Frequently Asked Questions – X-ray Powder Diffraction

Updated 2018

The most common use of X-ray powder diffraction (XRPD) is in the identification and characterization of crystalline solids, each of which produces a distinctive diffraction pattern. Both the positions (corresponding to lattice spacings) and the relative intensity of the lines in a diffraction pattern are indicative of a particular phase and material, providing a "fingerprint" for comparison. A multi-phase mixture, e.g. a soil sample, will show more than one pattern, allowing for determination of the relative concentrations of phases in the mixture.

https://en.wikipedia.org/wiki/Powder_diffraction

Q: What diffractometers do you use?

A: We have multiple Rigaku SmartLab systems in house to give greater flexibility in the type of materials we can study and to ensure that there is always an appropriately configured system to run GMP methods. These XRPD units make use of the D'teX scanning linear position sensitive detector that give enhanced sensitivity. These instruments can be configured into a number of different X-ray geometries including the traditional powder geometries of reflection Bragg-Brentano and transmission Debye-Scherrer.

Q: What Sample Size do you need for XRPD?

A: The sample holders we use require between 10 to 50 mg of powder sample (depending on density). If you have 100mg of each sample, that would be great. For best results, the grain size should be between 5 to 30 um. If your samples are a heavy inorganic powder, then transmission measurements might not possible without mixing the sample into a low-density carrier.

Q: Do you offer GMP XRPD testing?

A: **Yes**. We offer both GMP and non-GMP testing. We are registered with and audited by the FDA (February 2016 with no 483's and no observations).
For COA issuance a validated (or verified existing) method must be developed and release specifications set.

Q: Do you follow USP XRD Methods?

A: **Yes**. We can perform a comparison by running X-ray powder diffraction and by visually comparing the resulting data collected on an API with similar data from the reference materials. This is essentially following USP 941 (general visual comparison to USP reference material). If you are using a specific USP method, then we may have to run a 'verification' study before bringing it in-house.

Q: Do you offer rush or priority testing?

A: **Yes**. We offer three levels of service:

Non GMP per sample:
Priority - 24hr Guaranteed
Express - 48hr Guaranteed
Standard - 3-5 Business days

Data interpretation is available for an additional charge. We also offer three levels of GMP Testing

GMP per sample (includes QA review and report)
Priority - 3-5 Business days
Express - 5-7 Business days
Standard - 7-10 Business days

Q: Can you perform quantitative analysis?

A: **Yes**. Quantitative method development continues to be a required aspect of drug development. Solid-state assays, such as the determination of polymorphic (phase) purity or amorphous/crystalline content. For solid-state systems the impact of the sample matrix must be accounted for during method development. The ICH Q2 guideline functions well for quantitative method development when matrix effects are not observed (e.g. an ideal powder or ideal liquid system). However, for the majority of solid-state assays, matrix effects can be problematic. Matrix effects are usually driven by variables such as particle size, inhomogeneous mixtures, preferred orientation, absorption effects, and density differences between components. The extent and diversity of these effects vary between different analytical techniques.

The largest source of matrix effect error is often the standard samples themselves which are used to develop the calibration curve or model. Ideally, calibration samples for any drug product assay are generated by the actual production process used to produce the drug product. This approach will typically manifest far less matrix error than the artificial, laboratory-generated standard mixtures. Specific matrix effects can be random in nature and can be driven by mixing and sample preparation or may occur only for specific concentration ranges and mixtures. Matrix effects driven by particle-size differences between components or absorption differences, for example, are often systematic in nature while crystalline orientation effects often appear as specific matrix effects.
Recognizing that the difference in matrix effects between artificial standard mixtures and the actual drug product may be the largest source of error for a solid state quantitative method, Triclinic Labs has developed a novel approach for drug product based semi-quantitative methods. These "standard-less" semiquantitative methods make use of correlated variance in raw analytical response with known drug product variance (Chemometrics) as the analytical methodology. Typically, these methods are robust and can be transferred between laboratories making them ideal for drug product characterization.

Q: Can you perform semi-quantitative analysis?

A: **Yes.** If reference patterns can be generated for all significant solid phases in your sample, then we can estimate quantities using a full pattern method. These semi-quant numbers will be relative numbers with respect to the other identified components within the sample.
Reference patterns can be generated using the following methods: measurement of reference materials, direct extraction from a powder diffraction data-base or by calculation using known crystal structures. If some of the major components remain unidentified, then the semi-quantitative analysis becomes more complex and is very much a customized procedure.
The presence of multiple non-crystalline solid phases will almost certainly require the measurement of reference material if the individual concentrations are required.

Q: Can you perform Rietveld Analysis?

A: **Yes**. We routinely perform Rietveld analysis for both semi-quantitative mixture analysis and materials property characterization. The property characterization covers structural properties (e.g. unit cell parameters), micro-structural properties (e.g. crystallite size and micro-strain) and macro-structural properties (e.g. preferred orientation). For a given initial crystal structure we also routinely study molecular conformation and orientation modifications, changes in solvent (hydration) state and salt versus co-crystal issues. We are able to carry ab-inito studies but we usually recommend trying single crystal analysis or synchrotron X-ray powder diffraction as the preferred methods.
Routine semi-quantitative analysis using the Rietveld method ideally requires that all crystalline components are identified and that a reference single crystal structure is

available for each phase. For custom methods, we are able to work with non-crystalline phases and unknown crystalline forms.

Q: Are you able to analyze inorganic materials?

A: **Yes**. We routinely perform powder X-ray diffraction for inorganic materials covering a wide variety of different disciplines and industries (e.g. geology clays and minerals, petroleum and petrochemicals, ceramics, semiconductors, superconductors, battery and technological materials, nanomaterials, forensics, archeology and art investigations). The majority of our work with inorganic materials involves crystalline phase identification. To that end, we use a number of inhouse database that include two general powder diffraction and single crystal reference databases and in addition a focused mineral database. We have also created a limited number of reference patterns for common non-crystalline materials (carbon and silicon based). As part of the crystalline phase identification we run the data and identified crystalline phase lists through a Rietveld full pattern fitting procedure to ensure the completeness and accuracy of the identified phases.
We are also able to perform the same Rietveld services as offered for organic materials (see Rietveld QnA section).

Q: Can you perform thin-film analysis?

A: **Yes**. We do have the capability to perform thin-film XRPD analysis depending on the type of results you are looking for. Our in-house XRPD equipment is able to perform glancing incidence analysis of polycrystalline films. The glancing incidence XRPD measurement is a surface sensitive measurement that probes the crystalline phase composition of the film (i.e. which crystalline forms (if any) are present in your film). Limited depth profiling is also possible by changing the glancing incidence angle. The geometry we use is not able to probe the in-plane crystal structure. For films with optical quality surface flatness and roughness we also have some capability to measure film thickness by X-ray reflectivity.

Q: Are you able to perform variable temperature XRD?

A: **Yes**. We are able to perform variable temperature XRPD analysis under an inert gas. We use a transmission X-ray geometry with a focused incident beam and specially designed stage. We prefer this approach as there are no significant thermal displacement effects to worry about. The total cost of such a measurement depends on the number of temperature points. The transmission cell has been designed for organic materials. If your material of interest is a heavy X-ray absorber than we will probably not be able to analyze it without some form of dilution.

Q: Can you perform indexing?

A: **Yes**. We are able to offer unit cell indexing (unit cell and space group). As part of the indexing we can perform a Rietveld 'scratch' refinement. This Rietveld approach uses a random electron density cloud to model the peak intensities. While this does not include a full structural solution, it does verify that the correct space group is assigned. For single phase crystal structures that are not triclinic, our success rate for indexing is high (>90%). For complex triclinic structures (large unit cells and multiple molecules in the asymmetric unit) the success rate drops to around 50% to 60%.

Q: Can you generate data comparing the polymorphic form of the API present in drug product to that of pure API or an unknown?

A: **Yes**. We have a number of state of the art XRPD systems which we routinely use for polymorphic form identification both at the API and drug product level. Data can be collected in both reflection and transmission geometries that allow us to work with loose powders and intact tablets (depending on tablet thickness). Identification of crystalline form is automatically performed by searching against our in-house powder diffraction and single crystal databases. Powder diffraction is able to identify the crystalline forms present within a mixed powder system by matching diffraction peaks observed in the measured data to reference patterns collected on known materials. We currently use a combination of different reference databases for known crystalline materials with close to 1 million reference patterns in total. For novel API materials not present in our data bases, we can match directly to measured reference patterns or to single crystal structures if available.
We are also able to investigate specificity and detection limits. The API and a placebo are measured using our standard conditions in order to establish an analytical region of interest around the strongest API peaks and within an acceptable LOD level. By optimizing measurement parameters and sample preparation, we have managed to achieve signal to noise LODs (3.3 sigma) of < 0.05% w/w of crystalline API in drug product. Routine measurements will typically have signal to noise LODs (3.3 sigma) of about 1% w/w crystalline API in drug product

Q: Can you perform micro-diffraction?

A: **Yes**, we do have the ability to perform micro diffraction. However, for a low loading drug product, we would typically use a large volume sample with a broader beam. By sampling larger volumes of sample, we have developed methods with LOD's around 0.02%w/w for specific APIs.

Q: Can you characterize amorphous (i.e. non-crystalline) materials?

A: **Yes** - we perform a wide range of characterization studies on amorphous material. These include (but are not limited to):

1.) X-ray powder diffraction
2.) Total Diffraction Analysis ***with material stability ranking (a Triclinic Labs' exclusive offering)***

3.) Pair-wise distribution (PDF) function analysis
4.) Thermal analysis (modulated DSC & TGA – relaxation studies)
5.) Absolute Heat Capacity
6.) Vibrational spectroscopy (IR and Raman – including phonon mode low frequency Raman).
7.) Dynamic Vapor Sorption (DVS)

Q: Do you offer XRD mapping?

A: **Yes**, we do have the capability of performing X-Y mapping of an extended sample in reflection geometry. Our Rigaku SmartLab systems have a range of different pin-hole collimators that can be selected to fine tune the illuminated surface area for each measurement. A poly-capillary optic is mounted before the pin-hole collimators to boost X-ray intensity and we use a position sensitive detector to speed up data collection time. The maximum mappable area is between 3 and 4 square inches depending on sample geometry. For samples with irregular surfaces, we can use parallel beam diffraction to perform the mapping, although this may significantly increase the overall measurement time.

Q: Do you offer morphology characterization?

A: **Yes**. For extend bulk samples, we can map the morphological distribution of specific solid-phase using our X-Y mapping capabilities (see XRPD mapping question above). The pin-hole optics we use for mapping are usually too big to map out individual crystalline morphologies (shapes and orientation). If you are more interested in the average crystalline habit (morphology) then we are able to indirectly probe this property using anisotropic peak broadening (requires average crystal size << 100nm) and through the analysis of preferred orientation (requires larger regular crystals).

Q: How do I obtain a quote?

A: Please email us at info@triclinclabs.com or call 765.588.6200 to speak to a scientist. You can also fill out an online request by clicking here.

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For more information on our XRPD services please visit:

http://tricliniclabs.com/directory/solid-state-development-services/physical-and-analytical-chemistry/express-XRPD-xray-powder-diffraction-analysis-services.html