White Paper

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Integrating Microcrystal Electron Diffraction as a Mainstream Work Tool in Solid Form Development and Structure Elucidation

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Abstract

Structural elucidation in solid form development is often limited by the dependence of X-ray diffraction on large, high-quality single crystals, creating delays when materials exist only as microcrystalline powders. Microcrystal Electron Diffraction (microED) overcomes this constraint by enabling molecular structure determination directly from sub-micron crystals, eliminating the need for crystal growth and reducing timelines from weeks to days.

Recent advances in automation and data processing are transforming microED from a specialized technique into a scalable, routine analytical tool. When combined with expert crystallographic interpretation and complementary methods, microED provides a rapid and reliable pathway for structure elucidation of complex solid forms and impurities, positioning it as a first-line approach in modern solid-state development.

Keywords

Microcrystal Electron Diffraction, microED, X-ray diffraction (XRD), Solid form development, Structure elucidation, Microcrystalline materials, Powder structure determination, Crystallography, Polymorphism, Pharmaceutical development, Impurity structure elucidation, Electron diffraction, Crystal growth limitation, Analytical workflow optimization.

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Introduction

Structural elucidation remains a critical bottleneck in solid-form development. Traditional single crystal X-ray diffraction (XRD), while foundational, is constrained by its reliance on large, well-formed single crystals. This is something many real-world pharmaceutical materials simply do not provide. This dependency slows timelines, limits insight, and introduces unnecessary development risk.

Microcrystal electron diffraction (microED) fundamentally alters this landscape. By enabling molecular structure determination from sub-micron crystals and even heterogeneous crystalline powders, microED removes crystal growth as a gating step. What was once a niche, expert-driven technique is now evolving into a scalable, high-impact tool, driven by advances in automation, data processing, and integrated workflows.

MicroED is no longer just a workaround for difficult samples – it is becoming the fastest and most direct path to structure in modern solid-state chemistry.

The Structural Bottleneck in Solid Form Development

Solid form development depends on rapid, reliable structural insight to guide decisions on polymorphism, salt selection, cocrystal formation, and impurity characterization. However, the traditional reliance on single-crystal XRD introduces a dependency that is often misaligned with reality. Many compounds exist only as microcrystalline powders, exhibit disorder, or resist crystallization entirely under practical conditions.

This creates a persistent blind spot at precisely the stages where structural clarity is most valuable, namely early development, impurity identification, and intellectual property positioning. Programs are frequently delayed, not because the structure is unknowable, but because it is inaccessible through conventional means.

MicroED as a Paradigm Shift

MicroED leverages electron diffraction within a transmission electron microscope to obtain crystallographic data from crystals orders of magnitude smaller than those required for XRD. Because electrons interact much more strongly with matter than X-rays do, meaningful diffraction can be obtained from nanocrystals that would otherwise be invisible to traditional techniques (Figure 1).

This shift reverses the traditional workflow. Instead of engineering crystals to meet the requirements of the analytical method, microED allows the method to adapt to the material as it is received. The practical implication is significant: structure determination can proceed directly from crystalline powders or minimally-processed samples, dramatically reducing time and uncertainty.

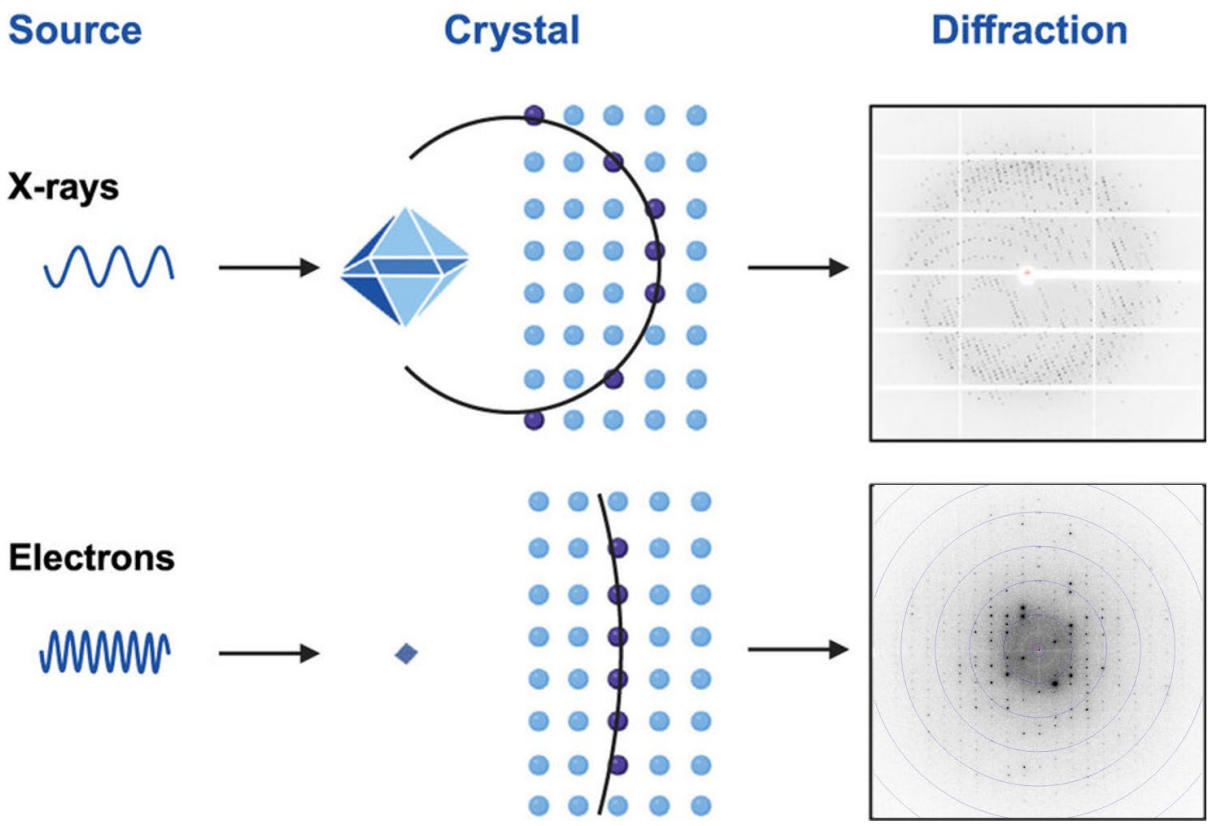

Figure 1. Schematic comparison of X-ray diffraction (XRD) and microcrystal electron diffraction, sample requirements, and resulting diffraction patterns. XRD relies on large single crystals, whereas microED uses nano-sized particles. The X-ray wavelength produces diffraction patterns typically ranging from −160° to +160°. The short wavelength of electrons produces diffraction patterns over a much smaller range (−2° to +2°) and is therefore only measured in a transmission geometry. Adapted from ResearchGate

Solving Structures from Powders

Powder XRD is widely used for phase identification but is inherently limited in its ability to solve complex structures. Peak overlap, preferred orientation, and mixture complexity often obscure the level of detail required for definitive structural assignment. Even when the highest quality data is acquired using synchrotron radiation, peak overlap still occurs and, moreover, the Friedel pairs cannot be separated. Therefore, by definition, the absolute configuration cannot be determined from powder XRD data.

MicroED overcomes these limitations by isolating and analyzing individual crystallites within a powder. Each particle is effectively subjected to an individual single-crystal experiment, enabling full structure solution rather than pattern-based inference. This capability is particularly impactful in systems where growth of large crystals fails, impurities are present at low levels, or multiple phases coexist.

In these contexts, microED transforms previously intractable problems into solvable ones.

Eliminating the Crystal Growth Bottleneck

The requirement to grow suitable single crystals has long been one of the most unpredictable and time-consuming steps in structural analysis. It introduces variability, consumes resources, and often fails without a clear explanation.

MicroED removes this dependency to a great extent. In many cases, structures can be determined from the material already available, bypassing weeks or months of crystallization work. In fact, in most cases, the crystals in existing materials are too big for microED and need to be reduced to nano-sized crystals. This shift is not incremental—it is transformative. For time-sensitive applications such as impurity identification, formulation decisions, or patent filings, the ability to obtain structural data without delay provides a decisive advantage (Figure 2).

Improving Productivity

"The lion share of the SC-XRD timeline is consumed by preparation of a suitable sample, a step eliminated by microED. With that requirement removed, structure determination has become a purely analytical task rather than a crystal growing challenge."

- Steef Boerrigter, Ph.D. Head Crystallographer and Research Fellow, Triclinic Labs, LLC.

Historical Limitations of MicroED

Despite its promise, microED has historically been constrained by technical and practical limitations. For one, electron diffraction data are influenced by dynamical scattering effects, which complicate the interpretation of intensities relative to X-ray methods. With modern instruments, dynamical scattering is mitigated with continuous rotation methods and higher energy electron beams, allowing for dynamical scattering effects to be reduced. Moreover, fully automatic data collection allows for dozens or even hundreds of particles to be analyzed instead of just a handful and the dynamical effects average out using larger datasets. Beam sensitivity can also impact organic materials, requiring careful

handling and data collection parameter optimization to preserve data quality. Modern automatic data collection reduces particle exposure to the electron beam to a minimum.

Operationally, early microED workflows were highly manual, requiring expert selection of crystals, precise alignment, and significant user intervention. As a result, successful implementation depended heavily on specialized expertise and was very time consuming, limiting broader adoption. With recent advances in technology, the difference between SC-XRD microED is dramatic:

- ~90% of XRD time = crystal growth + optimization
- MicroED = minimal time spent making the sample “acceptable.” No amorphous materials

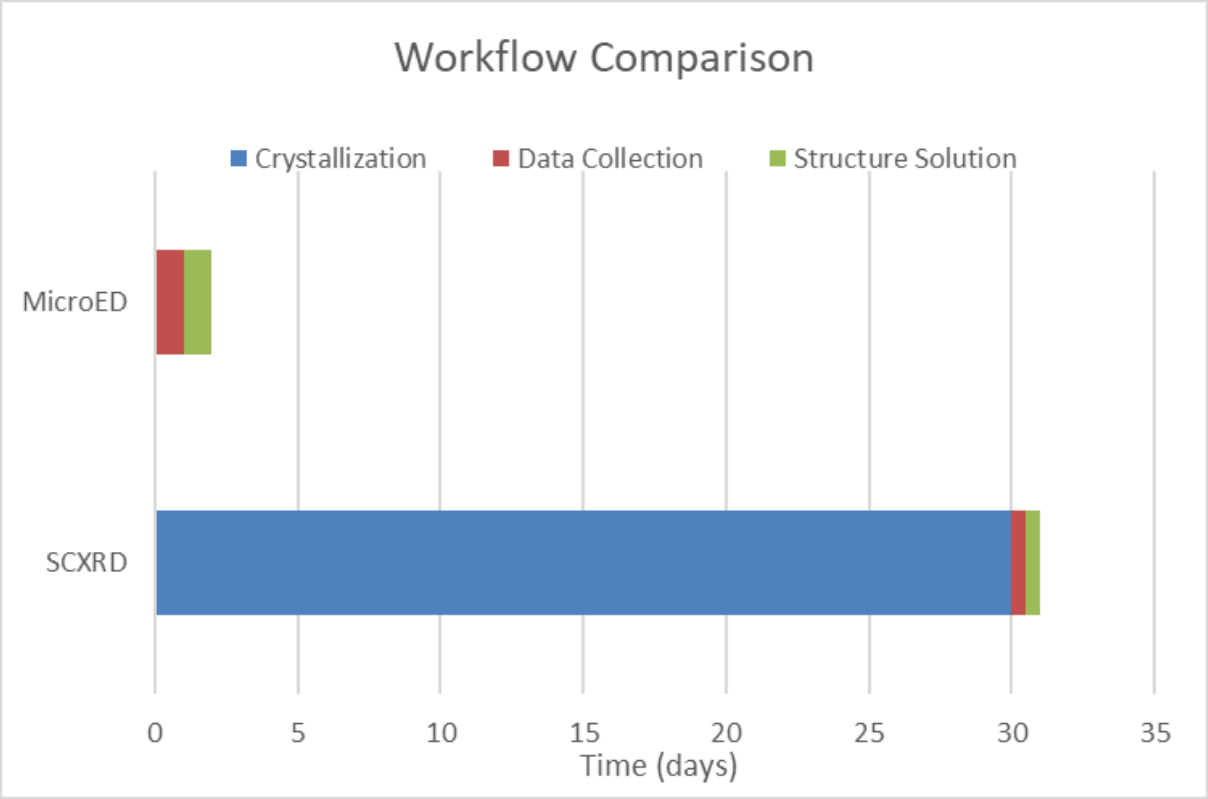

Figure 2. Stepwise comparison of structure determination workflows using XRD versus microED. The XRD timeline is dominated by crystallization and optimization, while microED enables direct progression from microcrystalline sample to structure.

Some materials display poor crystallinity of the particles even at the nanometer level; especially when desolvation takes places. This can quite often be overcome by a relatively short curing period in the solvent from which the crystalline phase was originally obtained followed by the application of a rapid cryo-cooling step and collecting the microED data under cryogenic conditions. Data collection under cryogenic conditions has the additional benefit of reducing electron beam damage.

Automation and the Transition to Routine Use

Recent advances are rapidly removing traditional barriers. Automated crystal screening now allows rapid identification and targeting of suitable particles within heterogeneous samples. This means that, when the sample contains a mixture of crystalline phases, they can be separated at the indexing stage of the structure solution and result in multiple structure solutions from one and the same sample.

Equally important are developments in software. Integrated pipelines now support automated indexing, integration and merging of datasets, structure solution and refinement, incorporating models that better account for electron-specific scattering behavior.

Together, these advances are transforming microED from a specialized technique into a repeatable, scalable workflow. The method is still relatively young, but becoming less dependent on individual operator skill and more aligned with the expectations of routine analytical deployment.

The Role of the Crystallographer

Despite these technological advances, microED is not a fully automated solution. Its effective use still depends on a crystallographer who understands the fundamental principles of diffraction studies.

Electron scattering behavior, dynamical effects, radiation damage, and data quality all require careful interpretation. The ability to distinguish meaningful structural features from artifacts remains critical, particularly in complex or lower-quality datasets.

In practice, the combination of advanced instrumentation and expert interpretation is what unlocks the full value of microED. Without this expertise, there is a risk of misassignment or overinterpretation. With it, microED becomes one of the most powerful tools available for structural determination.

Integration into Hybrid Analytical Workflows

MicroED delivers the greatest impact when integrated with complementary analytical techniques. When combined with high-resolution mass spectrometry, it enables definitive structure elucidation of trace impurities with unknown/ambiguous structures, even when the crystallite size is extremely small. Pairing with powder XRD provides both phase identification and structural confirmation, while spectroscopic techniques such as Raman or IR add orthogonal insight into molecular interactions. **Triclinic Labs is the only North American contract development lab that has in-house MicroED and a team of scientists who bring all these techniques together.** Leverage this powerful tool to expand your asset understanding and your intellectual property.

This integrated approach is particularly valuable in regulatory-driven environments, such as impurity investigations under ICH guidelines, where both structural certainty and supporting evidence are required. MicroED serves as a central structural tool within a broader analytical framework.

Path to Mainstream Adoption

The remaining barriers to adoption are no longer primarily technical; they are organizational and perceptual. MicroED is still often viewed as a specialized method reserved for difficult cases, rather than a first-line tool for rapid structure determination.

As workflows become more standardized and automation continues to improve, this perception will shift. The most effective approach is not to position microED as a replacement for XRD, but as a complementary technique that expands structural access and accelerates decision-making.

Organizations that integrate microED early into their development workflows will benefit from faster timelines, reduced risk, and stronger intellectual property positions.

Conclusion

MicroED removes one of the most persistent constraints in solid form development: the need for large, well-formed crystals. Enabling structure determination directly from crystalline powders provides a faster, more direct path to critical insight.

With the maturation of automation and data processing, microED is transitioning from a niche capability to a mainstream analytical tool. Its successful deployment, however, depends on coupling the technology with expert interpretation and embedding it within a broader analytical strategy.

The implication is clear. Structural insight is no longer limited by crystal growth—only by whether the right tools are being used.

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