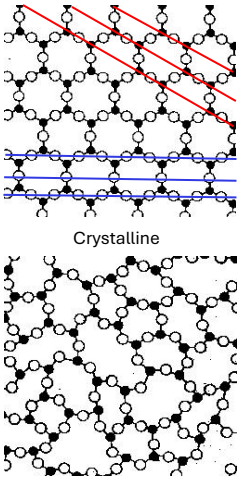


Figure 3: Types of Crystal Planes



How it Works

X-ray beams are directed at a sample and the angle of diffraction is detected. In transmission mode x-rays pass through the sample and in reflection mode they are reflected off the surface. Long-range interactions within the crystal lattice with large spacing between layers give smaller angles of diffraction and short-range interactions give larger angles.

Figure 4: Diagram showing Bragg's Law

Bragg's Law: nλ = 2dsinθ

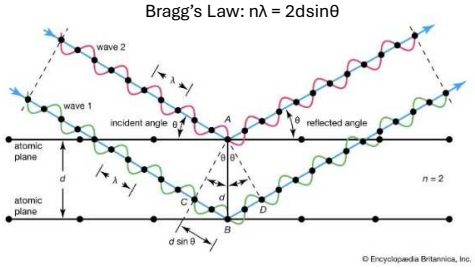


Figure 5: Diagram of Bragg-Brentano Type Diffractometer

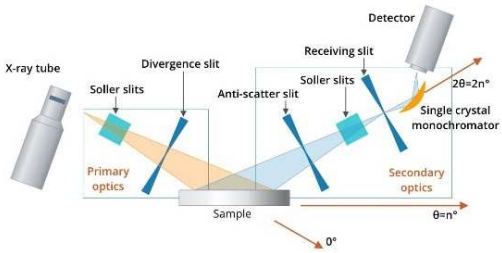


Figure 6: Diffractometer in Transmission Mode

Figure 7: Diffractometer in Reflection Mode

The sample is spun to counteract preferred orientation effects, ensuring more orientations are aligned with the x-ray beam to detect less intense peaks. Samples can also be ground to expose more crystal planes.

Figure 8: Diagram showing Orientation Effects

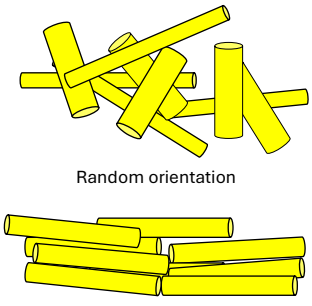
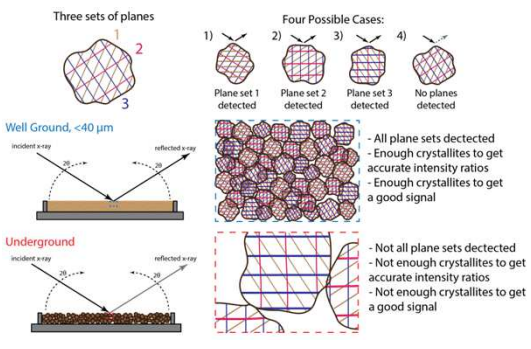


Figure 9: The Effect of Grinding Sample Material

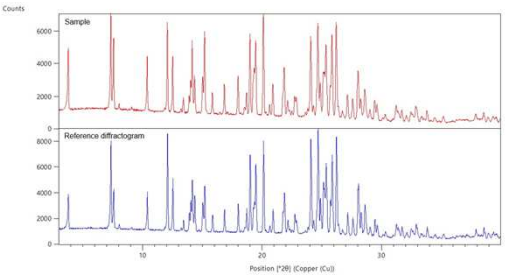


Types of Testing

Qualitative

For identification testing the presence or absence of peaks is detected when compared against a reference diffractogram.

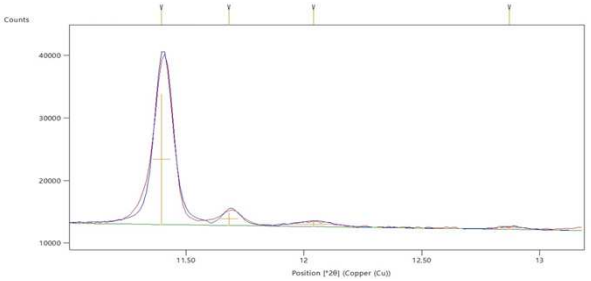
Figure 10: Diffractograms showing Sample against Reference Diffractogram



Quantitative

Quantitative analysis is used to determine the Detection Limit (DL) or Quantitation Limit (QL) of a polymorphic form from a crystalline reference mixture.

Figure 11: Diffractogram showing Quantitative Testing used to Determine % w/w of Polymorphic Forms assessed using Certified Reference Standards



Validations

Methods are validated using tests such as specificity, linearity, accuracy, repeatability and robustness. The extent depends on the type of analysis to be performed (qualitative or quantitative) and phase of project (e.g. commercial or Phase I/II).

Figure 12: Diffractogram showing Preparations 1-6 for Repeatability