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Advanced Analysis of Non-Crystalline (X-ray Amorphous) Materials and Dispersions.

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A non-crystalline material is one where the measured X-ray powder diffraction (XRPD) pattern is essentially continuous in appearance. These types of powder patterns are often referred to as X-ray amorphous. The characterization of non-crystalline materials is a further application of the Total Diffraction Analysis services offered by the Computational Chemistry Practice at Triclinic. Through the application of in-house analytical software based upon the Debye diffraction theory (atom-atom pair correlation), the local amorphous structure can be elucidated from an X-ray amorphous powder pattern.

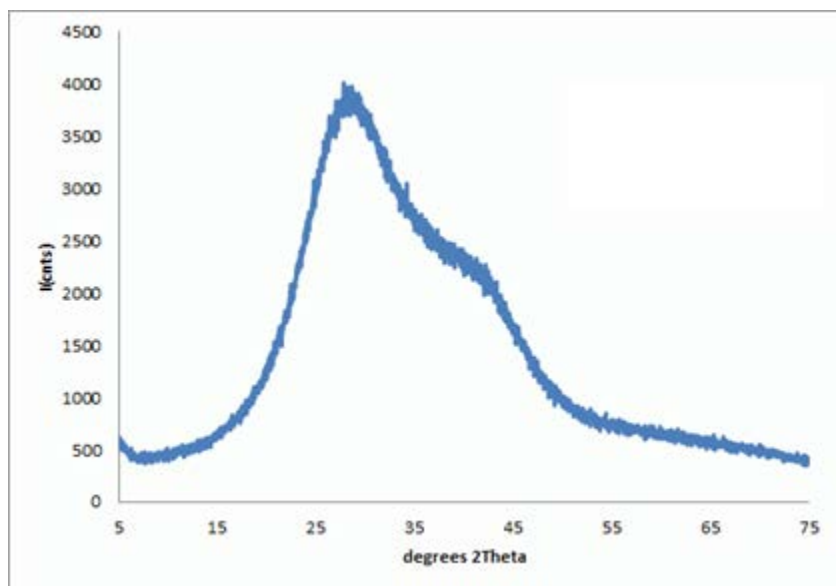


Figure 1: A continuous X-ray diffraction pattern for water; measured in-house. Liquids are thermodynamically stable non-crystalline forms.

An ideal gas (no molecular interactions), ideal liquid and ideal glass (all molecular interactions equal and isotropic) all represent the same highest symmetry state for a molecular system and when averaged over a suitable time period and spatial volume the probability of finding a molecule at any point in space is a constant related to density. These high symmetry states have the full translation and rotation symmetry of free space and full conformation degrees of freedom appropriate for the system temperature. These systems are considered to be macroscopically uniform and isotropic. Any effective reproducible local molecular order will involve single molecules and will be related to just the rigid (reproducible) intra-molecular structure itself. In reality, the high density and high viscosity of a glassy system along with molecular interaction anisotropy will force the formation of locally rigid and high density arrangements of molecules where the nearest neighbor positional relationships will be driven the repulsive inter molecular forces (i.e. molecular shape). With respect to the locally ordered groups, the full translation and rotation symmetry of free space is maintained keeping the macroscopically uniform nature of a glass. It is these locally rigid arrangements of molecules that give rise to the observed X-ray amorphous powder patterns.

Glassy materials are just one example of solid state systems that will give rise to X-ray amorphous powder patterns. Any non-crystalline solid or liquid with reproducible short-range molecular order and no long-range molecular order will give rise to an X-ray amorphous powder pattern. Characterization of the local molecular order is a fundamental component in understanding the chemical and physical stability of non-crystalline materials.

Total Diffraction Analysis as a structural analysis tool.

Total diffraction analysis is one of the main characterization methods for determining the local structure within non-crystalline materials. It makes use of the complete diffraction signal from a sample and treats each data point as an individual observation. This allows the subtle changes in slope that define a continuous powder pattern to be directly incorporated into the analysis. A number of general material properties can be determined via direct analysis of the X-ray amorphous powder pattern. Because of the nature of random packing in the solid state, a randomly packed material will give X-ray amorphous halos whose width follows a known functional form as a function of diffraction angle. As such, a quick determination of the observed halo widths can be used to determine the departure from random packing for a particular sample. A detailed structural analysis, however, requires the use of novel analytical methods based upon the Debye diffraction theory and the use of a continuous structure factor. The Debye approach can be applied directly through the use of Pair-wise Distribution Functions (PDF) or indirectly through molecular modeling.

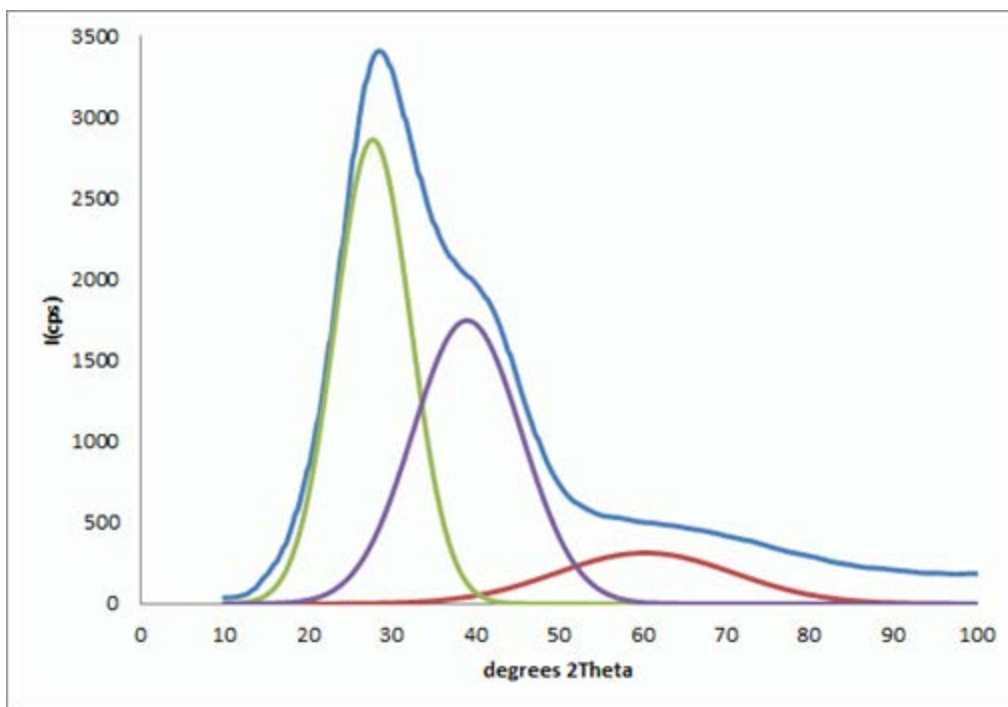


Figure 2: Specific halos observed in the continuous X-ray diffraction for water can be modeled according to the universal peak width idea for randomly packed materials. For this data the exponent describing random packing came out to be 4.93; a randomly packed material has $N \sim 5$ as determined by XRPD.

Local Molecular Order

Characterization of a significant number of non-crystalline materials has shown that different types of local molecular order can exist for organic molecular systems. In more than half of the studied materials, the X-ray amorphous powder pattern can be described using a local molecular model that matches structural motifs seen in one or more of the crystalline polymorphs. As might be expected, these types of X-ray amorphous forms appear to crystallize readily. The remaining non-crystalline materials gave X-ray amorphous powder patterns that can be described using local molecular models that maximize density and minimize the short range repulsive forces. For approximately flat 2D molecules, this usually results in stacking of the molecule. In some instances the type of local order observed can be modified by adopting a different production path way. Glassy materials are kinetic in nature and as such, the micro-structure of each glassy sample made from the same molecule will be dependent on the production pathway used to make the glass. For the most part, the micro-structural differences are subtle and not easily accessible to direct characterization. However, changes induced in the local molecular order by using different production pathways can be characterized by Total Diffraction Analysis.

Changes in the local structure observed as a function of time, temperature, humidity, solvent vapor or physical stress can often be seen as precursors to structural instability and re-crystallization. Characterization of local structure changes can be critical to the design of an effective aging study as very often the humidity and temperature conditions used for aging actually change the local structure before the study begins.

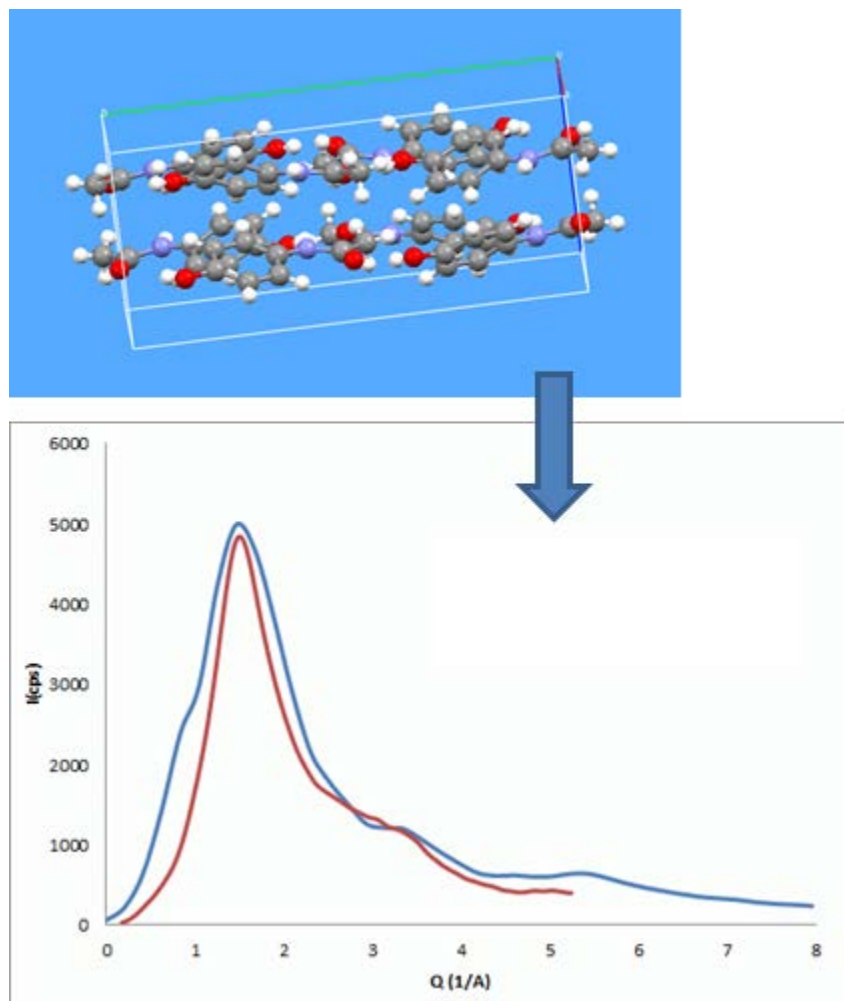


Figure 3: A calculated X-ray diffraction trace (blue) for a glassy material having the local molecular order corresponding to Form-II acetaminophen crystal structure (image above) gives a reasonable description of the measured XRPD trace for glassy acetaminophen (red).

While Total Diffraction Analysis provides the initial characterization of local molecular order, for some systems the changes in the X-ray amorphous profile can be subtle and

a more robust analysis will benefit from a combination of different analytical techniques (for example IR/Raman spectroscopy, thermal methods and X-ray powder diffraction).

Amorphous Stability

A common method to improve the physical stability of an amorphous API is to manufacture a 'dispersion' of the amorphous API in an amorphous matrix. The most common matrix materials employed to date are polymers with high glass transition temperatures although in principle many different types of matrix materials may be used. **The primary physical property that determines the performance ability of the amorphous dispersion to stabilize the amorphous state of the API is the degree of mixing between the API and the amorphous matrix.** In the liquid or solution state the API and matrix components may be intimately mixed at the molecular level but on formation of the solid state system, the API may begin to phase separate. The degree to which the phase separation has occurred in the solid state will govern the resulting physical stability of the amorphous 'dispersion'. To be a 'successful' dispersion, physical stability is just one requirement. In addition, the intermolecular mixing between the API and the matrix should be maintained under dissolution conditions to reap the benefits of enhanced initial solubility. Because Total Diffraction Analysis works equally well for liquids and solids, the change in molecular mixing resulting from exposure to different solvents can also be studied.

Systems where the API can be considered to be phase separated will behave like the pure amorphous API but will often undergo physical changes more slowly. Systems where the API and matrix remain a solid solution with intimate molecular mixing may form a stable single phase system with no driving force to crystallize. The concepts of molecular solid solutions and phase separated systems are defined by the physical structure and spatial relationships of the molecules within the solid-state. These are exactly the properties measured by X-ray (and neutron) diffraction. The same in-house software Triclinic has developed to characterize the local molecular order of single phase X-ray amorphous materials can be utilized to determine the degree of mixing between an amorphous API and an amorphous carrier matrix.

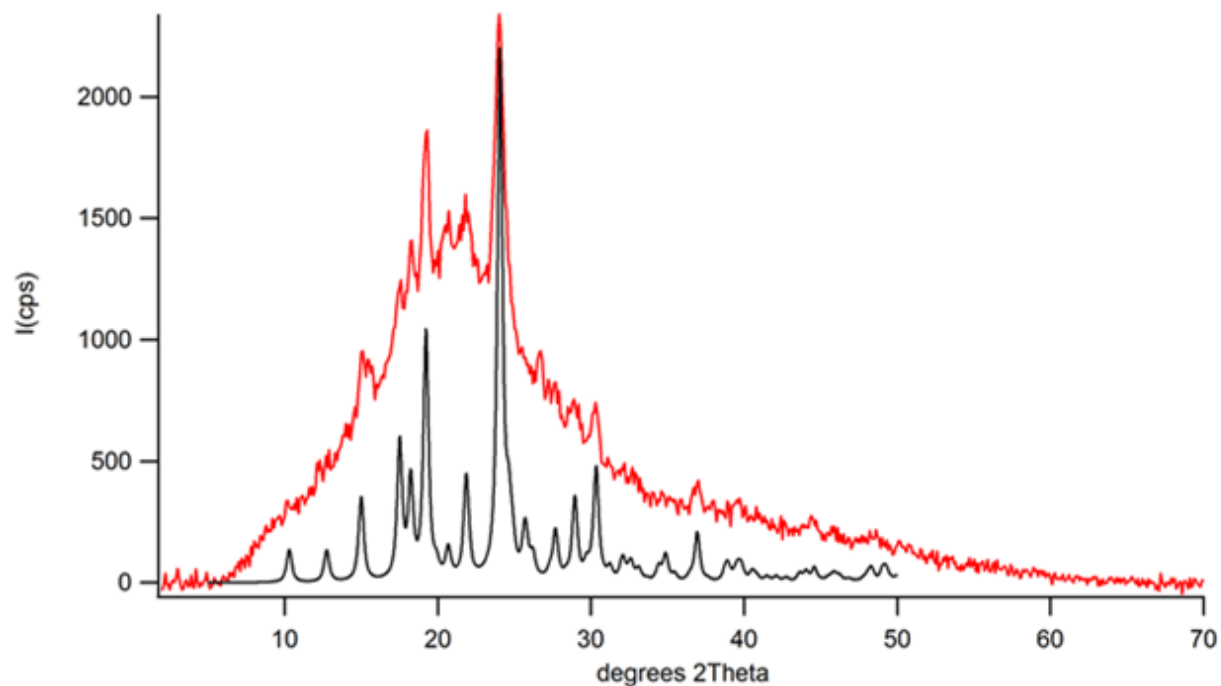


Figure 4: Glassy acetaminophen which gives an X-ray diffraction trace similar to the calculated trace from a theoretical glassy Form-II sample, is seen to readily re-crystallize to Form-II.

Use of Multiple Analytical Techniques

MDSC measurements of glass transition temperatures will also give some idea as to the degree of mixing between an amorphous API and an amorphous matrix. Typically, if the observed glass transition temperature of the amorphous 'dispersion' (assuming one can be measured) is between the glass transition temperatures of the pure amorphous API and pure amorphous matrix then some degree of molecular intermixing is taking place. Although for some dispersion systems showing a single intermediate glass transition temperature characterized by Total Diffraction Analysis as actually being phase separated and not molecularly dispersed. It is believed that for these types of systems, the domain sizes of the separated phases are very small ($\sim < 30\text{nm}$).

For robust characterization of amorphous materials, a combined analytical approach using spectroscopic, thermal and diffraction methods is the preferred approach. With recent advances in characterization software, considerably more information can now be extracted from amorphous materials using diffraction techniques than was previously possible. Characterization of the local molecular short-range order using X-ray powder diffraction data provides unique insight into single phase and multi component amorphous systems that is often directly related to the physical and chemical stability of the amorphous system.

Recent Applications of Total Diffraction and Amorphous 'Structure' Determination

While the determination of the local structure in amorphous materials may seem to be a topic of mainly academic interest, general examples taken from recent client projects at Triclinic Labs illustrate the significant impact this type of analysis can have on real world production problems.

The first example involves an API production process where the client was experiencing flow problems for certain batches. Traditional analytical chemistry methods using the traditional tools (Thermal, Structural and Vibrational analysis) were unable to find any correlation between the flow problem and the analytical responses from samples taken from the various API batches. Total Diffraction Analysis, however, revealed the presence of a mesomorphic component in some batches of the material and that the flow problem correlated well with the concentration of this component.

A second example centers on a Hot Melt Extrusion drug product where an increase in physical instability was noticed for some batches of the material. A combination of Total Diffraction Analysis with a chemometric method developed at Triclinic labs was able to identify the degree of API phase separation for each batch and thus the degree of risk associated with the different drug product batches.

A third example represents a study of different lyophilization procedures in order to characterize the ratio of free to bound water. Total Diffraction Analysis is more than capable of quantifying the amount of phase separated water within a lyophile sample.

Total Diffraction Analysis is a structural analysis tool:

Returns 'structure' of the amorphous phase.

Consider density of amorphous forms – typically within a few percent of crystalline forms. True random packed materials have significantly lower densities than crystalline materials.

- There is considerable short range order in molecular organic amorphous materials – often very similar in nature to crystalline order.
- Makes use of all the diffraction signal from the sample
- Every data point is an observation

- Requires different analytical tools than traditional Bragg diffraction analysis (peak based): Debye diffraction theory
- Requires building molecular models
- Pair Wise Distribution Function (PDF) is utilized
- Continuous structure factor based

Ultimately, the Total Diffraction Analysis approach pioneered by Triclinic Labs allows for a better understanding of amorphous material “manufacturability”, stability, process induced change, and intellectual property.

For more information or to discuss how to apply the discussed techniques to your molecules, please contact:

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