Importance of Monitoring the Synthesis of Light-Interacting Nanoparticles – A Review on In Situ, Ex Situ, and Online Time-Resolved Studies

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This review paper analyzes the importance of monitoring the synthesis of plasmonic and optoelectronic materials to provide a mechanistic understanding of their nucleation and growth, as well as crucial kinetic insights to enable their future development. Light-interacting nanoparticles present strong size–property relationships, such that size control is at the core of any synthetic development. However, conventional ex situ characterization of these materials has heavily limited their development to simple trial-and-error approaches. Over the last decade, the development of in situ and online characterization capabilities has transformed the understanding of mechanistic models. In addition, time-resolved data are able to reveal the step rate, even for phenomena taking place in the microsecond timescale (i.e., nucleation), thanks to the use of micro-flow-reactors. However, the literature contains a few disagreements and inaccuracies, which are considered to be due to the general lack of attention and control on mixing (relevant when mixing time is comparable to the reaction time), and the presence of additives during synthesis (e.g., stabilizers). Finally, it is believed that recent in situ monitoring development coupled with reactor design brings unique opportunities to not only synthesize nanoparticles in a reproducible and controllable manner, but also gives data-rich approaches for self-regulated and automated systems.

1. Introduction: Properties of Plasmonic, Photonic, and Optoelectronic Materials

Reducing the dimensionality of materials from bulk thin films and single crystals to nanocrystals (NCs) and quantum dots (QDs) leads to exciting new possibilities. These include the ability to tune the bandgap through the size of the QDs via quantum confinement effects, as well as achieving higher photoluminescence quantum efficiencies (PLQEs) through increased exciton binding energies.\(^1\)\(^-\)\(^4\) Furthermore, the collective oscillation of free electrons in NCs (i.e., plasmons) due to interactions with incident light can lead to enhancements in light absorption and scattering.\(^5\)\(^-\)\(^8\) These effects have significant implications on catalysis, display, lighting, lasing, biomedical, photovoltaic, and information technology applications.\(^1\)\(^-\)\(^4\)\(^,\)\(^6\)\(^-\)\(^8\)

For example, the fine bandgap tunability and efficient, sharp luminescence achievable in QDs make them highly appealing for the next generation of ultra-high-definition displays.\(^4\) As another example, metal nanoparticles (NPs) have been used to enhance the Raman scattering of surface-adsorbed molecules (i.e., surface-enhanced Raman scattering), enabling detection levels close to the single-molecular level.\(^9\) Across all these applications, it is critical to have fine control over the size of the materials, since this strongly influences their properties at the nanoscale. In this review, we will examine the different techniques used for the characterization of the physical properties of NCs for optoelectronic and plasmonic materials during or after their synthesis.

Optoelectronics are devices converting energy between light and electricity and include light-emitting diodes (LEDs), lasers, photovoltaics (PVs), and photodetectors. Some of the most common optoelectronic NC materials are (conventional) II–VI compounds (e.g., CdSe, PbS), pnictides (namely InP), and (more recently) lead-halide perovskites (e.g., CsPbBr\(_3\)).\(^3\)

Quantum confinement effects have been used to achieve materials with bandgaps from the near-infrared (e.g., large InAs-based NCs) to in vivo optical imaging\(^10\) to the visible range (e.g., small CdSe-based QDs for blue LEDs\(^11\)\(^,\)\(^12\)). Indeed, by changing the size of CdSe-based NCs, emission in the red, green, and blue can be achieved, giving rise to the components needed to make displays or solid-state white lighting.\(^13\) These quantum confinement effects have been exploited in lead-halide perovskites to achieve blue emitters with high PLQE.\(^13\) While the bandgap of cesium lead halides (CsPbX\(_3\)) can be increased
from the green wavelength range (pure bromides) to the blue wavelength range (by mixing chlorides with bromides), this leads to the formation of deep traps that substantially reduce the PLQEs, thus limiting LED external quantum efficiencies (EQE).[14,15] These limitations can be avoided by making nanoplatelets from CsPbBr₃. By reducing the thickness to a couple of monolayers, the emission can be shifted to the blue wavelength range with sharp photoluminescence (PL) peaks (full width at half maximum (FWHM) down to 11 nm)[16] and high PLQEs reaching close to unity in colloidal solution.[15] Importantly, across all these examples, the NCs can be synthesized with precise control over the size and with a high degree of uniformity (i.e., low polydispersity),[18] which is important for achieving the narrow emission linewidths. More details and other examples can be found in recent reviews: lead-halide perovskites[1–3] and II–VI compounds.[4,19]

Plasmonics encompasses devices making use of the resonant oscillations of free electrons in response to electromagnetic radiation (i.e., surface plasmons).[20] These surface plasmons can propagate at interfaces (surface plasmon polaritons), or occur as localized surface plasmon resonances (LSPRs).[20] Applications in the latter case include localized heating, data storage, catalysis, energy harvesting, and optical nanoantennae.[21,22] LSPRs have particularly been achieved using metal nanoparticles, owing to their strong plasmonic response to visible light, as well as the well-established routes to synthesizing these in colloidal form.[20,23] A wide range of metals have been considered, including Au, Ag, Al, Mg, and Pt, as well as more complex structures (e.g., Ag–Au core–shells), which were investigated to improve the response to near-infrared light for biomedical applications.[20] While Au nanoparticles have been found to be mostly stable, Ag, Mg, and Al have demonstrated lower stability. This has been a motivating factor for developing compound-based plasmonic nanoparticles.[20] Across all applications, control over the size of the nanoparticles is critical. The synthetic method also needs to be carefully controlled to avoid the formation of aggregates, agglomerates, or precipitates.[21] Such as through the use of stabilizers.[21,24] More details on Ag[23] and Au[24–26] nanoparticles for plasmonics can be found in recent literature.

Control over the size of both optoelectronic and plasmonic NCs requires an understanding of the synthetic process in the initial stages of nucleation and growth following supersaturation. A combination of experiment and theory is needed to elucidate the mechanism behind NC formation and growth, and the factors that influence the shape of the NCs, such as whether they form spherical particles, cubic structures, or anisotropic nanoplatelets.[1,27–29] For example, the traditional La Mer-type model describes the diffusion of the solvated and supersaturated monomers to form nuclei exceeding the critical size that then grow through the diffusion and addition of further monomers (see ref. [30] for details). However, there has been intense debate regarding whether these traditional La Mer-type models can accurately quantitatively describe experimental results.[23] More recent works on II–VI (e.g., CdSe) and IV–VI compounds suggest that alternative mechanisms may be present, such as a surface-reaction-controlled growth.[28,30] The La Mer model also does not account for complex ligand–NC and ligand–ligand interactions, and their influence on nucleation and growth. Furthermore, these ligands used during synthesis can influence the size and shape of the NCs by changing the reactivity of the precursors,[28] by leading to anisotropic growth of low-dimensional nanoplatelets rather than nanocubes,[29] or by simply interacting with the NC surfaces. In addition to the mechanism of synthesis, the final size distribution of the NCs is also influenced by the rate at which the different steps take place; how nucleation (i.e., whether all nuclei form in a narrow time window),[28,32] how the growth rates of the different facets of the NCs vary over time,[28] and whether the size of the NCs influences whether they dissolve or increase in size. NCs can also grow through a combination of phenomena, namely coalescence, metal-surface-catalyzed reduction, and Ostwald ripening (in which smaller NCs can dissolve, and the solvated monomers deposit onto facets of larger NCs, which can lead to broader size distributions).[31,34] Ostwald ripening depends on the chemical system, and it can be avoided by controlling the early synthesis process to avoid the rapid depletion of the monomers.[28] Monitoring the initial stages of nucleation and growth is therefore critical, but this is complicated by the short time window for most NCs (e.g., halide perovskite NCs are usually formed within 1–3 s), and Au nanoparticles are sometimes formed over the course of milliseconds.[25]

Traditionally, the lab discovery and development of these materials have taken place using batch reactors as they are easy to set up without requiring expert skills and they offer wide chemical compatibility. Batch syntheses are typically performed under stirring to achieve homogeneous temperature and mixing of the reaction medium. However, the actual level of mixing and homogeneous conditions is known to be strongly dependent on the stirring rate, type of impellers and bafflers, size, and geometry of the reactor.[33] The importance of mixing (e.g., mass transfer) is normally overlooked during the initial development of chemical reactions, and nanoparticle synthesis is no exception. Mixing is considered critical for fast reactions such as NC synthesis, being important to ensure that the mixing time (i.e., time to achieve homogeneous conditions in the reactor) is considerably shorter than the reaction times (i.e., the characteristic time of a reaction).[36] When considered quantitatively, the Damkohler numbers (Da and DaII) are important in assessing the mixing rate in the reaction system and whether it affects the observed reaction kinetics. The first Damkohler number (Da) is defined as the ratio between reaction rate and convective mixing rate. When Da << 1, the reaction is in the kinetic regime, being possible to accurately monitor the material synthesis rate. Differences in mixing rates (when Da >> 1) is one of the main reasons behind the lack of reproducibility and thus the batch-to-batch variability characteristic of batch reactors.[37] The second Damkohler number (DaII) is defined as the ratio between reaction rate and diffusive mixing rate (in the absence of convection). Short diffusion lengths (e.g., in microreactors) lead to fast mixing rates, promoting small DaII values.

Over the last decade or so, flow reactors have also been deployed for the synthesis of NCs, either by translating batch synthetic protocols into flow reactors or by being used for the development of new synthetic methods and/or material development.[18] A number of drivers are behind this, from the need to overcome the disadvantages of batch reactors in terms of a lack of reproducibility, to the overall desire to
develop continuous platforms for the large-scale synthesis of nanoparticles to accelerate their deployment in devices and applications.

Independent of the type of reactor used, a number of characterization techniques have been used to monitor the physical properties of nanocrystals during (in situ) and after (ex situ) synthesis (refer to Table 1 and Figure 1). In situ monitoring refers to the acquisition of data without disrupting the system, i.e., the reaction is taking place as if there is no measurement. Ex situ monitoring is as straightforward as taking samples out of the reaction system and measuring them externally, during which process sample preparation is often involved.

In this review, we examine the critical topic of the importance of monitoring nanocrystal synthesis, particularly during the early stages of nucleation and growth to not only elucidate the mechanistic steps involved but also to understand the strong influences of kinetics on the physical properties of optoelectronic and plasmonic materials. We begin by discussing the key physical size, structure, morphology, composition, and optical properties of NCs and the pros and cons of the different

### Table 1. Summary of the different suitable characterization techniques and their applicability toward in situ, ex situ, and online inspection.

| Techniques                  | Characteristics             | NP sample state | Information                              | Application                        | Analytical time                      | Limitations                                               | Artifact reviews |
|-----------------------------|-----------------------------|-----------------|------------------------------------------|-----------------------------------|--------------------------------------|----------------------------------------------------------|------------------|
| UV–vis spectroscopy         | • Particle concentration    | Suspension and dry | • Particle size                         | Ex situ: batch and continuous     | Rapid (in situ, ex situ, and online): ≈100 ms per sample | Chemical environment affects the final spectra             | [79]             |
|                            | • Bandgap and excitonic    |                  | • Particle shape                        | Online: continuous                | Rapid (in situ, ex situ, and online): ≈1 ms per sample | Difficult to identify samples with a bimodal distribution |                  |
|                            | absorption                 |                  | • Particle number concentration         | In situ: batch and continuous     |                                      | Only applicable to samples that interact with light       |                  |
|                            | • Surface plasmon          |                  | • Surface plasmon resonance peak        |                                   |                                      |                                                          |                  |
|                            | resonance peak             |                  |                                          |                                   |                                      |                                                          |                  |
| Photoluminescence (PL)      | • Bandgap emission         | Suspension and dry | • Particle size and size distribution   | Ex situ: batch and continuous     | Rapid (in situ, ex situ, and online): ≈1 ms per sample | Only detects the lowest bandgap position of a sample      | [168]            |
|                            |                            |                  | • Lattice structure                     | Online: continuous                |                                      |                                                          |                  |
|                            |                            |                  | • Surface compositions                  | In situ: batch and continuous     |                                      |                                                          |                  |
| Raman spectroscopy          | • Chemical structure and   | Suspension and dry | • Particle size and size distribution   | Ex situ: batch and continuous     | Rapid (in situ, ex situ, and online): ≈1 s per sample | Cannot be used on metal NPs                           | [169]            |
|                            | states                     |                  | • Particle size                         | Online: continuous                |                                      |                                                          |                  |
|                            |                            |                  | • Particle shape                        | In situ: batch and continuous     |                                      |                                                          |                  |
| Electron microscopy (e.g., | • Topographical imaging    | Suspension and dry | • Particle size and size distribution   | Ex situ: batch and continuous     | Rapid (in situ): ≈1 ms               | TEM: only 2D information                                | [170]            |
| TEM)                        | • Crystallinity            |                  | • Lattice structure                     | Online: continuous                | ≈1 s per sample                      | Multicomponent analysis is not quantitative              |                  |
|                            | • Elemental map            |                  | • Surface compositions                  | In situ: continuous cell          |                                      | with STEM–EDX Cannot be used for samples with a low      |                  |
|                            |                            |                  |                                          |                                   |                                      | particle concentration                                 |                  |
| Nuclear magnetic            | • Surface composition      | Suspension and Dry | • Particle size                         | Ex situ: batch and continuous     | Short (in situ): ≈5 min per sample   | Low sensitivity                                          | [163]            |
| resonance spectroscopy      |                            |                  | • Lattice structure                     | Online: batch and continuous      | Slow (ex situ)                       |                                                          |                  |
| (NMR)                      |                            |                  | • Surface compositions                  | In situ: batch and continuous     |                                      |                                                          |                  |
| X-ray techniques (e.g.,     | • Crystal structure        | Suspension and dry | • Particle size and size distribution   | Ex situ: batch and continuous     | Short (in situ): ≈5 min per sample   | Less sensitive for nanosized crystallites and crystal    | [92]             |
| SAXS, XANES)               | • Particle size information|                  | • Crystalinity                         | Online: batch and continuous      | Slow (ex situ): depending on the     | grains                                                  |                  |
|                            |                            |                  | • Grain size                           | In situ: batch and continuous     | sample                                    |                                                          |                  |
|                            |                            |                  | • Precursor composition and concentration|                                  |                                          |                                                          |                  |
| Dynamic Light              | • Dynamic particle size    | Suspension        | • Particle size and size distribution   | Ex situ: batch and continuous     | Short (ex situ): ≈5 min per sample   | Biased toward small or big particles                     | [171]            |
| Scattering (DLS)            | sizing in liquid media     |                  | • Lattice structure                     | Online: continuous                |                                      | Assumes particles as spheres                            |                  |
| Mass spectroscopy (SP-ICP- | • Single-particle mass     | Suspension        | • Mass histograms                      | Ex situ: batch and continuous     | Short (ex situ): ≈1 min per sample   | Requires calibration per element analyzed and sample     |                  |
| MS)                        | mass inspection            |                  | • Particle size distribution            | Online: continuous                |                                      | preparation Different elements have different lower      |                  |
|                            | • Multicomponent analysis  |                  | • Particle composition                  |                                  |                                      | size limits                                              |                  |
|                            | • Particle and ionic       |                  | • Lattice structure                     |                                  |                                      |                                                          |                  |
|                            | concentration              |                  | • Surface compositions                  |                                  |                                      |                                                          |                  |
2. General Remarks on Synthesis and Characterization of Plasmonic and Optoelectronic Materials

2.1. General Remarks on the Synthesis

The methods for nanoparticle synthesis can be broadly divided into physical, biological, and chemical methods. Physical methods offer good control over kinetics via, e.g., evaporation–condensation and laser ablation, resulting in easily tunable particles over a thin film, being free of solvent contamination and chemical reagents. However, physical methods sacrifice scale, in that they are not suitable for the large-scale production of nanoparticles. In addition, they normally require significant energy consumption, e.g., due to the furnace power consumption and preheating time, hindering their industrial large-scale deployment. By contrast, biological methods of nanoparticle synthesis are normally cheap and eco-friendly (especially in comparison to chemical methods). Biological syntheses are typically performed by the reduction of a metal precursor using proteins and enzymes found in living organisms (bacteria, plants, mold, and algae). The main drawback is the significant lack of repeatability/reproducibility, affecting the kinetic control over the process, which limits their general use. Specifics about biological synthetic methods and respective outcomes and applications are extensively explored in a recent review from Salem and Fouda. The advantages and disadvantages of biological methods have been reviewed by Parveen et al.

In this review, we will focus on chemical methods for the synthesis of plasmonic and optoelectronic materials. Chemical methods are popular due to their simplicity, balancing the drawbacks and advantages of the physical and biological methods, being more cost-effective than physical methods (which need a high-energy laser focus on a solid surface to form a plasma) and improved kinetic control compared to biological methods. Numerous synthetic strategies can be applied via chemical methods, such as i) chemical reduction, ii) photoreduction, iii) electrochemical reduction, iv) microwave-assisted chemical reduction, v) coprecipitation, and vi) thermal decomposition. Details of these methods have been compiled and described for plasmonic and optoelectronic materials somewhere else.

2.2. General Remarks on Key Physical Properties and Characterization Techniques

A range of physical properties such as size, size distribution, morphology, number density (number of particles per volume), optical response, etc., is critical to monitor the synthesis of the plasmonic and optoelectronic nanoparticles. Indeed, mechanistic and kinetic models are based on this critical information, especially when time-resolved data (e.g., variation of size as a function of synthetic time) are available. As such, a wide range of characterization techniques is used to evaluate such properties with dedicated reviews. In this review, we focus on how the most frequently used techniques provide information about these key physical properties during (in situ) and after (ex situ) the synthetic process (as schematically represented in Figure 1). On some occasions, online characterization refers to the direct analysis of the reaction media by pumping it to a probe or cell outside the actual reactor. In these cases, the reaction conditions are disrupted during the analysis, affecting (or not) the progress of the reaction. In this section, we will evaluate in-depth how these different physical properties are currently monitored, including the advantages and limitations of each of the characterization techniques as well as their associated models (Table 1). This information will set the foundation of...
the critical review in Sections 3 and 4 about how these techniques are currently used to monitor the synthesis of nanoparticles in batch and flow reactors, respectively.

2.3. Size and Size Distribution

The particle size and its distribution (curve type, average, and standard deviation) can be inspected using spectroscopy (UV–visible spectrophotometry (UV–vis), PL, and single-particle inductively coupled plasma mass spectrometry (SP-ICP-MS)), scattering (small-angle X-ray scattering (SAXS), and dynamic light scattering (DLS)), and electron microscopy (e.g., transmission electron microscopy (TEM) and scanning electron microscopy (SEM)). All these techniques can be applied to in situ time-resolved monitoring of particle size information (listed in Tables 2 and 3), except for SEM (not yet adopted to monitoring nucleation and growth).

UV–vis is widely used for the determination of nanoparticle size and distribution due to its easy implementation and short analytical time (time to fully characterize a sample, $t_d$), aiding in establishing the particle formation mechanisms with time resolution.\textsuperscript{61–63} The size information can be directly related to the LSPR position (plasmonic materials) and bandgap (optoelectronic materials) with the broadening of the peak being normally attributed to the size polydispersity.\textsuperscript{64} Numerous models are used for the determination of size and distribution by assessing the differences between the experimental data and theoretical response of monosized particles (e.g., analytical, Mie theory/ Mie–Gans theory,\textsuperscript{65} or numerical, discrete dipole approximation (DDA)\textsuperscript{66–68}). The Mie-theory-based algorithms have been successfully applied to Au,\textsuperscript{61,63,68} Ag,\textsuperscript{66,67,70} Al,\textsuperscript{68,71} Pt,\textsuperscript{72,73} and Mg\textsuperscript{74} in specific size ranges. In terms of applicability, Mie and Mie–Gans theories are limited to spherical and spheroidal particles,\textsuperscript{84} respectively. Despite the popularity of UV–vis, absorption spectra suffer from a complicated superposition of effects related to, for example, the local chemical environment (e.g., concentration of reducing agent, surfactant, and solvent), multiple size distributions (e.g., aggregates), excitons, and defect states, and presence of different morphologies.\textsuperscript{61,65,75} These affect the oscillation of conduction electrons driven by the electric field.\textsuperscript{65,74,76} In addition, light artifacts that are commonly present in UV–vis spectra are related to variations in the performance of the light transmission (relevant to in situ measurements), sample fluorescence, traces of unwanted light, bubbles trapped in the cuvette/optical cell, and low light transmission in some wavelengths of the spectra.\textsuperscript{23,27} The latter occurs when using materials (e.g., cuvettes, optical fibers, etc.) with low optical transmittance.\textsuperscript{78} Further details about the limitations and perspectives of in situ UV–vis have been reported by Hendel et al.\textsuperscript{79}

The size of optoelectronic materials can also be assessed using PL spectroscopy, which is a facile and rapid technique.\textsuperscript{80–83} PL can also be applied to determine the sizes of plasmonic materials, but this is not common.\textsuperscript{84} The sizes of optoelectronic nanoparticles are inferred by relations such as the effective mass approximation,\textsuperscript{85,86} which assumes spherical particles and deviates from other realistic shapes, such as cubes, plates, rods, etc. The size of plasmonic materials is inferred by the free-electron model.\textsuperscript{84} Time-resolved PL has been widely applied to study the formation mechanism and synthesis kinetics of optoelectronic materials, usually in combination with UV–vis spectroscopy.\textsuperscript{80–86} However, the energy of the emitted photon in relation to the bandgap depends on many factors, such as defect states or self-trapped excitons.\textsuperscript{89} The presence of defect sites and complex morphology will significantly affect the PL spectra, complicating the extraction of information on nanoparticle size. Similarly, in concentrated polydisperse samples (high polydispersity index), energy transfer from smaller (higher energy) to adjacent larger (smaller energy) particles upon excitation can lead to the masking of the small particles.

In terms of scattering techniques, SAXS provides information on particle size, being more sensitive for crystalline samples (hence crystallite size). The advantages of SAXS include nondestructive analysis, suitable for dry and wet samples, and no requirement for any special sample preparation steps. Details of the operation and data analysis of SAXS have been reviewed previously.\textsuperscript{82} SAXS can effectively detect the average radius of agglomerates and primary particles and is suitable for characterizing amorphous materials at a relatively low resolution.\textsuperscript{83} Sizes inferred from SAXS match those from TEM images accurately for spherical nanoparticles, while corrections are required for particles with arbitrary shaped.\textsuperscript{90} The limitation of SAXS lies in the models used to calculate particle size, the accuracy of which is influenced by the polydispersity. It is reported that particles smaller than 1 nm in diameter are hardly detectable due to a low signal-to-noise ratio.\textsuperscript{84} This means that a high-energy X-ray from a synchrotron source is required for such low sizes (the scattering intensity scales with the sixth power of the radius\textsuperscript{85}). It is noteworthy that SAXS setups require a transparent narrow window for focused X-rays to penetrate the reaction medium.

DLS is another easy-to-use technique to determine the particle size and distribution of nanometer- to micrometer-sized particles and clusters. The Stokes–Einstein equation used to correlate diffusion coefficients (raw data) to hydrodynamic sizes assumes spherical particles in a highly diluted media; therefore, DLS is unable to resolve particles with complex geometry. The sensitivity is related to particle size (intensity proportional to $d^6$ based on Rayleigh approximation, where $d$ is the characteristic diameter of the particle), and the inaccuracy, therefore, increases when the particles are very small, e.g., diameter $<5$ nm.\textsuperscript{85} If the system is composed of monodisperse spherical particles, DLS can provide reliable results.\textsuperscript{90} However, it is less reliable when there is high polydispersity (≥50%). Nevertheless, DLS is often used to study the aggregation kinetics of nanoparticles.\textsuperscript{90} Limitations arise as its analytical time $(t_a)$ is considerably longer than UV–vis or PL measurements (Table 1), requiring at least 1 min to obtain size information accurately.\textsuperscript{90} As a result, it is not suitable for in situ monitoring in fast synthesis, when sizes vary significantly during the analytical time.

Microscopy, in particular TEM, provides a more accurate determination of the particle size and distribution when dealing with particles below 5 nm.\textsuperscript{90} However, it is important to ensure that the small sample volume analyzed is representative of the bulk of the system. Limitations when using TEM for analysis arise with electron-beam-induced particle dissolution and motion, particle–grid adhesion, contamination, and
Table 2. Summary of in situ and ex situ monitoring studies of the synthesis of plasmonic and optoelectronic materials in batch reactors sorted per material. Only studies containing kinetic data were added, which include direct and indirect time-resolved measurements. For the abbreviations, please check the section about characterization techniques.

| Material | Year | Size [nm] | Shape | Reaction time | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Characterization | Precursors | Synthesis conditions | Ref. |
|----------|------|-----------|-------|---------------|---------------|----------------------|-----------------------------|----------------|------------|---------------------|------|
| Ag       | 2010 | 4.7–100 nm| Spherical and triangular nanoprisms | 60 s to 48 h | Ex situ: TEM, UV–vis | Concentration, absorbance, and size versus time | ≈1 h variable | Ex situ: TEM, UV–vis | Silver nitrate | Sodium borohydride | 4 °C (ice bath) droppwise | In aqueous media | [189] |
| Ag       | 2010 | 2–6 nm   | Spherical | 10–120 min | Ex situ: UV–vis, XANES | Absorbance, XANES spectra, fraction of Ag species versus time | 10 min | Ex situ: TEM, UV–vis, XANES | Silver nitrate | Sodium acrylate (SA) | 373 K | In an aqueous media with NaOH | [279] |
| Ag       | 2010 | 7.1–23.8 nm| Spherical | Up to 90 min | In situ SAXS | Size versus time | 30 s | Ex situ: TEM, UV–vis | Silver perchlorate | Benzoil | Room temperature | In 1:1 water/ethanol | [227] |
| Ag       | 2012 | 40–110 nm | Spherical, hexagonal | 120 s | In situ TEM | Size versus time | 3 s | Ex situ: TEM | Silver nitrate | | 298–318 K | In aqueous media | [247] |
| Ag       | 2013 | Up to 8.8 nm| Spherical | 45 min | Ex situ UV–vis | Absorbance versus time | 20 s | Ex situ: UV–vis, DLS, TEM, XRD, FTIR, AAS | Silver nitrate | Hydrazine | Ammonia | | [226] |
| Ag       | 2013 | 3.5–20 nm | Spherical | 8 h | Ex situ TEM, XRD, DLS | Size, yield versus time, temperature | 10–20 min variable | Ex situ: XRD, TEM, UV–vis, DLS, TGA, FTIR | Silver nitrate | Oleylamine | Room temperature | In diphenyl ether | [185] |
| Ag       | 2014 | 18–28 nm | Spherical | 20–110 s | In situ BF-TEM | Size, number of particles, and particle interaction versus time | 1 s | In situ BF-TEM | Silver nitrate | | | | [266] |
| Ag       | 2015 | 7.3–14.3 nm| Spherical | Up to 180 min | Ex situ TEM, UV–vis | Size, pH, reductant concentration | Minimum 5 min | Ex situ: UV–vis, TEM | Silver nitrate | Adrenaline | 25 °C in water with cetyltrimethylammonium bromide (CTAB)/sodium dodecyl sulfate (SDS) | [237] |
| Ag       | 2016/2017 | 9.9–103.6 nm | Spherical (estimated) | 40 min | In situ HE-XRD | Size versus time | 1 min | In situ HE-XRD | Silver nitrate | 140 °C | In ethylene glycol with PVP stabilizer | | [245, 246] |
| Ag       | 2017 | 10–180 nm | Nonspherical | 400 s | In situ STEM | Size versus time | 1 s | In situ STEM | Silver nitrate | Trisodium citrate | 90 °C | In aqueous media with stabilizers | [241] |
| Ag       | 2020 | Distribution 1: 1–3 Distribution 2: 10–40 | Spherical | 60 s to 72 min | Online: SAXS | Size, volume fraction, and absorbance versus time | 1 min | Online: SAXS | Silver nitrate | Glucose | | | [248] |

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| Material | Year | Size [nm] | Shape | Reaction time | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Characterization | Precursors | Synthesis conditions | Ref. |
|----------|------|-----------|-------|---------------|--------------|----------------------|-------------------------------|-----------------|------------|---------------------|------|
| Ag       | 2021 | 20–50 nm  | Spherical | 40 min | Ex situ UV–vis | Size versus pH, precursor concentration | 5 min | Ex situ: TEM, UV–vis, FTIR, FE-SEM, XRD | Silver nitrate | Tannic acid | 30 °C in water | [280]|
| Ag       | 2021 | Diameter 40–80 nm Length 5–35 µm | Wires and spherical | 220 min | Ex situ UV–vis | Diameter and length versus time, concentration | 1 min irregular intervals | Ex situ: UV–vis, FE-SEM, TEM, AAS | Silver nitrate | Ethylene glycol | 120–160 °C in ethylene glycol with PVP as stabilizer | [234]|
| Al       | 2019 | 50–150 nm | Nanocubes | 30–120 min | Ex situ optical analysis | Absorbance versus time | ≈20 min | Ex situ: TEM, SEM, UV–vis, EPR, XRD, DFM | Dimethylethylamine alane | Tebbe’s reagent | 70 °C in toluene | [68]|
| Al       | 2019 | 62–157 nm | Hexagons and cubes | Up to 60 min | Ex situ optical analysis | Absorbance versus time | 5 min | Ex situ: TEM, NMR, UV–vis, EPR, XRD, TGA | AlH₃ from dimethylethylamine alane (DMEAA) Lewis base | ≈40 °C | In several solvents: dioxane, tetrahydrofuran (THF), tetramethylethylenediamine (TMEDA), and NMP (N-Methyl-2-pyrrolidone) | [182]|
| Au       | 2007 | ≥20–40 nm | Spherical | ≈30–1200 s | Ex situ: TEM, UV–vis | Absorbance, pH, size/shape image versus time | ≈30 s (variable) | Ex situ: TEM, UV–vis, DLS | Chloroauric acid | Trisodium citrate | Boiling temperature in aqueous media with HCl or NaOH | [215]|
| Au       | 2007 | ≥21–150 nm | Spherical | Up to 1200 s | Ex situ: DLS, UV–vis, SEM | Absorbance, DLS size versus time | ≈1 min (variable) | Ex situ: DLS, UV–vis, SEM | Tetrahydroauric acid hydrate Oleylamine | Reflux solution of oleylamine in toluene with odecanol | [265]|
| Au       | 2008 | 5–22 nm | Spherical | Up to 2 h | In situ: SAXS, UV–vis | Size, particle number, and extinction versus time | 1–60 s variable | In situ: SAXS, UV–vis | Chloroauric acid | Trisodium citrate | UV and X-ray activation process at room temperature in aqueous media | [242]|
| Au       | 2010 | 2–16 nm | Spherical | 60–6000 s | Online: SAXS | Size and number of particles versus time | ≈1 min | Online: SAXS | Chloroauric acid | Trisodium citrate | 75 °C in aqueous media | [195]|
| Au       | 2010 | 4–16 nm | Spherical | 30–5400 s | Ex situ: SAXS/XANES | Size, number of particles, absorbance, polydispersity, and oxidation state versus time | 5 min | Ex situ: SAXS/XANES, TEM, SEM, and UV–vis | Chloroauric acid | Trisodium citrate | 75 °C (Turkevich method) in aqueous media | [24]|
| Au       | 2011 | 25–120 nm | Spherical and aggregates | 50–2000 min | Ex situ: AFM, DLS, UV–vis, SAXS | Hydrodynamic diameter, absorbance, volume fraction versus time | ≈50 min | Ex situ: AFM, DLS, UV–vis, SAXS, XPS, X-ray, TEM, EDX | Chloroauric acid | Trisodium citrate | 70 °C in aqueous media with NaOH | [243]|
| Au       | 2012 | 4.0–6.0 nm | Spherical | 30–9000 s | In situ SAXS, UV–vis | Size, absorbance, and intensity versus time | ≈30 s (variable) | In situ: SAXS and UV–vis | Chloro gold(I)-triphenylphosphine (I)-butylamineborane complex | Room temperature | In toluene with stabilizers | [175]|
| Au       | 2015 | 17.4–21.4 nm | Spherical | 5 s to 25 min | Ex situ: UV–vis, SEM, and SAXS | Size, absorbance, and reproducibility versus time (reaction) | ≈15 s (variable) | Ex situ: UV–vis, SEM, and SAXS | Chloroauric acid | Trisodium citrate | Boiling temperature | In aqueous media | [232]|
### Table 2. Continued.

| Material | Year | Size [nm] | Shape | Reaction time | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Characterization | Precursors | Synthesis conditions | Ref. |
|----------|------|-----------|-------|---------------|---------------|-----------------------|-------------------------------|-----------------|------------|----------------------|------|
| Au       | 2015 | 24–111    | Spherical and polygonal | 2 min to ≈24 h | Ex situ: UV–vis, TEM, DLS | Hydrodynamic size, polydispersity index, TEM size, absorbance versus time | ≈30 min (variable) | Ex situ: UV–vis, TEM, DLS | Chlorauric acid | Trisodium citrate | Room temperature in aqueous media | [229] |
| Au       | 2015 | 25–320    | Triangular, hexagonal, truncated octahedral | Up to 300 s | In situ TEM, 3D STEM | Size (atoms) versus time, electron dosage | 20 s | In situ TEM, 3D STEM | Chlorauric acid | Electron beam reduction | [244] |
| Au       | 2015 | 200–1000 | Triangular, hexagonal | Up to 120 s | In situ TEM | Size (area) versus time | 1/30 s | In situ TEM | Chlorauric acid | Electron beam reduction | [260] |
| Au       | 2015 | 2.4–6     | Spherical | Up to 200 min | In situ SAXS, WAXS, UV–vis | Size versus time | 5 min | In situ SAXS, WAXS, UV–vis | Chloro gold(I)-triphosphine t-butylamineborane | 22–45 °C | In toluene | [212] |
| Au       | 2015 | ≈2–10 (estimated) | Spherical | Up to 60 min | Ex situ UV–vis, Ex situ: DL, ICP-AES | Estimated size, hydrodynamic size, concentration, and absorbance versus time | ≈1 min | Ex situ UV–vis, Ex situ: DL, ICP-AES | Chlorauric acid | Plasma sputtering method in a quartz cell having NaCl | [281] |
| Au       | 2016 | 10–32     | Spherical | 20 min to 8 h | Ex situ optical analysis | Concentration and absorbance versus time | ≈10 min | Ex situ: UV–vis, XRD, TEM, zeta potential | Chlorauric acid | Trisodium citrate | Room temperature in aqueous media | [206] |
| Au       | 2018 | 3–5       | Spherical and aggregates | Up to 24 h | In situ: AFM and TEM, Ex situ: TEM | Size versus time | ≈1 s | In situ: AFM and TEM, Ex situ: TEM, UV–vis | Chlorauric acid | Trisodium citrate | Room temperature in aqueous media | [282] |
| Au       | 2019 | 10–24     | Spherical | Up to 1500 s | In situ: UV–vis, pH, and Eh, Ex situ: TEM | Size and concentration versus time | ≈1 s | In situ: UV–vis, pH, and Eh, Ex situ: TEM | Chlorauric acid | Trisodium citrate | 40–70 °C hot injection in aqueous media | [61] |
| Au       | 2020 | 2.6–16    | Spherical | Up to 40 min | In situ UV–vis, Ex situ: SAXS, TEM | Size, absorbance versus time | Less than 1 min | In situ: UV–vis, Ex situ: SAXS, TEM | Chlorauric acid | Trisodium citrate | 85 °C | [63] |
| Au       | 2020 | 2–10      | Spherical | Up to 1 h | In situ TEM | Size versus time | 10 s | In situ TEM, Ex situ: XRD | Gold–ethylene diamine complex salt | Chlorauric acid | Oleylamine Morpholine–borane complex (MB) | [239] |
| Au       | 2021 | 2.5–8.5   | Spherical | 2.5–500 s | In situ: SAXS and UV–vis | Size, polydispersity, absorbance, and gold ionic fraction versus time | 0.5 s | In situ: SAXS and UV–vis | Chlorauric acid | Oleylamine Morpholine–borane complex (MB) | [261] |
| CdSe     | 2021 | 4.4       | Spherical | 3 s to 32 min | In situ SAXS | Size versus time | 100 ms | Ex situ: UV–vis, PL, TEM, Ex situ: SAXS | Cadmium acetate Selenium: tri-n-octylphosphine oxide (TOPO) | 290 °C hot injection in octadecene | [193] |
| CsPbBr₃  | 2016 | 8.4–9.6   | Cubes | 1–40 s | Ex situ TEM | Size versus time | ≈3 s (variable) | Ex situ: UV–vis, PL, TEM, XRD | Cesium carbonate Lead(I) bromide | 170 °C in octadecene with oleic acid and oleyamine | [228] |
| Material | Year   | Size [nm]       | Shape          | Reaction time | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Characterization | Precursors                          | Synthesis conditions                                                                 | Ref.       |
|----------|--------|-----------------|----------------|---------------|---------------|----------------------|--------------------------------|-----------------|------------------------------------|--------------------------------------------------------------------------------------|------------|
| CsPbBr₃  | 2017   | 6–8 nm          | Spherical      | 0–25 s        | In situ TEM   | Size, number of particles versus time | 0.5 s               | In situ TEM | Methylammonium bromide Lead(II) bromide | Electron-beam-induced solvent evaporation                                           | [253]      |
| CsPbBr₃  | 2018   | 6–10            | Cubic          | 8–25 min      | Ex situ TEM   | Size versus time    | ~7 min              | Ex situ: UV–vis, PL, TEM, XRD | Cesium carbonate Lead(II) bromide | Microwav-assisted synthesis in octadecane                                              | [283]      |
| CsPbBr₃  | 2019   | 3.9–10.7        | Spherical, cubic | 1–11 min      | Ex situ TEM   | Size versus time    | 1 min               | Ex situ: UV–vis, PL, TEM, XRD | Cesium bromide Lead(II) bromide | 0, 30, and 60 °C Coprecipitation in continuous stirred tank reactor (CSTR) in toluene | [284]      |
| CsPbBr₃  | 2021   | 9.9–12.5 nm     | Cubic          | 5 s           | Ex situ optical analysis | Size versus temperature | –                  | Ex situ: UV–vis, PL | Cesium oleate Lead(II) bromide | 100–180 °C hot injection in octadecane                                              | [235]      |
| CsPbI₃   | 2016   | 7.5–13.5 nm     | Nanoplates     | 1–40 s        | Ex situ TEM   | Size versus time    | ~3 s (variable)       | Ex situ: UV–vis, PL, TEM, XRD | Cesium carbonate Lead(II) iodide | 145 °C in octadecane with oleic acid and oleylamine                                   | [228]      |
| MAPbBr₃  | 2017   | 2–5 nm          | Spherical      | A few seconds | Ex situ TEM   | Size versus concentration | –                  | Ex situ: UV–vis, PL, TEM | Methylammonium bromide Lead(II) bromide | Ligand-assisted reprecipitation in toluene                                             | [236]      |
| Mg       | 2022   | 80–500 nm       | Hexagons and rods | 1–1000 min   | Ex situ: STEM, SEM | Size versus time    | 5 min variable     | Ex situ: STEM, SEM, ICP-MS | MgBu₂, Lithium naphthalenide | Room temperature In THF in the presence or not of additives (metal chloride salts) | [181]      |
| PbS      | 2011   | 20–30 nm        | Various        | 20 min        | In situ TEM   | Size versus time, precursor ratio | 403 ms              | In situ: TEM | Lead acetate Thioacetonamide | Electron beam decomposition                                                          | [256]      |
| Pt       | 1995   | 1.8–7.0 nm      | Spherical      | Up to 8h      | Ex situ UV–vis | Absorbance versus time | 1 h                 | Ex situ: UV–vis, TEM | K₂PtCl₄ Hydrogen Trisodium citrate | 100 °C In aqueous media (with sodium polyacrylate for hydrogen reduction)             | [285]      |
| Pt       | 1995   | ~2.5 nm         | Spherical      | Up to 1200 s  | Ex situ UV–vis | Absorbance versus time | 5 min               | Ex situ: UV–vis, TEM, pH | H₂PtCl₆ Methanol | 100 °C In aqueous media with PVP Boiling point In aqueous media with PVP and 30–90% of alcohol | [286] [233] |
| Pt       | 1999   | 1.9–5.05 nm     | Spherical      | Up to 180 min | Ex situ UV–vis | Concentration and absorbance versus time | 2 min               | Ex situ: UV–vis, TEM, FTIR, XPS | H₂PtCl₆ Methanol or ethanol or propanol | 160 °C in ethylene glycol with sodium nitrate and PVP Room temperature In aqueous media with PVP | [238] [262] |
| Pt       | 2004   | 7–10 nm         | Spherical, octapods, and tetrapods | 30–600 s | Ex situ UV–vis, TEM | Absorbance versus time | ~30 s              | Ex situ: UV–vis, TEM | H₂PtCl₆ Ethylene glycol | 70 °C in toluene In aqueous media with PVP | [252]      |
| Pt       | 2006   | 3.1–7.8 nm      | Spherical and tetrahedron | Up to 60 h    | Ex situ TEM   | Tetrahedral % versus time | 2 h                 | Ex situ: UV–vis, TEM, Raman, SEM | K₂PtCl₆ Hydrogen | Room temperature In aqueous media with PVP | [262]      |
| Pt       | 2009   | 6.5–24 nm       | Cubic with branches | Up to 500 min | In situ XRD | Diffraction intensity versus time | 5–10 min            | In situ: XRD Ex situ: TEM | Pt(acac)₂ Oleylamine | 70 °C in toluene In a media with o-dichlorobenzene | [104]      |
| Pt       | 2009   | 0.8–3.6 nm      | Spherical      | Up to 5 min   | In situ TEM   | Size and number of particles versus time | ~0.5 s              | In situ: TEM | Pt(acetylacetonate)₂ Oleylamine and electron beam | 70 °C in toluene In a media with o-dichlorobenzene | [104]      |
Table 2. Continued.

| Material | Year | Size [nm] | Shape | Reaction time | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Characterization | Precursors | Synthesis conditions | Ref. |
|----------|------|-----------|-------|---------------|---------------|---------------------|-----------------------------|----------------|------------|---------------------|------|
| Pt       | 2012 | 1.4–3.0 nm | Spherical | 40–440 min | Ex situ: SANS | Size versus time | 30 min Ex situ: SANS, TEM | H₂PtCl₄ | Trisodium citrate or ethylene glycol | Boiling temperature assisted with PVP in aqueous media [230] |
| Pt       | 2012 | 1.8 nm     | Spherical | 3–180 min | In situ: QXAFS (Quick-scanning XAFS (QXAFS)) | Pair distribution function (PDF) (Pt–Pt and Pt–Cl) versus time | 3 min In situ: QXAFS Ex situ: UV–vis, XANES | H₂PtCl₄ | Ethylene glycol Citric acid | Photoreduction in an aqueous ethanol solution with PVP [250] |
| Pt       | 2012 | Up to 3 nm | Spherical, nanowire | Up to 180 min | In situ XAFS and UV–vis | Absorbance, Pt–Pt bond lengths versus time | 70 s In situ: XAFS, UV–vis Ex situ: TEM and XANES | K₂PtCl₄ | Ethylene glycol | 60 °C in three-neck flask assisted with PVP in ethylene glycol or water [264] |
| Pt       | 2012 | 0.9–2.1 nm | Spherical in hydrotalcite support | 3–20 min | Ex situ TEM and XANES | Size and absorbance versus time | 3 min variable In situ: TEM Ex situ: UV–vis, XANES | H₂PtCl₄·6H₂O | Starch | In aqueous media with NaOH and hydrotalcite [287] |
| Pt       | 2014 | 1–4 nm     | Nanocubes | 2–150 s | In situ TEM | Size versus time | ≈0.5 s In situ: TEM | Pt(acetylacetonate)₂ Oleylamine and electron beam | In a media with pentadecane [225] |
| Pt       | 2015 | 4.9 nm     | Cubic | Up to 70 s | In situ: X-ray | PDF (Pt–Pt and Pt–Cl) versus time | ≈1 s In situ: X-ray total scattering, XAFS Ex situ: TEM | H₂PtCl₄·6H₂O | Ethanol | Capillary reactor pressurized to 250 bar and heated to temperatures of 250 °C in a media with ethanol 70–75 °C in alcohol with and without a CO atmosphere [251] |
| Pt       | 2020 | Low SAXS signal: 0.1–0.5 nm, Good SAXS signal: ≈0.5–3.0 nm | Spherical | 20 min to 6 h | In situ: SANS | Size versus time | ≈10 min In situ: SANS Ex situ: TEM, FTIR, GC–MS, Raman, fluorescence, and zeta potential | H₂PtCl₄ | NaOH Alcohol (methanol or ethanol) | Room temperature and 59 °C in methanol [204] |
| Pt       | 2021 | 1.0–1.9 nm | Spherical | Up to 180 min | In situ: SANS, XAS | Size, PDF (Pt–Pt and Pt–Cl) versus time | ≈1 min In situ: SANS, XAS Ex situ: TEM, UV–vis, Raman | H₂PtCl₄ | NaOH Methanol | 60, 70, 80, and 90 °C in ethylene glycol (and in some cases carbon support was added) [263] |
| Pt       | 2021 | 1.9–3.2 nm XRD: 1.5–3.1 nm | Spherical | Up to 30 min | In situ: visual inspection and UV–vis | Visual color change and absorbance versus time | ≈30 s In situ: color, UV–vis Ex situ: XRD | H₂PtCl₄·6H₂O | Ethylene glycol Formic acid | In a media of oleylamine with cetyltrimethylammonium chloride, nickel acetylacetonate, and molybdenum hexacarbonyl [273] |
| Pt       | 2021 | Rod diameter: 2–4 nm, Rod length: 2.5–5.0 nm | Spherical and rods | Up to 120 min | In situ: SANS | Size and aspect ratio versus time | ≈1 min In situ: SANS Pt(acetylacetonate)₂ Oleylamine | H₂PtCl₄ | Oleylamine | In a media of oleylamine with cetyltrimethylammonium chloride, nickel acetylacetonate, and molybdenum hexacarbonyl [273] |
| ZnO      | 2011 | 3.6–5.8 nm | Spherical | Up to 400 min | In situ SANS, UV–vis, XAFS | Size versus time XAFS 210 s UV–vis 1 min SANS 30 s | In situ: SANS, XAFS, UV–vis | Zinc oxoacetate Potassium hydroxide | 40 °C in ethanol [255] |
| ZnO      | 2019 | 3–4.6 nm | Spherical | 0–1200 s | In situ SANS Ex situ TEM | Size versus time Minimum 30 s | In situ: SANS, XAFS, UV–vis Ex situ: TEM | Zinc oleate Tetrabutylammonium hydroxide | 40 and 50 °C hydrolysis in THF [254] |
Table 3. Reaction time and characterization techniques per material synthesized for the particle growth for nanoparticles using flow synthesis. Only studies with kinetic data were added, which include direct (where size is the raw data) and indirect (where size is obtained through calculation of raw data) time-resolved measurements. For the abbreviations, please check the section about characterization techniques.

| Material | Year | Size | Shape | Reaction time [s] | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Type of reactor and flow | Characterization | Precursors | Synthesis conditions | Ref. |
|----------|------|------|-------|------------------|--------------|----------------------|-------------------------------|---------------------------|-------------------|------------|----------------------|------|
| Ag 2004  | 7.4–8.7 nm | Spherical | 10–83 s | – | – | – | Helical reactor, single-phase flow | Ex situ: UV–vis, TEM | Silver pentfluoropropionate trioctylamine | 100–140 °C | [329] |
| Ag 2012  | 5–200 nm | Spherical and polyhedral | 0–90 s | In situ STEM | Size and number of particles versus time | 1 s | Fluid stage | In situ STEM | Silver nitrate | Beam electrons ($E_0 = 200$ keV) | 23 °C in aqueous media | [247] |
| Ag 2012  | 2–14 nm | Spherical | 0–100 min | In situ SAXS | Size versus time | 100 ms | Microstructured mixer with straight tube | Ex situ: TEM, SEM | Silver perchlorate sodium borohydride (with or without PVP) | 23 °C in aqueous media | [23] |
| Ag 2017  | 4.6–5.0 nm | Spherical | 23–50 s | – | – | – | Helical reactor, single-phase flow | Ex situ: UV–vis, TEM | Silver nitrate | In an aqueous media | 60 °C | [294] |
| Ag 2017  | 8.4–84.3 nm | Nanowires | 0–100 min | In situ SAXS | Size versus time | 100 ms | Microstructured mixer with straight tube | Ex situ: TEM, SEM | Silver perchlorate sodium borohydride (with or without PVP) | 23 °C in aqueous media | [247] |
| Ag 2017  | 2.7–19.0 nm | Spherical, plates, polygonal, wires | 9–54 s | Ex situ UV–vis SEM | Size and absorbance versus reactant ratio | – | T-mixer with a helical reactor, single-phase flow | In situ: UV–vis, TEM | Silver nitrate | Ascorbic acid CTAB | Room temperature in aqueous media | [289] |
| Ag 2018  | Up to 70 nm | Spherical | Up to 24 min | Ex situ analysis | Ionic concentration, absorbance, and hydraulic diameter versus time | 3 min (variable) | Continuous stirred-tank reactor, single-phase flow | Ex situ: UV–vis, TEM, DLS, AAS | Silver nitrate | Trisodium citrate | 80–90 °C in aqueous media | [200] |
| Ag 2019  | 2.7–19.0 nm | Spherical | 9–54 s | Ex situ UV–vis | Size and absorbance versus flow rate | 10 s | T-mixer with a helical reactor, single-phase flow | Ex situ: UV–vis, TEM | Silver nitrate | Ethylene glycol | 85–90 °C in an aqueous media with ethylene glycol and PVP | [304] |
| Ag 2020  | 5–80 nm | Spherical and spheroids | Up to 8 min | Seed-mediated growth with in situ optical analysis | Size and absorbance versus time | 5 min | Helical reactor, continuous flow | Ex situ: UV–vis, TEM | Silver nitrate | Trisodium citrate | 90 °C in aqueous media | [70] |
| Ag 2021  | 4–100 nm | Spherical | Up to 250 min | Seed-mediated growth with in situ optical analysis | Size and absorbance versus time | 5 min | Helical reactor, continuous flow | Online: UV–vis, TEM | Silver nitrate | Trisodium citrate | 90 °C in aqueous media | [62] |
| Ag and Au 2006 | Au: ~25–40 nm rod | Au: nanorods | Au: 20 min | Online UV–vis analysis with ex situ TEM | Size (absorbance) versus time | Au: 5 min | T-mixer with a helical reactor, single-phase flow | Online: UV–vis, TEM | Silver nitrate | Chloroaic acid Ascorbic acid Sodium borohydride | 30–50 °C ramped in aqueous media Seeded growth | [318] |
Table 3. Continued.

| Material | Year  | Size            | Shape       | Reaction time [s] | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Type of reactor and flow | Characterization | Precursors | Synthesis conditions |
|----------|-------|-----------------|-------------|-------------------|---------------|-----------------------|--------------------------------|--------------------------|-------------------|------------|---------------------|
| Au       | 2005  | 5–50 nm         | Spherical   | 0.06–1.02 s       | Pseudokinetics ex situ UV–vis, TEM | Size, distribution versus flow rate, precursor concentration | – | Split-and-recombine reactor, single phase | Ex situ: UV–vis, SEM | Chlorauric acid | Room temperature |
| Au       | 2007  | ~2.2–4.2 nm     | Spherical   | Nucleation: 1 s  | Growth: up to 16 s | Multiple in situ measurements | Absorbance, size, and yield versus time | UV–vis: 3 ms SAXS: 130 ms WAXS: 800 ms | Stopped flow device | In situ: UV–vis, SAXS, XAS | Gold chloride | Room temperature |
| Au       | 2010  | 2.0–7.6 nm      | Spherical   | Up to 16 s       | | | | | | | | Room temperature |
| Au       | 2010  | 1.6–3.6 nm      | Spherical   | Online: 0.1–136 s | Aging: up to 10 000 s | Online: UV–vis, SAXS | Size, concentration versus time | SAXS: 130 ms XANES: 117 ms | Stopped flow device | In situ: SAXS, XANES, Gold chloride TBAB | Room temperature |
| Au       | 2013  | 2–37 nm         | Nanorods    | 2–18 min         | Online UV–vis | Size (SPR peak) versus time | UV–vis: 1 min | Straight reactor, single phase flow | Online: UV–vis Ex situ: TEM | Chlorauric acid Trisodium citrate | Room temperature |
| Au       | 2013  | 24–36 nm        | Spherical   | 6.6–13.3 s       | Optical with pseudokinetics | Size versus flow rate | UV–vis: 2 ms | Capillary reactor, droplet flow | Online: UV–vis | Chlorauric acid | Room temperature |
| Au       | 2015  | 2.1–2.6 nm      | Nanorod     | Up to 70 min     | Ex situ UV–vis with SAXS | Size versus time | UV–vis: 2 min | Serpentine chip reactor, single-phase flow | Ex situ: SAXS and UV–vis | Gold(III) chloride hydrate | Room temperature 30 °C in an aqueous media with CTAB |
| Au       | 2017  | Seed: 15 nm     | Cubic       | Up to 120 s      | Seed-mediated growth with kinetic study | Size and concentration versus time | Absorbance: ~2 s SEM: 5 figures for 2–15 s | Serpentine microchannel on glass, single-phase flow | Online: UV–vis Ex situ: SEM | Chlorauric acid | Room temperature 21 °C In aqueous media with cetrimonium chloride (CTAC) |
| Au       | 2017  | 1.0–2.8 nm      | Spherical   | 18 ms            | In situ XAS to inspect the Au reduction | Absorbance versus time | ~4 ms | Microstructured serpentine static mixer, single-phase flow | In situ: XAS Ex situ: UV–vis, STEM, XRD, XPS, ICP | Chlorauric acid | Room temperature In aqueous media with PVP |
| Au       | 2017  | 17.9–25.5 nm    | Spherical   | 55.2–660 s       | Pseudokinetics with ex situ analysis | Size versus flow rate | – | Split-and-recouple (SAR) mixer and coaxial flow reactor (CFR), single-phase flow | Ex situ: UV–vis, TEM, DLS | Chlorauric acid Trisodium citrate | Room temperature 60-100 °C In aqueous media |
| Material | Year  | Size       | Shape          | Reaction time [s] | Kinetic study | Type of kinetic study | Kinetic data (time resolution) | Type of reactor and flow | Characterization | Precursors | Synthesis conditions | Ref.      |
|----------|-------|------------|----------------|-------------------|---------------|-----------------------|-------------------------------|--------------------------|------------------|------------|----------------------|----------|
| Au       | 2017  | 30–180 nm  | Hexagonal prism| 30–600 s         | Ex situ analysis| Size versus time     | ≈30 s                         | T-shaped with a serpentine reactor, droplet flow | Ex situ: UV-vis, TEM   | Chloroauric acid | Piperidine | 80 °C Aqueous media with CTAB | [309]    |
| Au       | 2021  | 12–15 nm   | Spherical     | 216–426 s        | No, but stability tests during operando | Size versus operando time | ≈1 s                         | T-mixer with a helical reactor, droplet flow | Online: UV–vis Ex situ: TEM | Gold(III) chloride | Trisodium citrate + Citric acid | [342]    |
| CdSe     | 2004  | 1.05–1.52 nm | –              | Up to 1600 s     | In situ optical analysis | Emission wavelength versus time versus temperature | Minimum 25 s Microchannel on glass, continuous flow | In situ: PL | Cadmium acetate–TOPO Selenium–tri-n-octylphosphine (TOP) | [305]    |
| CdSe     | 2016  | –          | –              | 1st: 0.2–2 s 2nd: 6–60 s or 20–250 s | Online optical analysis | Emission wavelength versus time | 1st: 10 ms 2nd: 1 s | Serpentine tube, droplet flow | Online: UV–vis | Cadmium oleate Selenium–TOP | 200–290 °C In ODE (1-Octadecene) | [323]    |
| CdSe     | 2017  | –          | –              | Up to 20 min Ligand exchange dynamics | Absorbance versus time | – | Oscillatory flow reactor, droplet flow | In situ: UV-vis | Cadmium oleate Selenium–TOP | Room temperature in toluene | [326]    |
| CdTe     | 2013  | 1.4 nm     | Spherical     | 66 s             | In situ optical microscopy image | Emission wavelength, size versus time, temperature | – | Microchannel on glass, droplet flow | In situ: PL Ex situ: TEM | Cadmium chloride Tellurium–glutathione | 81.5–91.0 °C In water | [327]    |
| CsPbI_x | 2019  | 14–60 nm   | Cubic         | 120–360 s        | Online optical analysis Ex situ TEM | Emission wavelength versus time, temperature, flow rate | Minimum 2 min Helical tube, continuous flow | Online: PL Ex situ: TEM, XRD | Cs PbI_x | Lead(II) halide (CI, Br, I) | 70–180 °C In ODE | [331]    |
| CsPbI₃   | 2021  | 8–12 nm    | Cubic         | 0.6–16 s         | In situ optical analysis Ex situ TEM | Emission wavelength, size versus time, precursor ratio | Minimum 0.6 s Serpentine tube, droplet flow | In situ: UV–vis Ex situ: TEM | Cs PbI₃ | Lead(II) iodide | 110–180 °C In ODE | [290]    |
| CsPbX₃   | 2016  | –          | –              | 0.1–12 s         | In situ optical analysis | Emission wavelength versus time versus temperature | 100 ms | Helical tube, droplet flow | In situ: UV–vis | Cs PbI_x | Lead(II) halide (CI, Br, I) | 120–180 °C In ODE | [87]     |
| FAPbX₃   | 2017  | –          | Cubic         | 9 s              | In situ optical analysis | Emission versus halide ratio versus temperature | 1/8 s | Helical tube, droplet flow | In situ: UV–vis | Cs PbI_x | Lead(II) halide (CI, Br, I) | 40–100 °C In ODE | [297]    |
beam-induced triggering of reactions.[100] In addition, there are artifacts related to sample preparation (e.g., “coffee ring” effect, subsequent particle aggregation). TEM imaging for fine structures is highly dependent on the proficiency of the researcher to handle the equipment and to perform data analysis (refer to ref. [101]). An inaccurately aligned microscope with a large defocus could lead to false images, which are common artifacts. Beam-sensitive materials suffer from degradation under high electron dose and long exposure,[102] hence limiting the choice of gun voltage and analytical time that result in reduced resolution. A relatively recent technique is liquid-phase TEM (LP-TEM) used to perform in situ batch kinetic studies. Currently, this technique is limited by the design of the sample cells and the narrow range of reaction conditions.[100] In particular, the solvent needs to have a very low vapor pressure to be compatible with the ultrahigh vacuum required by the microscope.[103] Some approaches use a sample cell with an electron-transparent window enclosing a liquid film with a thickness <1 µm.[104] State-of-the-art liquid cells are equipped with temperature control and can include electrodes, using modern microfabrication techniques. More detailed information about LP-TEM details and challenges can be found elsewhere.[100,103]

While inductively coupled plasma mass spectrometry (ICP-MS) has been traditionally used to measure elements at trace levels, over the last decade, the technique has been further developed to measure individual nanoparticles in what is called SP-ICP-MS,[105–108] allowing data-rich size distributions of thousands of individual particles. It operates by monitoring individual intensity pulses as a function of the analytical time. The pulses can be directly translated to the mass of each particle through a calibration curve. Details about the mathematical manipulation are reported elsewhere.[103,109] This technique normally requires little method development for a given matrix/analyte and a small concentration of sample material (=0.010 ng mL⁻¹ or in the ppt range).[109] Theoretical calculations of the minimum detectable particle sizes for 40 elements (from the detection limits) were published by Lee et al. in 2014[105] (e.g., ≈3 nm for Au and Ag), however recent advancements in the field have greatly reduced the limits of detection. Hadioui et al.[107] reported the lowest size detection level for silver nanoparticles as 3 nm when using SP-ICP-SF-MS (SF stands for high sensitivity sector field). The basis of this technique lies in the detection of the individual particle pulses above the background (instrumental/dissolved element), which depends on the signal-to-noise ratio. In SP-ICP-MS, the particle pulse needs to be at least 3 times the background, before producing a reliable individual measurement.[108,106] This means that particles that are below the limit of detection can be easily ignored. Such size resolution depends on the instrument used, the element analyzed, the operation mode (normal, collision, or reaction), the method (dwell time, analytical time, etc.), and the sample chemical matrix (solvent, presence of surfactant, etc.). Another limitation of SP-ICP-MS comes from the method used to calculate particle size, in which each particle is assumed as spherical,[109] thus, limiting the applicability of this technique to other geometries. So far, SP-ICP-MS has been successfully applied to plasmonic materials (Au,[111,112] Ag,[106,108,113] and Pt[113,114]) for size inspection but not to optoelectronic materials, probably due to their multicomponent nature.
2.4. Morphology

Particle morphology (geometry and facets) can be inspected using UV–vis, PL, X-ray diffraction (XRD), SAXS, TEM, and SEM. All these techniques can be applied to in situ time-resolved monitoring of particle size information (listed in Tables 2 and 3), except for SEM. However, the morphology of nanoparticles is normally mainly analyzed using TEM.

UV–vis can be used qualitatively/quantitatively to characterize the shape of plasmonic materials. The LSPR response under UV–vis light is not only size-dependent but also shape-dependent. As mentioned above, models such as Mie and Mie–Gans theory can only provide information on spherical and spheroidal nanoparticles. For different shapes, the association between sizes and spectral response is not easy (i.e., modeling is required using numerical approaches, such as DDA), which makes size quantification challenging when dealing with irregular shapes (i.e., non-quasispherical). Nevertheless, it is possible to qualitatively characterize the shape of the particles. Additional limitations of the UV–vis (applied to morphology) are in line with the ones previously expressed for size identification. It is also not possible yet to use UV–vis to identify the morphology of optoelectronic materials.

The shape of optoelectronic materials can also be inferred using PL spectroscopy. For plasmonic nanoparticles, photoluminescence can reveal complex nanostructures, such as Au nanoflowers where the branched structure leads to different photoluminescence intensity to polarized light at specific angles, so that the characteristic anisotropy distinguishes nanoflowers from spherical NPs. It has also been reported that anisotropic semiconductor QDs (e.g., InGaS, Eu@ZnO, or CsPbBr$_3$) have spectral shifts when particles with different aspect ratios were excited, therefore, correlating emission to the aspect ratio of the rods/pyramids. For example, the PL of CsPbBr$_3$ blueshifts as the size along the thickness dimension reduces, changing the materials from nanocubes to nanoplatelets and enabling quantum confinement effects to occur. The use of PL to infer nanoparticle shape is currently limited to anisotropic particles (e.g., plates, rods, etc.).

X-ray-based techniques (e.g., SAXS and XRD) have been applied to the morphological analysis of nanoparticles (e.g., facet and shape identification). SAXS is used to study the shape of nanoparticles (form factor), using an “indirect Fourier transformation” technique followed by the deconvolution of the pair distance distribution function. The analysis of SAXS spectra typically requires some type of prior sample knowledge to analyze one or more constraints. Normally, a given spectrum may have multiple solutions depending on the total number of combinations of particle shape and size, which is one of the limitations of SAXS for shape analysis. In general, there are two approaches to analyzing particle morphologies according to the form factor scattering (e.g., empirical process and direct model). Details can be found in ref. [92]. XRD is an effective technique for crystal structure analysis, providing information about the structure, phase purity, and particle size (XRD is limited to crystalline samples). XRD can also distinguish the growth of each crystal facet, which is proportional to the number of constituent facets with identical forms. As an example, XRD has been used to distinguish between cubic perovskite nanocrystals and nanoplatelets, the latter with extra diffraction peaks. Limitations arise when monitoring particle growth since the growth rate can differ in the presence of different polycrystalline structures, which makes it challenging to relate the growth of individual particles with a particular geometry. This is especially challenging when dealing with polydisperse samples (e.g., different shapes and growing stages). Due to the signal-to-noise ratio, it is difficult to inspect the nucleation/coalescence phase (few nanometers) using traditional XRD. To analyze small crystalline grains, two strategies can be followed, one is to use a high-energy (HE)-XRD and another is to extend the dwell time during data collection. However, the latter approach is not desired as it makes in situ analysis difficult to perform. XRD can be applied in ex situ in combination with other techniques, as elaborated in ref. [124].

Electron microscopes such as TEM provide the most direct information on the morphology of nanoparticles. TEM can image nanoparticles down to a few angstroms in normal bright-field imaging, and can even resolve the atomic structure of the nanoparticles under high-resolution TEM (HR-TEM) mode. TEM can resolve simple geometries, such as spheres, cubes, and polygons immediately from the image. For complex geometries, such as porous materials, depending on the choice of sample holders, 3D information can be obtained by taking image slices by tilting and shifting the grid, therefore, constructing a 3D model of the object. In addition, the structure and lattice contrast can be obtained for crystalline particles through selected area electron diffraction (SAED). The limitations of TEM are the same as the ones presented previously for particle size.

2.5. Composition

The sample composition (i.e., ionic precursor concentration and elemental structure of the particle) can be directly quantified using ICP-MS and TEM–energy-dispersive X-ray spectroscopy (TEM-EDX), and indirectly with UV–vis, PL, and X-ray absorption spectroscopy (XAS). All these techniques can be applied to in situ time-resolved monitoring of composition (listed in Tables 2 and 3), except for ICP-MS. The ICP-MS can be used to monitor the sample composition, and SP-ICP-MS can be used to monitor the individual particle composition. Traditional ICP-MS distinguishes between elements based on the mass to charge ratio, and allows the detection of multielemental traces in an aqueous or organic solvent matrix, reporting concentrations as low as ppb (ng mL$^{-1}$) or ppt (ng L$^{-1}$). This method is also capable of distinguishing isotopes, both stable and radioactive. Limitations arise with the high cost of the equipment when compared to UV–vis (+32 times more expensive), while also requiring a high set of skills and staff proficiency (e.g., knowledge about methodology development and sample preparation). In addition, there are polyatomic mass interferences that can lead to complications when quantifying elements. Nevertheless, there are ways to mitigate their effect – details in refs. [126–128]. There are also limitations coming from inconsistencies in the ion count rates and precision repeatedly measured, which are present when the samples are contaminated or when using a fouled sample.
tubing. The SP-ICP-MS permits the identification of individual particles without chemical digestion, by ionizing the nanoparticles (creating atomic and small polyatomic ions), followed by their respective detection. In terms of the outcomes, SP-ICP-MS allows collecting i) ionic concentrations of the unreacted (or dissolved) elements, ii) particle concentration (number and mass), and iii) mass fraction per element analyzed in an individual particle. The limitations are associated with the limit of particle detection (refer to the size information part for information) and the dwell/settling times of the equipment (for multielemental analysis in a single particle).\textsuperscript{[108,129]} Artifacts can be present when evaluating the composition since not all the elements have the same mass detection limit (directly related to size), it is possible that the technique is biased toward particular elements when analyzing multicomponent samples.\textsuperscript{[130]} The dwell time is associated with the mass pulse (or particle pulse) discretization time resolution and the settling time is the time to change the detector between the elemental mass being analyzed. The settling time is present when using a quadrupole ICP, but it can be neglected when using different ICP technologies, such as time-of-flight inductively coupled plasma. The multiple metal analysis is still under extensive development in SP-ICP-MS.\textsuperscript{[107,130,131]} For details about the limitation of SP-ICP-MS to inspect sample and particle composition, refer to refs. \textsuperscript{[110,131].}

Under bright-field TEM, particle composition for heavy elements (high Z number) against light elements (low Z number) can be qualitatively resolved due to the different contrasts, for example, core–shell Au/Fe\textsubscript{3}O\textsubscript{4} NPs show distinctive darker core and lighter shell under bright-field TEM.\textsuperscript{[132]} Core–shell Fe/Fe\textsubscript{3}O\textsubscript{4} NPs are also identified for the presence of O in the shell which reduces the average contrast of the shell.\textsuperscript{[113]} For elements with similar Z number or complex compositions, the scanning transmission electron microscopy (STEM)–EDX tool equipped in the microscope can directly resolve the composition by histogram as well as elemental mapping.\textsuperscript{[100,102,114]} The limitation of elemental mapping is associated with the similar emission lines from core electrons of different elements, e.g., Al K\alpha (1.486 keV) with Br L\alpha (1.480 keV), which needs to be manually corrected (if known) from the spectrum for higher accuracy. High resolution from EDX mapping is time-consuming (~40 min for a typical map of 200 × 200 nm\textsuperscript{2}), posing the risk of sample degradation, which is in line with the general limitations of the TEM technique. Over the scanning time, grid shift is another artifact that leads to misinterpretation of results. UV–vis can be used to monitor the bandgap of materials, which provides information on compositional changes, for example, when substituting the halide or A-site cation in lead-halide perovskite NCs in solution,\textsuperscript{[135,136]} or the degree of phase separation of mixed-halide perovskites under illumination (giving rise to a redshift in the optical bandgap).\textsuperscript{[117]} Higher-order absorption onsets can sometimes also be observed above the continuum of the absorption spectrum, and these can be due to the presence of phase impurities (e.g., nonperovskite phases that form simultaneously to CsPbBr\textsubscript{3}),\textsuperscript{[138]} higher-order energy transitions in the NC materials, or higher-order excitonic states.\textsuperscript{[139]} UV–vis is therefore invaluable in developing new synthetic strategies to control the composition of NCs and improve their photostability. In addition, UV–vis can be also used to inspect the ionic composition of the sample. For this, the spectral response at a given wavelength needs to be calibrated against concentration, following the Beer–Lambert law. Examples of this analysis have been applied for complexometric dye structures, which act as an indicator, forming a colored complex with metal ions. The limitations of UV–vis relate to superposition effects. Further limitations of this technique have been reviewed by Hendel et al.\textsuperscript{[79]}

XAS is a powerful technique to understand nanoparticle synthesis from precursor to nuclei such as oxidation states, coordination, local order, and surface properties.\textsuperscript{[140]} Depending on the energy of excited core electrons, the spectrum can be divided into X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS).\textsuperscript{[141,142]} XANES determines the precursor conversion by oxidation state, for example, Au(I) to Au(0) distinguished by edge jump.\textsuperscript{[24]} EXAFS detects the surrounding atoms and identifies bonding of the target element, for example, the conversion of ligand-associated P–Se to Cd–Se bond by Se K-edge jump.\textsuperscript{[143]} The time resolution of the XAS technique ranges from 1 to 100 ms\textsuperscript{[144,145]} making it suitable for in situ studies.\textsuperscript{[24,140,146]} Limitations with the XAS technique are mainly associated with an inability to resolve atoms with close Z numbers.\textsuperscript{[147]} Qualitative analysis requires careful calibration of standards; a related artifact is that residue (fouling) is deposited on the observation cell so that the quantification shifts and requires correction.\textsuperscript{[148]} XAS finds its specific advantage in kinetics studies though the information is limited to early stage conversion from precursor to monomer, dimer, etc., therefore, it is usually used as a complementary technique to other techniques in comprehensive studies.

### 2.6. Surface Composition

Herein, surface composition refers to the composition of the molecules chemisorbed on the surface of the nanoparticles such as organic ligands. Such compositions are mainly analyzed using Raman spectroscopy and nuclear magnetic resonance (NMR). Both techniques can be applied to in situ time-resolved monitoring of particle size information (listed in Tables 2 and 3). Additionally, X-ray photoelectron spectroscopy (XPS) and Fourier transform infrared spectroscopy (FTIR) have been widely used in ex situ characterization of nanoparticles, but they are rarely applied to time-resolved studies into the synthesis process, especially in colloidal conditions. In terms of XPS, the traditional instrument requires an ultrahigh vacuum (typically below 10\textsuperscript{−7} Pa\textsuperscript{[409]}) to extend the mean free path of electrons to the range of kilometers (i.e., minimum collision), so that the energy of emitted electrons can be correctly analyzed. However, this ultrahigh vacuum environment excludes the possibility of performing colloidal synthesis. A recent technique allows the characterization to be performed in near-ambient pressure (up to 100 mPa, known as NAP-XPS) for solid–gas interactions where a controlled gas flow is introduced into the chamber against the solid sample surface.\textsuperscript{[409]} This has been a successful approach for studying catalytic activities in situ.\textsuperscript{[150,151]} With respect to nanoparticle synthesis, gas-phase synthesis is only achieved by atomization of the source material,\textsuperscript{[152,153]}

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which at this stage is incompatible with the instrumental setup of NAP-XPS. It is worth noting that single metallic nanoparticles cannot be examined using XPS since the process does not involve a change in the chemical environment; therefore, the NAP-XPS instrument could be futuristically explored with multimetal-alloyed or core–shell nanoparticles. Nevertheless, neither FTIR nor XPS is detailed in this review due to lack of examples at the current stage.

Raman spectroscopy can provide information on a molecular level, and it is useful in nanoparticle characterization such as crystallinity and defects within particles as well as surface compositions. Raman spectroscopy provides a structural fingerprint (spectral patterns) of the chemical sample being analyzed. This information can be used to determine quantitatively or semiquantitatively the amount of substance in the sample, which can have a wide number of physical states (solids, liquids, or vapors). Nevertheless, it is challenging to properly calibrate Raman for quantitative analyte analysis/identification. Surface-enhanced Raman spectroscopy (SERS) relies on metal nanoparticles that enhance the signal from the adsorbed analyte by 10^9–10^11. In this way, SERS reveals the interactions between metal atoms and surface species. Batch-to-batch variations of the SERS plasmonic substrates are one of the limits of using SERS for the determination of organic molecules. In addition, in applications where SERS is performed using nanoparticles colloids (colloidal SERS-active), there are additional concerns with particle aggregation. Although aggregation is beneficial to enhancing Raman scattering, it is often time-dependent, rendering inconsistent measurements over time for a given analyte. An additional problem can be related to the drop-casting of the analyte over a SERS-active solid substrate, which generates a coffee-ring effect. To solve it, it is possible to use a microfluidic platform. Jahn et al. reported a review about the challenges, solutions, and applications for SERS coupled with microfluidic platforms.

NMR spectroscopy can also provide information on the species present on the surface of the nanoparticles. The atoms on the surface and inside the nanoparticles have different chemical environments. Under external magnetic fields, they respond differently to the input radio-frequency pulses, therefore producing chemical shifts on the spectrum. In this way, the ligand-coupled precursor species can be separated from core atoms in nanoparticles. Raman data provide valuable information for the analysis of the consumption of reactants and nuclei formation. However, NMR is limited by low sensitivity (magnitudes lower than other techniques to achieve a good signal-to-noise ratio) in determining synthesis kinetics. As a surface technique, the ligand–particle interaction can be determined, whereas the ligand shell adds another level of difficulty to access core atoms.

Apart from the techniques discussed above, there are other techniques that have been applied for time-resolved analysis. Nevertheless, they are less frequently used for kinetic studies; therefore, they are not detailed here but are present in Table 1. These techniques include oxidation–reduction potentials using an electrode (Eh), high-energy X-ray diffraction (HE-XRD), Fourier transform infrared spectroscopy (FTIR), atomic absorption spectroscopy (AAS), thermogravimetric analysis (TGA), scanning transmission electron microscopy (STEM), field emission scanning electron microscope (FE-SEM), electron paramagnetic resonance (EPR), dark-field microscopy (DFM), atomic force microscopy (AFM), X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDX), wide-angle X-ray scattering (WAXS), inductively coupled plasma-atomic emission spectrometry (ICP-AES), gas chromatography–mass spectrometry (GC–MS).

2.7. Prospective Techniques

In addition to the previous techniques, recent advances on probing acoustic vibration (four-wave mixing (FWM) technique) can also provide information about size, shape, and elastic properties, which relies on the acoustic vibrations of dielectric and metallic nanoparticles. According to Wu et al. in 2017, the mode vibration frequencies are strongly dependent on the size (average and size distribution), shape, and material type, being successfully applied to the monitoring of gold nanoparticle synthesis (time-resolved growth) using reducing agents (e.g., sodium borohydride). The method shows good agreement with SEM, and it can be applied in situ with an optical arrangement like extinction measurements.

3. Monitoring of Synthesis in Batch Reactors

Turkevich et al. pioneered the kinetic and mechanistic studies of metal nanoparticles with their work on the batch synthesis of quasishperical plasmonic Au nanoparticles in 1951. Their ex situ kinetic study of the chemical reduction of chloroauric acid was possible by analyzing periodic samples using an optical ultramicroscope. Over the past couple of decades, significant effort has been made to develop synthetic routes for nanomaterials using a range of physical, biological, and chemical approaches. Each synthetic approach offers different ways to achieve control over nanoparticle size and morphology by controlling the kinetics of the different steps involved in the synthesis (mainly nucleation and growth). Despite these efforts, exhaustive time-resolved kinetic data of nanoparticle synthesis are not widely reported. As a result, nanoparticle synthesis methods are still under substantial development, with emphasis on not only improving kinetic control but also reducing production cost and expanding the properties/applications of the nanomaterials.

In this section, we focus on the kinetic and mechanistic information obtained during the synthesis of plasmonic and optoelectronic nanomaterials in batch reactors with the aim of i) surveying time-resolved data with ex situ/in situ capabilities, ii) discussing selected studies to highlight the importance and differences between in situ and ex situ characterization, and iii) detailing the limitations of batch reactors in terms of reproducibility and time resolution.

3.1. Conventional Synthetic Methods in Batch Reactors

The conventional and most popular method for the batch synthesis of plasmonic nanoparticles (e.g., Ag, Au, Mg, and
Pt) consists of the chemical reduction of an ionic metal precursor by a reducing agent, normally in the presence of capping ligands for particle stabilization.[55,185,186] The process is normally conducted by hot injection (HI) or drop-casting of the metal precursor into a reactive medium. The resulting materials come in a form of spheres, nanowires, pyramids, octahedra, prisms, and cubes depending on the reaction conditions, with the nature of the capping ligands used having a strong effect.[185,187–190] Details about the synthesis of quantum dots and perovskites via this chemical route have been reviewed in 2017 and 2021 in refs. [1, 191]. By contrast, the synthesis of optoelectronic nanoparticles (e.g., CsPbBr$_3$, MAPbBr$_3$, and CdSe) typically consists of the HI of a precursor (e.g., Cs-oleate) into an organic solvent (e.g., 1-octadecane) which has the other precursor (e.g., PbX$_2$) mixed with acidic and amine ligands.[192] In HI, the precursor is injected while the reaction mixture is heated to a set temperature, and the reaction is stopped by cooling.[1,193] The cooling rate can influence the size and size distribution of the resulting nanoparticles. An alternative approach is ligand-assisted reprecipitation (LARP), which is similar to HI, but the reaction mixture is quenched by the addition of an antisolvent. Typically, nanoparticles are synthesized in a controlled, inert environment (e.g., in N$_2$ or Ar-filled Schlenk line), especially if the reaction mixture is heated (as in HI), but more recent work on LARP of perovskite NCs has shown that these NCs can be grown under standard lab conditions in open atmospheres.[1,194] The synthesized materials come in the form of quantum dots or nanoplatelets, depending on the precursors and ligands used, as well as the volume ratio of the precursors. Details on the synthesis of lead-halide perovskites have been reviewed in detail in 2021 in ref. [1].

Most of the material synthetic studies use batch reactors, which consist of a vessel that can be equipped with an impeller and/or baffles (added to promote mixing near the walls and avoid dead volumes), Figure 2. Typically, the mixing is initially promoted by the injection of some of the precursors (i.e., HI method), followed by high magnetic stirring rates inside the reactor, leading to a characteristic turbulent flow regime – chaotic fluctuations of pressure and flow velocity patterns.[196,197] Depending on the setup adopted (vessel/impeller/baffles) and operation conditions, it is possible to have the presence of different flow patterns and secondary flows, which result in well-mixed regions but also, potentially, segregated ones. These segregated regions can be islands of high concentration and stagnant dead flow zones. More details about the hydrodynamic features of stirred tank reactors can be found in refs. [197–199]. The presence of nonuniform local concentration profiles leads to different nucleation and growth rates within the reactor,[200] density number (particles per volume), particle sizes, and reaction yields. From a macromixing point of view, the mixing performance of a batch reactor is measured by the time the bulk requires to achieve homogeneity (mixing time), being

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**Figure 2.** A–D) Schematics of typical batch reactors/setups used to perform time-resolved studies of nanoparticle synthesis. The “measurement time resolution” (time interval between two consecutive samples) and the “initial measuring time” (time to reach homogeneous concentration and temperature) depend on the setup adopted. From left to right, setups are sorted by order of improving these parameters. The most promising apparatus in terms of minimizing initial measure times are systems based on flow reactors (discussed in Section 4), and the less suitable for time-resolved studies are batch reactors equipped with ex situ characterization. (A) Traditional batch apparatus with ex situ analysis. (B) Batch apparatus with in situ multiple probing (pH, UV–vis, and Eh). (C) Online batch apparatus with a recirculating line connected to a SAXS cell. Drawn based on ref. [195]. (D) Stopped-flow apparatus tailored to have a rapid and reproducible injection of the reagents into a probing cell (in situ SAXS). From a macromixing point of view, the mixing performance of a batch reactor is measured by the time the bulk requires to achieve homogeneity (mixing time), being
defined as uniform concentrations within the whole reactor (details about mixing time can be found in ref. [197]). In a similar way, heat transfer should be considered with a proper assessment of the time required to reach homogenous temperature across the reactor (heating time). Both, mixing and heating times will determine the initial measuring time (time to reach homogeneous concentration and temperature). This is especially relevant when considering fast kinetic time-resolved studies in batch.

Fast syntheses are considered those where high levels of conversion are achieved within a few seconds of reaction. Metal reduction with strong reducing agents such as sodium borohydride, and hot injection coprecipitation of CsPbBr₃, are typical examples. On the other hand, slow syntheses are those that require minutes (or longer times) for completion. There is a general agreement that in the reduction method,[23,189,201] a high nucleation rate can be obtained in the presence of excess strong reducing agent (e.g., sodium borohydride, $E_{\text{red}} \approx -1.24$ V vs standard hydrogen electrode (SHE)[202]), leading to nanoparticles with sizes below $\sim 5$ nm.[201,203] Mild/weaker reducing agents (e.g., methanol ($-0.39$ V)[204,205] trisodium citrate ($-0.18$ V)[26,189,203,206] ascorbic acid ($-0.33$ V)[46,207–209] and DMF ($\sim-1.9$ V) (N,N-dimethylformamide)[210] slow down the nucleation and reduce growth rates,[203] leading to particles sizes above $\sim 5$ nm. Such mild/weaker reducing agents are particularly interesting to limit secondary nucleation when growing initial seeds in the seed-mediated multistep synthesis.[31,34,211]

As a general rule of thumb, smaller particle sizes are formed at higher reduction rates, owing to an increase in the nucleation rate, which leads to a higher number of particles.[211] For instance, Hopper et al.[211] disclosed how different electron carriers ( biphenyl $E_{\text{red}} \approx -2.60$ V vs SHE, naphthalene $-2.51$ V, and phenanthrene $-2.46$ V) affect the final particle size of Mg nanoparticles. As the reduction potential becomes more significant (i.e., more negative), the nucleation rate increases, leading to smaller particles for biphenyl (size $\sim 120$ nm) when compared to naphthalene and phenanthrene (size $\sim 250$ nm). While this trend (smaller sizes for higher reduction rate) holds in many studies,[24,175,213,214] it is not always applicable, mostly because the mechanism can play a role in shifting the balance between nucleation and growth rates. For example, the case of gold nanoparticles synthesized using trisodium citrate at different pH values (with chloride and/or hydroxide as the ligand).[215] The reduction potential of Au(III) complexes formed during the synthesis is strongly pH-dependent,[215,217] which has an overall decreasing trend with increases in pH (starting at pH $\approx 5.8$). As reported by Ji et al.[215] at low pH (e.g., $\sim 3.7$), the reaction is too fast to be controlled, resulting in larger particle sizes (highly polydisperse, >30%) than when using a lower reduction potential (slower rates for pH $\geq 5.8$, polydispersity of $\approx 7\%$). The coarse growth at low pH relates to the presence of not-well separated seed particle formation and seed-mediated growth.[206] These examples emphasize that to tailor or control the final size and morphology of nanomaterials, it is critical to pinpoint the timescale and rates of the different mechanistic phases, such as nucleation/coalescence, growth, and cessation of growth.

For the fast reduction of gold precursors with sodium borohydride during the synthesis of gold nanoparticles, it is believed to achieve full conversion of the metal precursors in less than 1 s (nuclei generation) at room temperature.[218] The authors supported their claim based on a visual inspection of the change in color of the reaction solution mixture from light yellow to orange, indicating the reduction of gold ions into metallic gold. However, an additional 160 s of mixing and heating was necessary for nuclei growth by sintering until stability was reached (according to ex situ monitored by UV–vis). The stability means the final thermodynamic state when there is the cessation of particle growth. Similarly, claims of instant nuclei generation are also reported in the literature for the synthesis of other plasmonic metals such as silver[23,203] and platinum[219] when using borohydride as a reducing agent (ex situ monitored via UV–vis and TEM). For silver, Polte et al.[24] reported a prompt increase in the absorbance around $390$ nm up to $2$ s (related to the particle formation), followed by mild changes in the absorbance up to $7$ min. These observations were made by carrying out the synthesis inside a stirred UV–vis cell (in situ probing, measurement time resolution of $\sim 0.2$ s). In the same line as plasmonic materials, optoelectronic materials have a nucleation time of a few seconds (in this case via precipitation), followed by growth and stabilization, which can be extended up to tens of minutes. Prins et al.[193] reported nuclei formation (in situ monitored by SAXS) of CdSe nanocrystals within the first 5 s of reaction and quasistationary state after 16 min. For the optoelectronic material CsPbBr₃, the hot-injection coprecipitation method is also considered fast, being typically quenched within 5 s to obtain uniform size distribution (standard deviation as low as 8% (based on TEM), also characterized by narrow PL FWHM at around 80 meV).[220] To date, the hot-injection method is believed to follow a La Mer nucleation and growth mechanism, i.e., there are distinctive nucleation and growth stages divided by key monomer concentration levels.[221]

On the other hand, slow syntheses are normally complete after minutes of reaction. To monitor the slow reduction of metals with trisodium citrate, Polte et al.[24] monitored (ex situ SAXS/XANES) the reduction of chlorauric acid from 75 to 85 °C. Interestingly, only 20% of the gold precursor was transformed into nuclei (or particles) within the first 60 s at 75 °C, followed by aggregating for 20 min. At 75 °C, the process can take up to 70 min to reach stability, but only $\sim 25$ min are required at 85 °C. Comparable time-resolved results and trends have been reported in the literature for other plasmonic materials, such as silver[189] (ex situ TEM and UV–vis). In conclusion, the reaction timescales can greatly range from milliseconds (fast reactions) to tens of minutes (slow reactions) depending on the reaction kinetics, thus, both requiring different requisites to acquire time-resolved kinetic data and identify the different mechanistic steps.

There are numerous ways of controlling the kinetic rates and thus, the relevant timescales, such as varying the i) concentration of precursors, ii) relative ratio between precursors and ligands, iii) injection temperature,[222] to name a few. Although these parameters have been vastly explored for plasmonic and optoelectronic materials,[1,46] the number of data-rich kinetic time-resolved studies is only a small fraction of the literature data, with the typical study just focusing on single-point data of the final resulting material. This limitation is recognized in some studies, for example, Pan et al.[223] stated that their
3.2. State-of-the-Art Kinetic Studies of Material Synthesis in Batch Reactors

Monitoring nucleation and particle growth rate is central to establishing reliable (i.e., repeatable/reproducible) synthetic protocols in the lab, as well as getting critical information for the scale-up into large batch reactors. Conventionally, ex situ kinetic studies imply manual sample collection, sometimes reaction quenching (e.g., ice bath, change in pH, etc.), and/or stabilization, followed by ex situ characterization of the particle population. The time covering collection, quenching (if applicable), and sample preparation before a characterization analysis is defined as “sampling time” ($t_s$). By contrast, in situ kinetic studies use probes that collect real-time data directly from the reactive media (e.g., no need for sample collection). Some studies also consider “in situ” analysis when rapid sampling and instant analysis are performed without manipulation (i.e., rapid analysis using a UV–vis cuvette), however, this adds sampling errors (e.g., time differences), which need to be assessed (ideally with an error propagation study). In this review, we only consider in situ analysis where no sampling or manipulation is done, even if the authors follow a different classification. In both cases, ex situ, online, and in situ monitoring of nanocrystal synthesis, are limited by the same “initial measurement time” ($t_{m0}$), defined as the time required to ensure that the reaction medium is homogeneous (temperature and concentration) at which the first sample can be reproducibly taken. This concept considers both mixing and heating times, and its value depends on the mass and heat transfer rates as well as the reactor setup (e.g., volume, shape, presence of impellers/bafflers) and the synthetic method used (e.g., volume of the precursor solutions and injection position). Quantification or estimation of the initial measurement time is neglected in most of the kinetics studies with time-resolved data referred to in Table 2. Hence, initial measurements might be reported before a homogenous reactive medium is achieved, which leads to local concentration profiles inside the reactor – here the “initial reported time” ($t_{r0}$) is lower than $t_{m0}$. The lack of assessment of the initial measurement time is likely to be one of the reasons behind the persistent unreliable and/or unreproducible data at low reaction times (approximately seconds). Other two important parameters are the “measurement time resolution” ($\Delta t_m$) and the “analytical time” ($t_a$). The measurement time resolution (or just time resolution) is the minimum time difference between two consecutive samples analyzed. The analytical time is defined as the time required for a technique to analyze a sample (refer to Table 1 for the minimum time required for each technique). Following this nomenclature, a compilation of state-of-art kinetic time-resolved experimental studies is present in Table 2 for both ex situ and in situ characterization of plasmonic (Ag, Au Al, Mg, and Pt) and optoelectronic nanoparticles (CsPbBr₃, MAPbBr₃, and CdSe). It is important to note that different nomenclatures are used in different studies due to the lack of standardization; however, Table 2 offers a direct comparison of the data for the first time.

3.2.1. Monitoring of Nanomaterial Synthesis in Batch Reactors Using Ex Situ Characterization

Most of the kinetic studies reported in the literature on batch synthesis of plasmonic and optoelectronic materials involve ex situ analysis, through characterization techniques such as UV–vis, TEM, SEM, XRD, and SAXS. A combination of multiple analytic methods can be used for each of the sample points since a given sample volume can be shared between techniques (Figure 3A). In theory, ex situ characterization has no constraints on the number of techniques used per sample point considering that the reaction volume is large enough for sample collection. For ex situ analysis, the analytical time ($t_a$) is not relevant, as samples can be analyzed postsynthesis after quenching or stabilization. The main limitation of ex situ analysis is the low time resolution ($\Delta t_m = \text{the time between samples}$), being its minimum value determined by the sampling time ($t_{m0}$). The number of data points analyzed is normally scarce during time-resolved analysis, normally missing key kinetic data between consecutive collection points (or times). According to the ex situ studies listed in Table 2, the $\Delta t_m$ (time resolution) can be estimated to be greater than $\approx 30 \text{ s}$ for batch reactors (often reported in the minute timescale). Another limitation is the presence of errors that occurred during sample collection and preparation, which are normally directly associated with the skills of the researcher.

For fast reactions, where most of the precursor ionic concentration is consumed in the first seconds of the synthesis, a measurement time resolution of ($\Delta t_m \approx 1 \text{ min}$) impedes the access to early mechanistic information. As an example, to monitor the reduction of silver with sodium borohydride, it is necessary to have a time resolution of at least 200 ms or finer. Nonetheless, some studies attempted to follow kinetics with a much coarser time resolution ($\Delta t_m$) in the order of 1 s to 1 min. For instance, Kooyk et al. reported an ex situ HR-TEM study of CsPbBr₃ nanoparticles over four different growth durations (1, 4, 20, and 40 s), being able to track the focusing and defocusing of the NP size distribution. Even for slow reactions, when full conversion needs dozens of minutes to occur, a measurement time resolution of $\approx 1 \text{ min}$ can still hinder the extraction of mechanistic information. An example of this has been reported for magnesium synthesis by Hopper et al., where the synthesis continued for 1000 min before reaching a stable state (Figure 3B-Mg). The authors observed that two morphologies (hexagonal platelet and rod-shaped nanoparticles) are formed simultaneously from the beginning of the reaction ($t_{r0} = 1 \text{ min}$, where $t_{r0}$ is the initial reported time), having a yield of $\approx 2\%$ and particle sizes of $\approx 80$ and 90 nm. Although the authors reported that the synthesis of both morphologies have similar kinetic rates, this approach cannot provide information on the early mechanistic stages of the reaction within the first minute.
In addition to mechanistic information, ex situ monitoring of batch material synthesis has also difficulties providing information on the metal precursor consumption kinetic rate, which does not provide sufficient time resolution to provide a comprehensive inspection of the synthetic method. For instance, Polte et al.\cite{24} stated that increasing either the reaction temperature or the initial concentration of gold precursor accelerates the particle formation process. Quantitatively, increasing the temperature from 75 to 85 °C doubled the overall reaction rate (nucleation/coalescence phase at 85 °C is ≈10 min), but the final particle sizes (thermodynamic state) have similar values of ≈7.7 nm (radius). Although the kinetic data show a faster reduction of Au(III) at 85 °C than at 75 °C and different time frames per kinetic phase, thermodynamic stability plays an important role in the reaction.

### 3.2.2. Monitoring Synthesis in Batch Reactors with In Situ Characterization: Sampling Strategies and Benefits

In situ monitoring of batch material synthesis requires the placement of probe(s) in direct contact with the reaction media. Some strategies involve placing the probe in the batch reactor\cite{61,104,175,227,239} and the use of stopped-flow cells.\cite{193,212,240}

In the stopped-flow approach, the reactants are continuously mixed into the probing cell until the analysis starts (Figure 2D). At that point, the continuous liquid flow is stopped, and the system behaves like a batch. This approach aims to reduce the initial measurement time and could be considered in the interface between flow and batch reactors. Another strategy to monitor the reactive media is to partially recirculate the media into a probing cell (e.g., SAXS, UV–vis, TEM) using a peristaltic pump.\cite{195,241} (Figure 2C). This strategy assumes that the content of the bypassed solution is representative of the reaction media at the instant of analysis. Since there is a recirculation, there might be the presence of artifacts, therefore we have defined the strategy as an “online” approach. Typical systems equipped with in situ/on-line detectors (e.g., in situ SAXS) are shown in

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**Figure 3.** Examples of time-resolved data obtained using ex situ and in situ monitoring in batch reactors. A) Example of a time-resolved mechanistic study for gold synthesis where multiple characterization techniques were used (in situ SAXS, in situ UV–vis, and ex situ TEM). Adapted with permission.\cite{175} Copyright 2012, American Chemical Society. A1) Particle diameter (d) and the number of particles (normalized by its initial number) as a function of reaction time (3 h). B) Typical time-resolved kinetic data information (normalized by size) reported using different analytical techniques. The time-resolved data display the commonly reported times (t_m) and measurement time resolutions (Δt_m) for batch reactors according to the type of monitoring used. The particle size has been normalized according to the size reported at the end of the synthesis (d_l), which has the following values: 421 nm for Mg (ex situ TEM),\cite{181} 16.07 nm Au (online SAXS),\cite{199} 3.94 nm for in situ Au (in situ SAXS),\cite{193} 4.62 nm for CdSe (in situ SAXS),\cite{193} and 2.64 nm for Pt (in situ TEM cell).\cite{225}
Figure 2. So far, X-ray spectroscopy (SAXS, XANES, WAXS, and XRD), UV–vis, TEM, AFM, pH, and Eh (reduction potential) have been used in batch synthesis to characterize in situ plasmonic and optoelectronic nanoparticle synthesis (as listed across Table 2).

For metal nanoparticles, the literature contains a considerable number of studies for the synthesis of Au, Ag,[227,241,245–249] Al,[68,181,182] and Pt nanoparticles[204,225,250–252] with in situ/online analytics (refer to Table 2 for more studies). However, for Mg and Al, only ex situ kinetic studies have been reported in batch.[68,181,182] This can be related to difficulties when probing in situ chemical systems with pyrophoric precursors, which need a constant inert atmosphere,[81] but also the presence of chemical precursors that are not transparent to UV–vis and X-ray. Consequently, the probing cells and analytical method need to be tailored to such systems. In addition, both Mg and Al have different morphologies during synthesis, which adds extra characterization challenges, mainly because in situ techniques need to monitor multiple populations of different shapes during growth (e.g., particularly difficult when using UV–vis). The inability to monitor Mg and Al nanoparticle growth in situ introduces complications when attempting to determine the mechanism behind particle nucleation and growth. For instance, in 2019, a kinetic time-resolved ex situ study was reported by Clark et al. for alumina nanoparticles.[86] The reaction was monitored from 30 to 120 min, with a relatively large time resolution of 20 min. In this case, the synthesis of the Al nanoparticle is mediated by a stoichiometric catalyst (the Tebbe’s reagent), directing the earliest stages of nucleation and growth. Since this is fundamentally different from seed-mediated growth, it adds an extra layer of complexity, which only in situ probing can solve. Optoelectronic nanoparticles have also been monitored with in situ characterization (CdSe, CsPbBr3, ZnO, and PbS[182,193,253–256]). However, it is interesting to note that the number of studies (≈5) for these materials is considerably lower than those reported for plasmonic nanoparticles (≈30 studies). This difference can be associated with the maturity of the plasmonic field, and their characteristic rapid kinetics (often labeled as ultrafast synthesis of optoelectronic materials,[1,257] being usually completed within seconds of reaction time) for a wide variety of the precursors and reaction conditions.[193,220] This makes the batch synthetic approach of optoelectronic materials less suitable for studying kinetics.[258,259] These aspects will be further discussed in the flow synthesis section below.

In situ probing overcomes the measurement time resolution (ΔtM) limitations of ex situ characterization, being capable of providing time resolutions lower than 1 s.[193,212,260] when using, e.g., SAXS and UV–vis, which is a resolution suitable to access the early mechanistic information. Now, the time resolution is no longer restricted by the sampling time (t0 = 0) but instead is equal to the instrument/technique analytical time (ΔtM = t0). Details about the analytical time of the common techniques are listed in Table 1.

When monitoring a batch reactor with in situ probes, the main limitation is associated with the reactor mass and heat transfer rates. Both rates are key to defining when the system reaches homogeneity, and thus, they dictate the required time before starting measuring data reliably and reproducibly (t0). Based on the studies listed in Table 2 and Figure 3B, the lowest initial reported time (t0) can be roughly estimated as ≈30 s for traditional batch reactors (i.e., stirred tank reactors with a volume higher than 1 mL). This excludes studies performed with a liquid-TEM reactive cell or with stopped-flow devices. Such initial reported times are in line with typical values reported for mixing times inside a stirred vessel (e.g., ≈20 s).[197] It is important to highlight that it is possible to achieve t0 < 30 s using traditional batch reactors,[193] but the mixing in the device needs to be properly assessed (refer to ref. [197] for empirical correlations relating to mixing time and reactor characteristics). Interestingly, for stopped-flow devices, the mixing characteristics also need to be properly assessed. For instance, when using laminated stream mixers (µ-mixers; side-by-side contact of miscible liquids) with a 500 µm wide channel, the mixing time is reported to be ≈30 s,[15] but could go down to 0.2 s when using a channel with of 40 µm.[35] Some of the studies overcome this problem by slowing down both nucleation and growth rates at room temperature, adopting a nonconventional combination of gold precursor and mild reductants.[175,227] For example, Koerner et al.[175] monitored gold nanoparticle synthesis (in situ SAXS and UV–vis) using chloro(trimethylphosphine)gold(I) and t-butyamineborane as the metal precursor and reducing agent, respectively. The reaction was followed from 1 to 150 min with a measurement time resolution of ≈30 s, being able to reveal four distinct mechanistic regions: i) initial burst (<1 min; the size of ≈1.2 nm), ii) rapid growth/drop in number density (≤25 min), iii) slower particle growth, and iv) cessation of particle growth. For this reactive system, an ex situ study would have easily missed the initial burst and rapid growth, since the data will be scarce and not statistically significant to provide quantitative conclusions.

Unquestionably, the kinetic mechanism associated with particle nucleation and growth is closely linked to the studied material, as such, the number/characteristics of the mechanistic stages can be a motive of discussion in the literature.[190,227,261] Nevertheless, independently of the material, most of the ex situ studies reported in Table 2 can only monitor (with statistical significance) the later stages of the synthesis, with a focus on slow particle growth and cessation of particle growth (thermodynamic state). Thus, not being able to provide key information about the nucleation phase (e.g., number of particles, reaction rate, and nuclei size). This applies to cases with both rapid and slow kinetics systems. For instance, even for an especially slow system requiring 60 h[262] (a particular case of Pt nanoparticle synthesis), ex situ analysis could not provide the time resolution required to closely inspect all the mechanistic growth stages. Although the measurement time resolution could be reduced from 2 h to a few minutes, this would have implied a vast increase in the number of sampling points (manually collected). Hence, in situ monitoring is clearly beneficial to achieving kinetic information, since data collection is no longer a problem. This can be illustrated by two examples covering plasmonic and optoelectronic materials’ batch reactors.

For plasmonic materials, it is expected that increasing the metal precursor concentration (keeping the ratio of reducing agent/precursor), increases the reduction rate, leading to a higher number of particles and smaller particle sizes (final state).[24,210] However, Chen et al.[212] showed that this is not the case when studying the formation of gold nanoparticles.
using t-butylamineborane as a mild reducing agent for \( \approx 200 \text{ min} \). When the gold precursor concentration was increased, the particles became larger, and their number decreased. They suggested the existence of a parallel reaction that inhibited the reduction of free Au\(^+\) to produce Au\(^0\), promoting growth rather than nucleation. The in situ SAXS time-resolved data (\( \Delta t_{\text{nuc}} = 5 \text{ min} \) and \( t_{\text{0}} = 2 \text{ min} \)) coupled with in situ UV–vis and WAXS supported this theory, which would have been otherwise challenged if only ex situ characterization had been reported (no sufficient points, probing errors, etc.).

For optoelectronic materials, the importance of in situ monitoring in batch synthesis can be exemplified by the study by Prins et al.,\[193\] where CdSe hot-injection synthesis was monitored with a measurement time resolution (\( \Delta t_{\text{nuc}} \)) of just 100 ms (in situ SAXS) using cadmium oleate and trioctylphosphine selenium as precursors. The authors used a stopped-flow device (shown in Figure 2D) to lower \( t_{\text{exf}} \), reporting a \( t_{\text{0}} \) of \( \approx 3 \text{ s} \) (data shown in Figure 3B). Interestingly, this study revealed that under these conditions, nucleation and growth proceeded within \( \approx 300 \text{ s} \) (varying with temperature). The data-rich study allowed the authors to identify the presence of an extended nucleation stage (up to \( \approx 40 \text{ s} \)) along with growth during 15–20\% of the reaction time. The authors reported this being comparable to what is observed in some metal syntheses, where nucleation and surface-catalyzed growth is observed in contrast to the conventional La Mer mechanism. These studies represent the benefits of in situ monitoring of nanomaterial syntheses in batch reactors in comparison to ex situ characterization, mainly due to the enhanced time resolution and enlarged data set.

3.2.3. In Situ Coupled with Ex Situ Characterization

Despite the potential of in situ monitoring for the batch synthesis of nanomaterials, most of the studies combine real-time observations with ex situ analysis (Table 2). There are several main reasons behind such a combination of techniques: i) challenges of having several in situ probes accessing directly the same reactive media limits the number of in situ techniques that can be simultaneously used, ii) the impossibility of coupling some in situ techniques (e.g., in situ SAXS and in situ TEM), and iii) the large analytical time required for some of the techniques (ex situ TEM, DLS, etc.) which can be superior to the kinetic time resolution required (e.g., minutes to hours per sample). Koerner et al.\[175\] discussed that only a combination of characterization methods (e.g., in situ UV–vis + SAXS, and ex situ TEM) can reveal all the sufficient information required for a detailed kinetic study. Depending on the material studied, a kinetic study might need to include information about mean size, particle volume fraction, number density, and their distribution.\[175\] The authors indeed confirmed that individual use of UV–vis, SAXS, or TEM characterization cannot provide enough parametric information through the initial process of nucleation and growth. Individually, UV–vis spectroscopy cannot decouple size and concentration information, TEM normally introduces artifacts while dealing with scarce sample points, and SAXS cannot describe the shape of the particle distribution.\[175\] Very importantly, there is a general agreement among the studies using multiple techniques (in situ and ex situ), that it is important to monitor a single synthesis to avoid batch-to-batch variations leading to discrepancies between the different characterization techniques (e.g., collecting SAXS data and ex situ TEM) to improve the accuracy and reliability of the study. Nevertheless, due to the challenges of having multiple in situ probes, this is not always the case. Indeed, the literature contains several examples where kinetic studies have been carried out using a number of syntheses under the same reaction conditions but using a different characterization technique each time (e.g., UV–vis assessed in a cuvette + SAXS accessed in an X-ray cell \[23\]). Here, precautions need to be considered when combining the outcomes, since the results can be significantly different due to different mixing patterns (refer to flow section), slight changes in the reaction conditions,\[26,226,263\] etc. This will be discussed in more detail in the reproducibility section.

3.2.4. Potential Impact of Capping Ligands in Kinetic Studies

In the synthesis of plasmonic and optoelectronic materials in batch, it is common to find organic acids (e.g., long-chain carboxylic acids) and bases (e.g., alkanethiols and alkylamines) used as capping ligands\[51,54,100,185,264\] to prevent aggregation and/or promote preferential growth toward a desired size/shape. Most of the time-resolved kinetic studies listed in Table 2, with sporadic exceptions, use capping ligands, such as polyvinylpyrrolidone (PVP),\[214,218,245,246,264\] oleic acid,\[225,261\] oleylaminate,\[185,225,261,265\] ethylene glycol,\[214,218,264\] trisodium citrate,\[189,206,212,242,243\] etc. The presence of these molecules is known to affect the nucleation and growth rates. For Pt nanoparticles, the presence or absence of surfactants can go beyond particle stabilization. Surfactants can alter the ionic stabilization of polynuclear Pt\(_n\)Cl\(_m\) complexes, which are species present in the reaction media before particle nucleation is triggered.\[205\] Consequently, these complexes affect the nucleation and formation of Pt NPs.\[205\] Some capping ligands can also adsorb preferentially on the specific facets of particles, modifying their surface energy, playing a role in the relative growth rate of different facets. To highlight this behavior, a study was conducted for Pt NPs with in situ TEM and time-resolved data (from 2 to 150 s, \( \Delta t_{\text{nuc}} = 0.5 \text{ s} \)), using oleylamine and oleic acid.\[225\] The results show no blockage in the attachment of atoms to the nanoparticle surface during the early stage of growth (up to 70 s), having a similar growth rate for all the facets (111, 011, and 100). During the subsequent period (above 70 s), there is preferential growth in the facets (111) and (011). Hence, the authors concluded that the final shape is not defined by thermodynamic equilibrium, but by the ability to selectively attach ligands on the facets of the particle, affecting the growth rate. The presence of oleylamine (reducing and capping agent) was also studied for silver nanoparticle synthesis at \( \approx 160 \text{ °C} \)\[185\] (ex situ analysis), where the initial stage of nucleation and growth happened in the first 10 min with only \( \approx 7\% \) yield, followed by slow particle growth, which lasted several hours (up to 8 h for 80\% yield). The authors showed that the hydrodynamic size of the Ag nanoparticles decreased exponentially when increasing the oleylamine concentration. They suggested that as the concentration of oleylamine increases, the tendency of agglomeration decreases, increasing the electrostatic repulsion. This
will certainly affect the kinetic data. The importance of different ligands (length of alkyl chain) was also emphasized by an in situ time-resolved study for gold nanoparticles (Koerner et al.\textsuperscript{(175)})). They concluded that the length of the alkyl chain has a low impact on the overall growth process, having an effect only at higher reductant concentrations (1/11, ratio of metal precursor to reducing agent). For optoelectronic nanoparticles, there are no in situ time-resolved studies to inspect the effect of ligands (in batch). To date, CsPbBr\textsubscript{3} nanocrystal synthesis\textsuperscript{(223)} has been monitored using ex situ TEM (single-point analysis – final state) in the presence of several capping ligands, ranging different lengths of carboxylic acids and amines. Interestingly, the authors reported a correlation between the sizes and shapes of the crystal (nanocubes and nanoplates) with the chain length of the ligand, in that decreasing the length of carboxylic acid results in a more monotonic increase in the size of the perovskites. Nevertheless, due to the ex situ nature of the study, the authors stated that further understanding of the nucleation and growth would require more in-depth modeling and careful kinetic studies. In conclusion, ligands of different nature are normally used in batch synthesis to control and tune the size and morphology of plasmonic and optoelectronic particles. They are particularly key in controlling the agglomeration and/or aggregation of the nanocrystals under the characteristic turbulence type mixing in these reactors. As a consequence, the mechanistic and kinetic studies might be affected by their presence.

3.2.5. In Situ TEM versus Other In Situ Characterization Techniques

In situ TEM characterization of batch synthesis is inherently different from other in situ characterization techniques such as in situ SAXS, in situ UV–vis, etc. During in situ TEM synthesis, metal precursors are normally reduced directly by the electron beam, which has a higher reduction potential than using a chemical reducing agent in a conventional reduction synthesis. Indeed, in some cases, in situ TEM synthesis is considered closer to physical methods than chemical ones.\textsuperscript{(244,247,248,256,260,266)} In some cases, studies were designed to combine the beam-induced synthesis, followed by a chemical reduction, to better mimic the standard reduction chemical method. It is noteworthy that imaging liquids with in situ TEM is a recent technique,\textsuperscript{(100,104,247)} where research has been focused on the design of LP-TEM cells.\textsuperscript{(100)} The control of the reaction conditions in these TEM cells is challenging (in terms of temperature and/or pressure)\textsuperscript{(100)} as well as ensuring an efficient mixing of reactants during the synthesis.\textsuperscript{(267)} It provides interesting capabilities for the visual study of material transformations and particle growth.\textsuperscript{(231,247,248,249,256,260,268)} Most of the studies with in situ TEM listed in Table 2 reported a total reaction time ranging from seconds to a few minutes when using a liquid-TEM cell (e.g., \( \approx 25\) s to \( \approx 7\) min) in contrast to studies with conventional batch reactors which report longer reaction times normally until completion is reached. An example of such a study was reported by Zheng et al.\textsuperscript{(104)} for the synthesis of platinum nanoparticles. The reaction was achieved by confining reactants inside a TEM cell of about 200 nm in thickness. The chemical system consisted of platinum(II) acetylacetone and oleylamine as a salt precursor and reducing agent, respectively. The authors reported time-resolved size and number density with a resolution of \( \approx 0.5\) s for a reaction time of 115 s. Initially, the solution was exposed to an electron beam for a few seconds to trigger the formation of silver nuclei and to focus the imaging. Interestingly, it was shown that up to 21 s after the nuclei formation, the number density gradually increased up to a maximum value. Subsequently, it dropped considerably and eventually settled. This is a similar mechanistic trend that has also been reported for other plasmonic nanoparticles materials such as silver\textsuperscript{(21)} and gold,\textsuperscript{(24,175)} even if the kinetic rate of the different mechanistic stages is different. Although the TEM approach can only provide (to date) qualitative information about the rate of reactions, this technique provides key atomic level information that aids to explain particle growth in complex environments. For instance, it has been possible to follow particle growth in complex environments, such as the ones under preferential growth\textsuperscript{(225)} and the Kirkendall effect.\textsuperscript{(269)}

3.2.6. General Guidelines for the Selection of Ex Situ and In Situ Monitoring in Batch Reactors

Based on the 147 studies listed in Table 2, it is possible to conclude that traditional batch reactors with in situ analysis are normally suitable for time-resolved kinetic studies that do not need an initial measurement time \((t_{m0})\) below \( \approx 30\) s. The \( t_{m0}\) value can be further reduced, but assessments need to be made to evaluate the mixing and heating times before using a batch system. However, improvements can be achieved by applying stopped-flow apparatus (e.g., custom-build device\textsuperscript{(269)}) Time-resolved studies with only ex situ analytics are normally not suitable for kinetic studies, mostly due to an insufficient number of data points collected, but also due to sampling preparation errors. Nonetheless, ex situ can be applied to reactive systems with a long reaction time (\( \geq 30\) min), and when the reactive media is not compatible with in situ probing (e.g., when using pyrophoric chemicals\textsuperscript{(181)}).

Beyond the kinetic timescale, another important parameter is the particle size, which varies with reactive media (e.g., type/concentration of precursors and capping ligands) and operative conditions (refer to Table 2). Theoretically, the lowest particle size would correspond to that after the initial nucleation burst however, reported data depend on the kinetic rates and the type of analysis. The lowest minimum particle sizes reported per material in a time-resolved study are \( \approx 2\) nm for Ag, \( \approx 50\) nm for Al, \( \approx 1.2\) nm for Au, \( \approx 0.1\) nm for Pt (in situ TEM), \( \approx 80\) nm for Mg, \( \approx 4\) nm CdSe, \( \approx 1.5\) nm for CsPbBr\textsubscript{3}, \( \approx 1.8\) nm for ZnO, and \( \approx 2.2\) nm for MAPbBr\textsubscript{3}. To further guide the reader, we have briefly detailed a few batch studies which could be considered a successful implementation of ex situ and in situ analysis.

For gold synthesis with ex situ monitoring, Polte et al.\textsuperscript{(24)} used SAXS and UV–vis with \( \Delta t_{m} = 5\) min, and a \( t_{f0} = 1\) min. The synthesis consisted of the reduction of chloroauric acid by trisodium citrate (mild reducing agent) at 75 °C, for \( \approx 90\) min. The time-resolved data were reported for size, the number of particles, absorbance, polydispersity, and oxidation state. Both \( \Delta t_{m}\) and \( t_{f0}\) were low enough to identify three distinct mechanistic zones: i) nucleation/coalescence (\( \approx 60\) s to 20 min; 20% of
the gold precursor was converted into nuclei, ii) diffusional growth (≤50 min), and iii) rapid precursor consumption. The authors later assessed the same experimental study with online SAXS\cite{195} using a peristaltic pump connected to a probing cell (Figure 2C), to reduce the measurements resolution time (Δtᵣ) from ≈5 to ≈1 min. Nevertheless, the t₀ was similar between online and ex situ monitoring (t₀ ≈ 1 min). The online data confirmed the ex situ mechanistic stages (step-growth mechanism) but provided a more detailed description of the system ( slower Δtᵣ), which allowed the elucidation of a mechanistic model (i.e., overall growth and reduction rate). Similarly, Koerner et al.\cite{175} used in situ analytics (SAXS and UV--vis) to track gold synthesis. The authors were able to successfully identify the mechanistic stages in the early stage of the particle formation, using Δtᵣ = 30 s (varies) and t₀ = 30 s. They were able to identify the nucleation/coalescence stage below 5 min (initial burst <30 s, and rapid growth (drop in number density) ≤5 min). The synthesis was performed at lower temperatures (room temperature) with chloro(trimethylphosphine) gold(I) and t-butylamineborane as the metal precursor and the reducing agent, respectively (in the presence of surfactants, hexadecylthiophol).\cite{175} For a different material, such as silver nanoparticles, Garcia et al.\cite{241} observed nucleation and growth using online SAXS coupled with ex situ UV--vis analysis, having a Δtᵣ = 60 s and t₀ = 60 s (total reaction time of ≈75 min). Both time parameters were adequate to monitor the reaction of silver nitrate and glucose at 90 °C (mild reducing agent). Interestingly, the authors were able to report the presence of two sizes distributions at 60 s, one with ≈3 nm (average particle population) and another with 12.5 nm. Mechanistically, they stated that this synthesis is initially dominated by the coalescence of smaller particles, followed potentially by Ostwald ripening. Since the presence of smaller nanoparticles is observed throughout the synthesis, the authors concluded that the nucleation might be continuously formed and replaced by newly formed crystals.

3.3. Limitations of Monitoring Material Synthesis in Batch Reactions

Although time-resolved kinetic studies can be monitored by embedding in situ probes inside the reaction media in batch reactors, their placement is often limited to reactors with volumes larger than 100 mL, due to the required swept volume per probe. Since each probe can only detect a local position inside the reactor, it is of critical importance to ensure that the local volume monitored by each of the probes/sensors is representative of the whole reaction volume, avoiding local variations in temperature, concentration, and particle population.\cite{380} Similarly, the total number of in situ probes that can be used simultaneously would be limited by the total reaction volume. As an example, Reza Andalibi et al.\cite{61} required a reactor with a reaction volume of 500 mL to accommodate all the necessary probes: a UV--vis spectra probe, a pH glass electrode, and a combined gold ring electrode.

In addition, as mentioned on several occasions above, batch reactors can lead to variability in the kinetic data during both ex situ and in situ analyses due to the impact of effective mixing of reactants and/or homogeneous conditions (e.g., temperature) during the analyses, a parameter often neglected or overlooked (in most of the studies listed in Table 2). The effectiveness of mixing inside a batch reactor depends on parameters such as the position/velocity of the stirrer, reactor dimensions and geometry, and injection position, to name a few.\cite{270–272} Such mixing efficiency will determine the mixing time which should be negligible with respect to reaction time to provide reliable and reproducible data. If that is not the case, the kinetic data and mechanistic studies are likely to be affected by mass and/or heat transfer limitations. As stated in the previous section, the nucleation/coalescence stages for most plasmonic and optoelectronic chemicals often start at reaction times below 1 min, especially when dealing with a fast-reducing agent (instant nuclei generation; ≈1–5 s).\cite{51,193,203,218}

To measure the kinetic rate of the initial stages of the material synthesis, one should ensure that homogeneous conditions (heat and mass) are achieved in the batch reactors within a few milliseconds (e.g., t₀ ≤ 6 ms, this is suggested by a flow study\cite{146}). Unfortunately, this is not easily attainable in batch reactors, and as a result, some of the reported nucleation and growth rates might not have been measured under kinetic control. To intensify mixing, it is common practice to perform a rapid injection of the precursors in a small volume (i.e., hot injection) into the reactor, followed by vigorous agitation of the reaction media. Although some studies pay attention to mixing (e.g., stopped-flow apparatus\cite{195}), and magnetic stirring coupled with online SAXS\cite{195,241}), there are studies where no information about agitation after initial injection is provided (e.g., in situ SAXS\cite{175,193,271}), probably due to limitations of placing a stirrer inside the reactor which in some cases is also the probing cell itself.

Concerning the type of characterization technique adopted to monitor kinetics, there are several variations between ex situ versus in situ analysis, since the ex situ measurements require an extra layer of complexity, such as sample collection, quenching, and preparation. The difference in the information obtained by in situ and ex situ analysis was studied by Koerner et al.\cite{175} comparing the information obtained with in situ SAXS and ex situ SAXS and TEM for the same reactive mixture at the same reaction time (5 min) during the synthesis of gold nanoparticles. According to the authors, both ex situ TEM and ex situ SAXS agree with the determination of particle size (in this case, 1.3 nm radii). However, when comparing both ex situ measurements against in situ SAXS, the in situ analysis showed a significantly smaller particle radius (0.7 nm). The authors stated that the unsuccessful quantitative comparison is mostly due to uncontrollable phenomena during sample preparation. Interestingly, even when the authors attempted to minimize the artifacts by performing a rapid quenching, there were differences between in situ and ex situ measurements. This study highlights the importance of ensuring that the samples taken during ex situ monitoring of the synthesis are truly representative of the reaction media as well as the importance of accurately quantifying the reaction time during ex situ measurements.

3.4. Limitations of Built-In Characterization Techniques within Batch Reactors

In situ SAXS presents a number of limitations. One of the most important ones is the fact that the setup often requires
a high-energy X-ray beam from a synchrotron source. In addition, SAXS is less sensitive to noncrystalline materials. As a noninvasive technique, SAXS has been integrated in situ (direct probing of the reactive media) and online (reactive media recirculates outside the batch reactor) using X-ray transparent windows with a time resolution above 100 ms. Fortunately, complementary XAS studies enhance this time resolution. For photo reduction processes, kinetics are difficult to measure with clarity at the beginning of the photoreduction, since the excess scattering intensity is quite small for the nanoparticles when compared to a metallic ionic solution. It is also reported that particles smaller than 1 nm in diameter are hardly detectable due to the low signal-to-noise ratio. It is noteworthy that SAXS setups require a transparent narrow window for a focused X-ray beam to penetrate the reaction medium. SAXS can be integrated through a detection flow cell or capillary. In a batch reactor, this is normally achieved by using a standard vessel. Garcia et al. designed a circulating loop from the batch reactor to the liquid sample holder. Here, despite the vigorous pumping of the reacting sample to the holder, there is a time delay from the vessel to the sample holder. Therefore, the in situ detection setup could not access the reaction in the first minute.

In situ XRD measurements have been implemented but limited to formation and deformation studies of solid-state materials rather than colloidal synthesis. This is due to the low signal-to-noise ratio during fast scans on small crystallites; one typical in situ XRD scan takes 5–10 min being unsuitable to study reactions that finish within a few seconds to a few minutes.

The use of LP-TEM monitoring during in situ batch kinetic studies is also challenging, requiring the solvent to be compatible with the ultrahigh vacuum present in the instrument. In some approaches, a sample cell with an electron-transparent window is used, enclosing the liquid to a thickness <1 mm. The liquid cell can support temperature control and even include electrodes, using modern microfabrication techniques. Nevertheless, artifacts can be present when triggering the nucleation process with the electron beam, which can last a few seconds. Additionally, the chemical and reactive conditions used in situ TEM differ from the ones commonly used (refer to Tables 2 and 3), which may have very different kinetics. So far, several time-resolved studies have been reported for the synthesis of nanomaterials using in situ TEM: Au, Ag, and Pt. This is also mentioned in Table 2 for more information. Nevertheless, the data obtained using LP-TEM are normally affected by the artifacts associated with the triggering of nucleation by the electron beam, which can last a few seconds. This can lead to different particle densities and sizes at the nucleation stage, which will affect the growth rate (i.e., different numbers of particles to grow).

In situ characterization by carrying out the synthesis in a sample tube inside a NMR equipment, such as the study done for fluoride-based inorganic nanocrystals using 19F NMR and ligand-exchange reaction. A combination of ex situ and in situ H, 31P, and 13C NMR over long reaction times (96 h) has been reported to reveal the mechanism of Au NP, Pt NP, and Au–Pt alloy NP formation.

Incorporating UV–vis and PL spectroscopy into batch setups often requires a custom-made optical cell/probe when coupled with other techniques for in situ measurements (e.g., coupling SAXS and UV–vis). Limitations in their implementation are related to variation in the overtime light source performance, sample fluorescence, traces of unwanted light, bubbles trapped in the cuvette/optical cell, and low light transmission in some wavelengths of the spectra. The presence of nanoparticle deposition and fouling over the optical window also can lead to artifacts. Further details about the limitations and perspectives of in situ UV–vis have been reported by Hendel et al.

### 3.5. Reproducibility Issues in Batch Monitoring

The synthesis of nanomaterials in batch reactors can suffer from repeatability issues, consequently affecting the accuracy and reproducibility of time-resolved kinetic data obtained using both in situ and ex situ characterization. These repeatability issues can be ascribed to heterogeneous temperature/concentration profiles in the reactor, aging of the stock solutions, uncontrollable speciation of the chemical species and human error (to name a few). The literature contains few scattered reproducibility studies; however, it is clear from their conclusions that special attention needs to be taken to ensure the accuracy of the results. Kettemann et al. reported a detailed repeatability study of the synthesis of gold nanoparticles using citrate as a reducing agent in batch reactors. The authors conducted the syntheses in triplicates paying special attention to the precursor solutions. Particle size variations of ~5% were obtained when using the same stock solutions, however, the variation increased to ~27% (5.5 vs 7.0 nm, radius) when using different stock solutions. They related the lack of reproducibility due to the variations in the speciation of the gold precursor (H4AuCl4) in the stock solution. As a result, they managed to decrease the relative standard deviation to 1.6 to 3.6% by controlling the pH of the solutions (the standard deviation varies inside the pH optimal range). The results cover the use of three different gold solutions, some of them 4–8 months old. Scarabelli et al. reported a detailed practical guide to minimize the sources affecting reproducibility during the synthesis of gold nanorods (e.g., discard solutions when there is a dark lid of AgNO3, yellowish color for ascorbic acid, and insoluble material for H4AuCl4). Other considerations are also mentioned, such as how to prevent and monitor secondary nucleation during growth. Unfortunately, a similar approach to Kettemann et al. has not been extended to other plasmonic metal materials. To the best of our knowledge, no reproducibility studies of time-resolved kinetic data (number density and size) have been reported for batch synthesis to confirm the error associated with rates of nucleation and growth. In other words, a reproducibility study should consider the kinetic rates, rather than just the final state (when stability is achieved). The closest is the study proposed by Koerner et al. where the authors obtained time-resolved data during the synthesis of gold nanoparticles with different alkyl thiols. They noticed that although similar particle sizes were obtained (~1.9 nm, radius) in different syntheses (thiol C12 vs C16), the kinetic rate and the number density differed during the syntheses. These studies highlight the difference in reproducibility of the thermodynamic state (e.g., final product) and the kinetic data (dynamic state).
For optoelectronic materials, it is generally accepted that batch syntheses present poor batch-to-batch reproducibility.[180,277,278] However, to the best of our knowledge, only one study has attempted to quantify such reproducibility. Swarnkar et al.[199] reported PL variations of ±5 nm wavelength from CsPbBr$_3$ perovskite nanoparticles synthesized in batch reactors, which in terms of particle size distribution corresponds to an ≈18% deviation. As another example, we have found from our personal experience that the synthesis of CsPbBr$_3$ perovskite nanoplatelets by ligand-assisted precipitation leads to batch-to-batch variations in the number of monolayers achieved, such that the emission wavelength changes between batches, despite using the same precursors, concentrations, volumes, and set mixing conditions. Therefore, the PL emission wavelength needs to be checked ex situ at the end of each batch of colloidal nanoplatelets.

4. Synthesis of Materials in Flow (Micro)Reactors with Ex Situ, In Situ, and Online Characterization

Flow (micro)reactors have been increasingly adopted over the past couple of decades for the synthesis of nanomaterials to benefit from their small reaction volumes, facile ability to perform iterative studies, and low energy and material consumption. Thus, the literature now presents a number of studies where traditional syntheses carried out in batch reactors have been adopted into flow setups, using the same precursors and conditions.[185,209,288] For example, the synthesis of Ag NPs has been carried out in both batch and flow reactors using the same precursors (silver nitrate and ascorbic acid).[189] Both reprecipitation and hot-injection type approaches have also been used in the flow synthesis of lead-halide perovskite NPs.[290,291] In this section, we review how the properties of flow reactors can benefit not only the synthesis of nanomaterials but most importantly enable their kinetic and mechanistic understanding using ex situ as well as integrated in situ and online characterization techniques. We highlight studies using flow reactors that provided time-resolved data from very early stages (e.g., starting from 6 ms[146]), which showed many advantages versus batch reactors discussed in the previous section. In addition, a wide range of kinetic studies based on size-dependent optoelectronic properties of the nanoparticles is discussed in terms of indirect size estimation (e.g., PL and UV-vis) and discrepancies with direct size measurement (e.g., TEM). Table 3 provides a summary of the main studies discussed in this section. Finally, we discuss the current limitations of in situ and online kinetic studies using flow reactors in relation to the available techniques.

4.1. Comparison of Flow versus Batch Reactors

The small channel diameters (from sub-millimeter to a few millimeters) of milli- and microreactors result in low Reynolds numbers characteristic of the laminar flow regime (Re ⩽ 100). Such fluid dynamics has several advantages for the synthesis of nanoparticles. First, it promotes rapid heat and mass transfer in the radial direction despite mass transfer being dominated by diffusion due to the small diffusion radial distances providing precise control over reaction conditions that normally surpass the batch reactors.[185,292] The characteristic diffusion time is defined by the square of diffusion path length divided by the diffusivity of the species.[133] This property is especially important during fast syntheses when one should ensure that the mixing time is considerably shorter than the reaction time.[293] Second, under laminar flow, the different synthesized nanoparticles have parallel path lines, reducing their tendency to aggregate, making ligand-free synthesis feasible while keeping narrow size distributions.[294,295] In comparison, batch reactors normally operate under turbulent flow to ensure homogenous conditions, during which nanoparticles tend to aggregate upon collision, which is conventionally minimized by the presence of ligands and stabilizers.[35] As discussed above, the presence of the ligands can have an effect on the kinetics of synthesis, but could also interfere with the final application (e.g., catalysis).[296,297] Third, the small dimension of the channels makes microreactors capable of isolating air- and/or water-sensitive compounds, thus obviating the need for complex inert atmosphere setups.

However, the characteristic laminar flow in flow reactors also presents many challenges associated with its characteristic parabolic velocity profile. As a result, the residence time distribution becomes broad, potentially leading to the broadening of the particle size distribution.[298] In addition, laminar flow is responsible for potential fouling on the walls of the reactor, which can lead to non-steady-state conditions, interferences, and low metal efficiency.[299,300] A conventional approach to overcome these issues is by using biphasic or segmented flow. The addition of a second, inert phase will lead to segmented Taylor flow. This approach can effectively mitigate fouling due to the recirculating motion of the reactive phase, minimizing the boundary layer.[299,300] In addition, such fluid recirculation enhances radial mixing, narrowing the residence time distribution.[301] Another way of overcoming the disadvantages of the laminar regime in microchannel flow reactors is by modifying the conventional straight channel geometry of the microchannels into a 3D one, e.g., adding bends, turns, and baffles. In this way, secondary flows are induced, such as Lagrangian turbulence or Dean vortices. A large number of purposely designed microfluidic devices, such as serpentine, zigzag, and split-and-recombine (SAR) channels[293] as well as 3D channels such as helical and braided tubes[302,303] have been proposed and studied through fluid dynamic simulations and experimental data. However, only a few of these (e.g., helical tubes[294,304] and serpentine microfabricated chips[144,305]) have been applied to the production of nanomaterials, being mainly used in organic reactions.[35] Details of the different approaches in monophasic and multiphase reactors have been previously reviewed.[304,306,307]

The different efforts to improve mixing in microreactors have brought substantial improvements to the size and distribution of solution-processed nanomaterials.[308] For example, the helix diameter in helical reactors is an important parameter determining the size and size distribution of synthesized Ag NPs in absence of a capping ligand.[294] When the helix diameter was 14 mm for a 130 cm helical reactor, the average size of Ag NPs is 5.0 ± 1.1 nm, whereas it was increased to
8.9 ± 4.6 nm when the helix diameter was increased to 100 mm. The reactor channel diameter is another critical factor; the 1/16 in. tubing is better in terms of mixing times over 1/8 in. tubing, which was exemplified during Au NP synthesis, such as particle size was reduced from 30 ± 5 to 12 ± 2 nm.\[309]\] Additionally, Okafor et al.\[299]\ proposed an advanced 3D reactor geometry known as the “miniaturized continuous oscillatory baffled reactor (mCOBR)” where the residence time distribution was narrowed with respect to a standard tubular reactor, as verified using a tracer with online UV–vis spectroscopy.\[299]\] Using the mCOBR for Ag NP synthesis, the particle size and distribution were reduced to 5.0 ± 1.2 nm, in comparison with the 8.3 ± 3.0 nm achieved in a straight tubular reactor. Gao et al.\[310]\ compared several coiled reactors and demonstrated that the alternating-axes reactor can minimize the size and distribution of Ag NPs (4.3 nm with 25% standard deviation) in comparison to other coiled reactors. Using fluid dynamic simulations, they demonstrated that the decrease in size is directly related to the degree of mixing in the reactors. In particular, the alternating-axes reactor enhances radial mixing by not only promoting the formation of Dean vortices but also by breaking the stagnant volume within the vortices by frequent and periodic changes in the coil, which therefore changes the direction of the Dean vortices.\[130]\]

In agreement with the enhanced mixing in microreactors, different properties are often observed in nanoparticles synthesized using batch and flow reactors under the same conditions.\[310]\] For example, Hemmati et al. synthesized Ag nanowires using a polyol-mediated process in batch reactors, but various amounts of Ag NPs were frequently found in the product mixed with nanowires. Under the same synthesis protocol (chemicals, residence times, and temperatures), helical millifluidic reactors yielded 100% nanowires without phase impurities. The observations were valid for a wide range of temperatures (130–198 °C).\[311]\] Kinhal et al. reported the kinetic-controlled synthesis of uniform triangular Ag NPs in a spiral reactor with a size of 140 ± 30 nm, while in a batch reactor, the size increased to 400 ± 100 nm.\[289]\] The effect is further amplified at a larger scale, for example, Epps et al. observed a clear redshift in the photoluminescence from colloidal CsPbBr\(_3\) NCs synthesized in a 20 mL batch reactor versus a 2 mL vial. By contrast, when using a segmented flow reactor instead, the blue photoluminescence was consistent regardless of the collected volume.\[90]\]

Despite the numerous advantages of flow reactors for the synthesis of materials, one should note that their use in slow or multistep synthesis is still challenging due to the significant pressure drop associated with long reactors required (following the Hagen–Poiseuille equation). Thus, slow nanomaterial syntheses requiring tens of minutes are still preferentially carried out in batch reactors.

4.2. Integration of Characterization Techniques into Flow Reactors

4.2.1. Monitoring of Nanomaterial Synthesis in Flow Reactors Using Ex Situ Characterization

Batch and flow syntheses are similar in terms of ex situ characterization, as both require sample collection and preparation. As discussed in the previous section, the kinetics studies using ex situ characterization are less satisfactory since the data points are discrete, and the coarse sampling time (\(t_s\)) and time resolution (\(\Delta t\)) limits the ability to study very fast reactions. A selection of studies using ex situ characterization with flow reactors are listed in Table 3.

Despite similar limitations in both reactor types, flow reactors often offer narrower particle size distributions compared to batch reactors.\[380,312]\] Abou Hassan et al. reported a reduction in the size distribution from 35% (batch reactor) to 20% (coaxial flow device) for iron oxide NPs.\[311]\] Baber et al. investigated several flow reactors including a coaxial flow reactor (CFR), a coiled flow inverter (CFI), and SAR reactors to promote the mixing of the precursors for Au and Ag NP synthesis.\[314,315]\] The particle sizes were analyzed by ex situ TEM and UV–vis. Using the SAR reactor in series with a CFR one, sizes of Ag NPs were found to decrease with increasing concentrations of silver nitrate precursor, and this was attributed to the improved mixing in the SAR reactor.

Flow reactors additionally provide high reproducibility that benefits ex situ measurement from a very early initial measurement time (discussed later). In batch reactors, the early initial measurement time is constrained by achieving homogeneity across the reaction vessel, therefore, ex situ measurements are often affected by a lack of reproducibility. In flow reactors, initial measurement times are comparably shorter (as discussed above) although not negligible, hence, it is still crucial to consider the mixing to ensure the initial measurement time is sufficient.

4.2.2. Monitoring Synthesis in Flow Reactors with In Situ and Online Characterization

The monitoring of nanomaterial flow synthesis with online and in situ techniques has the potential to provide unique kinetic and mechanistic information owing to its fast and continuous time-resolved data acquisition, overcoming some of the issues encountered in batch reactors. By definition, in situ characterization refers to the integration of the characterization probe/cell within flow reactors in the way that measurement takes place without the need of collecting samples, hence the sampling time \(t_s = 0\). For example, direct photoexcitation on a reacting droplet in a flow channel and instant photoluminescence spectra acquisition is an in situ optical measurement. On the other hand, online characterization refers to measurements when the reaction needs to be stopped or paused in order to take the measurement. A typical example is an absorption flow cell placed at the outlet of the flow reactor with no temperature control. If the synthesis takes place at high temperatures (e.g., 140 °C), this is likely to quench the reaction. However, if the reaction continues, then, online characterization will introduce experimental errors in time-resolved experiments. As such, for online characterization, the sampling time \(t_s\) is the time taken by the fluid to reach the sampling point/cell, and it is nonzero despite being very small in most cases (although commonly nonquantified). As a result, flow reactors with in situ or online characterization can provide insights into the early stage reaction mechanisms by providing data with microsecond...
to millisecond time resolution, overcoming the limitations imposed by ex situ characterization.\cite{136,137}

The first online monitoring of the flow synthesis of nanoparticles was published in 2004, where optical fiber online fluorescence spectroscopy was coupled to a glass microfluidic reactor for the synthesis of CdSe QD.\cite{305} The setup allowed photoluminescence measurements from CdSe QDs at the fixed “observation zone” on the reactor which is effectively a fluorescence flow cell. A series of measurements were carried out by changing the flow rate, therefore, the spectra were correlated to reaction times from 32 to 1600 s. It is worth noting that changing the flow rate also changes the fluid dynamics, which would require a controlled experiment to be decoupled. In terms of plasmonic nanoparticles, the first online monitoring study used UV–vis spectroscopy in 2006 to measure changes in absorbance during the synthesis of Au and Ag NPs to understand the effect of temperature on growth. The measurement time resolution (\(\Delta t_m\)) is 5 min for Au and 1 min for Ag, and the initial reported time is \(\approx 32\) min. It was discovered that increasing the temperature shifted the extinction maximum toward shorter wavelength representing shorter and smaller aspect ratio Au nanorods. The optical fiber cell allowed swift temperature adjustments in the bath without stopping the reaction.\cite{338} It is worth noting that, during online monitoring, it is important to minimize the difference between conditions in the measurement cell/probe and the reaction condition (e.g., temperature and mixing), to make the data obtained as close to in situ characterization as possible. For example, online monitoring of the synthesis of Ag NPs using an XAS spectrometer requires the extraction of the reaction medium from the reactor to the spectrometer through a peristaltic pump. In this bypass, the mixing conditions changed, together with potential small changes in temperature.\cite{309}

A range of setups has been developed over the last two decades for the in situ and online monitoring of nanomaterial synthesis in flow reactors. The different setups can be classified as single-point, static multipoint, and moving multipoint analyses (Figure 4). They will be reviewed in detail below, with a summary of the reported experimental conditions listed in Table 3, and the typical times (\(\Delta t_m\) and \(t_0\)) are referred to in Figure 5.

The single-point in situ analysis is the easiest of the three to be implemented. It involves the integration of a flow cell and/or probe at a certain point within the flow reactor or at its outlet (Figure 4A1). This approach allows easy integration with existing reactors and characterization techniques; however, single-point analysis can only provide a snapshot at a given residence time, without having time-resolved capabilities. Having said that, it is common practice to expand the range of reaction times by changing the flow rate through the reactor, however, one should notice that this approach modifies the fluid dynamics in the reactor which are expected to influence mixing and thus, potentially on the synthesis kinetics. Alternatively, stopped-flow devices paired with a single flow cell can reveal information on the reaction kinetics, with short initial measurement times (refer to Figure 4A2). The stopped-flow devices considered here operate based on the same characteristic of microfluidic flow reactors, in contrast to those in Section 3. Here, the mixing is achieved by passing fluid through a micro mixer follow by a microfluidic reactor (a few microliters, e.g., 300 \(\mu\)L). Once steady state is achieved, the flow is stopped, and characterization takes place. For instance, in the case of SAXS, the X-rays then pass through the quartz capillary containing the reactive media as soon as the fluid becomes stagnant.\cite{312} The apparatus is “in principle” the same as flow setups, the only difference is that the reaction is monitored when the flow is stopped.

To obtain time-resolved data under the same fluid conditions, multiple sampling/characterization points are needed across the reactor. The static multipoint analysis uses multiple flow cells or probes at specific points along the flow reactor so that the data can be acquired at several discrete residence times (Figure 4C1,C2). The in situ monitoring exploits the steady-state operation of continuous flow reactors in the way that the analytical time (\(t_a\)) is no longer a limitation, hence allowing longer scans at a fixed sampling point. The moving in situ multipoint analysis involves a more complicated setup where a motorized stage (moving scaffold) carrying either the reactor or the optics (i.e., optical probe or fiber assembly) is used to “scan” through the entire reactor. In the cases of biphase reactors, the motorized stage enables the optics to track a reactive droplet as it moves along the reactor.\cite{89,90} For example, Figure 4B1 presents a setup where the helical reactor is coiled over a copper heating rod that is driven by a motor. As the droplets flow through the reactor, it has both angular motion and axial motion. The motor then counteracts the motions of droplets by pushing and rotating the reactor at the same rate as the flow motion, so that the droplets have static locations with respect to the optics.\cite{89} Another strategy is applied to straight microfluidic tubing, where the optical fiber assembly moves along the reactor at the same speed as the droplets in order to track them.\cite{90} The moving multipoint analysis approach is the most data-rich method for the study of kinetics since it can provide information from very early initial measurement times until the end of the reaction (assuming that the reaction is complete within the reactor). One potential drawback of this type of setup is associated with the complexity to build the motorized system as well as the potential need for algorithms (e.g., in biphase flow). In biphase systems, the motor must ensure that the optics follow closely the movement of the droplet to avoid loss of signal, raising the requirement for high-precision manufacturing and rigorous control of the motors.

In general, in situ and online spectroscopic characterization are possible, thanks to the use of optical fibers, with sampling either directly through the transparent reactor tubing/substrate or through bespoke optical flow cells. The former allows the sampling point (the small light-focused area on the reactor from which the spectrum is acquired) to be moved freely along the reactor, therefore, obtaining time-resolved data. Note that the reactor tubing/substrate needs to have no spectral distortion across the interested wavelength to ensure the accuracy of the signal. On the other hand, flow cells allow liquid flow in designed paths, and the spectra are obtained through quartz windows (or silicon nitride for X-rays) which are transparent to the desired signals. Flow cells have specific path lengths such as 1, 2, 5, and 10 mm, which is important for UV–vis absorption measurements when the solution is too dilute or too concentrated. As such, a range of UV–vis absorption flow cells
with a range of optical path lengths have been manufactured, so that the absorbance can be controlled within a reasonable range (i.e., to avoid saturating the spectrometer detector)\cite{62,70} by choosing a suitable cell based on the concentration of the solution.

In addition to kinetics studies, online and in situ monitoring of reactions in flow reactors can also provide valuable mechanistic information on nanomaterial synthesis. The versatility of in situ measurement setups not only allowed time-resolved data but also enabled parameter screening.\cite{147,141,319} Moreover, in situ characterization in flow reactors can also provide data at long timescales from minutes to tens of minutes as discussed in detail below.

### 4.3. State-of-the-Art of Kinetic Studies of Material Synthesis in Flow Reactors

#### 4.3.1. Importance of Understanding Early Stage Kinetics

It is well accepted that the synthesis of plasmonic and optoelectronic materials normally follows complex mechanisms with multisteps. In addition, it is also well-known that the rate of reaction of the initial stages (e.g., nucleation and supersaturation) determines the final size and in some cases size distribution of the resulting nanomaterials. As a result, understanding and controlling the kinetics of the different mechanistic steps is a crucial step for the synthesis of size-controlled nanoparticles.

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**Figure 4.** Schematics of typical ex situ, online, and in situ characterization techniques integrated into flow reactors. When monitoring online or in situ, the flow reactors can be categorized according to the position of the analysis, A) single-point, B) moving multipoint, and C) static multipoint. The single-point analysis (A) is carried out in a fixed position in the reactor using A1) an in situ apparatus or A2) stopped-flow capillary system. The multipoint analysis (B and C) is performed in several locations in the reactor. The moving multipoint analysis (B) is the most comprehensive yet complicated setup for kinetic studies as it can track the reaction with minimum initial measurement times. C1,C2) Alternatively, static multipoint approaches can be used. (A1) shows a setup for silver rods synthesis.\cite{318} Drawn based on ref. [318]. (A2) shows a stopped-flow microfluidic setup for Au NPs\cite{212} Adapted with permission.\cite{318} Copyright 2015, American Chemical Society. (B) shows a moving probe setup for PbS QDs.\cite{89} Reproduced with permission.\cite{89} Copyright 2015, Wiley-VCH. (C1) shows a static multipoint apparatus applied to the synthesis of Au NPs\cite{144} (drawn based on ref. [144]). (C2) shows a static multipoint apparatus applied to the synthesis of Ag and Au NPs\cite{62} (Adapted from ref. [62] under the terms of a Creative Commons Attribution License, copyright 2021, The Authors).
**Time-resolved data for flow reactors**

A) Synthesis of PbS NPs with multiple in-situ and ex-situ analysis

- **Analytical apparatus**
  - LED
  - Halogen Lamp
  - Flow direction
  - Optical Fiber
  - In situ probing

A1) Reaction time

- 0.4 s
- 0.6 s
- 0.8 s

- Interval of 0.2 s

- Absorbance (a.u.)

- Wavelength / nm

800 1000 1200

A2) In situ UV–vis spectra as a function of the reaction time (0.4–1.5 s from blue to red)

A3) Ex situ TEM collected at the end of the 8.5 s reaction time

B) Time-resolved kinetic data (normalized by size) information reported for a different type of monitoring system (ex situ, in situ single-point, in situ multipoint, in situ using a stopped-flow apparatus, and in situ with a liquid phase STEM cell).

- Initial reported times ($t_0$) and measurement time resolutions ($\Delta t_m$) for flow reactors as a function of characterization technique; illustrating access to early stages data, thanks to low initial reported times (approximately milliseconds).

- Particle size has been normalized according to the size reported at the end of the synthesis ($d_f$), which has the following values: 2.59 nm for Au (ex situ SAXS), [320] 44 nm for Ag (in situ STEM), [247] 3.40 nm for Au (in situ single-point SAXS), [25] 12.6 nm for CsPbI$_3$ (in situ PL multipoint), [87] and 1.36 nm for Au (in situ SAXS stopped-flow). [240]

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**Figure 5.** Examples of time-resolved data obtained using ex situ and in situ monitoring in flow reactors. A) Time-resolved mechanistic study of PbS QD synthesis where multiple spectroscopic techniques were used to monitor the composition of a droplet in the reactor (in situ PL, in situ UV–vis, and ex situ TEM). Adapted with permission. [89] Copyright 2015, Wiley-VCH. A1) In situ photoluminescence spectra as a function of the reaction time (0.4–3.8 s from blue to red). A2) In situ UV–vis spectra as a function of the reaction time (0.4–1.5 s from blue to red). A3) Ex situ TEM collected at the end of the 8.5 s reaction time.

B) Typical time-resolved kinetic data (normalized by size) information reported for a different type of monitoring system (ex situ, in situ single-point, in situ multipoint, in situ using a stopped-flow apparatus, and in situ with a liquid phase STEM cell). The data show initial reported times ($t_0$) and measurement time resolutions ($\Delta t_m$) for flow reactors as a function of characterization technique; illustrating access to early stages data, thanks to low initial reported times (approximately milliseconds). The particle size has been normalized according to the size reported at the end of the synthesis ($d_f$), which has the following values: 2.59 nm for Au (ex situ SAXS), [320] 44 nm for Ag (in situ STEM), [247] 3.40 nm for Au (in situ single-point SAXS), [25] 12.6 nm for CsPbI$_3$ (in situ PL multipoint), [87] and 1.36 nm for Au (in situ SAXS stopped-flow). [240]
In this context, careful design of flow reactors is of key importance to reveal such early stage kinetic information to ensure that the initial measurement time is minimized. As previously discussed, it is of key importance to ensure that homogeneous mixing and temperature are achieved as early as possible and well below the reaction time. As an example, Gao et al. quantified the mixing at the entrance of microreactors using mixing index (MI), finding out a direct relationship between MI and particle size for the synthesis of Ag nanoparticles. The size of Ag NPs was reduced from 6.5 to 4.6 nm when the MI was increased from 0.19 to 0.5–0.6. In a different study, Au NPs with sizes of 1.0 ± 0.4 nm were achieved, thanks to the fast reduction of Au(III) precursor to Au(0) within 10 ms with additional growth for a further 10 ms. Such kinetic data were enabled using a flow reactor equipped with in situ XAS characterization with $t_{\text{res}}$ of 6 ms. In addition, the use of flow reactors can also allow fast quenching of reactions at low residence times, being able to isolate such small nanoparticles.

4.3.2. Single-Point In Situ Analysis in Flow Reactors

In situ, multiple static sampling/characterization points across flow reactors enable the collection of discrete time-resolved data without the need to change the fluid dynamic conditions (e.g., variations of flow rates). For example, the synthesis of large plasmonic Ag NPs was reported using a number of microreactors in series with bespoke optical cells between each reactor where the UV–vis spectra were measured. A fast multiplexer directed the light source to the different flow cells with a fast rotation rate (e.g., microseconds), providing real data information on the Ag NP growth process. Such real-time data can be used to control the final particle size, with tunable capabilities between 5 and 80 nm by modifying the reactant flow rates.

Using intricate setups for X-ray techniques, Sun et al. studied the initial kinetics of CdSe QDs using in situ, static multipoint XAS across a straight channel microfluidic device. There were 8 sampling points on the channel for XAS analysis, corresponding to reaction times between 0 and 8.1 s. The initial measurement time of Se K-edge EXAFS spectra was 1.1 s to detect the conversion of the Se–P bond in the phosphine-ligand-complexed precursor to the Se–Cd bond in the CdSe QDs. Burst nucleation within 2 s was observed upon rapid heating in the microfluidic channel followed by a rapid size increase up to 3 s. Further growth was slower as shown by the flatter consumption curve of Se precursor, eventually reaching a plateau. Due to fouling issues during continuous operation, a thin layer of CdSe formed on the reactor wall, affecting the EXAFS signal that deviated to overestimate precursor consumption rate. This was corrected by scaling down the edge jump absorbance by multiplying a ratio of the average edge jump to the initial edge jump. The authors proposed a surface-reaction-driven kinetics equation to describe the synthesis and presented an analytical expression of size and concentration in terms of Se precursor consumption. For plasmonic nanoparticles, Tofighi et al. synthesized Au NPs using a serpentine microfluidic channel with in situ XAS directly on the channel at different points corresponding to 6, 10, and 18 ms, respectively. Thanks to the small 300 µm width channel, 6 ms of the reaction corresponded to an approximately cm reactor at which the X-ray can be precisely focused. The setup is presented in Figure 4C1. The Au(III) scattering peak disappeared at the 10 ms spectrum showing that the reduction of oxidized Au by NaBH₄ is complete within this time. The reaction was quenched after 20 ms residence time so that the particle size is preserved (with help of PVP as a stabilizer). The setup hence revealed the fast kinetics of Au(III) reduction to Au NPs, thanks to rapid mixing in the microchannel. Polte et al. also used online SAXS to study the formation of Au NPs in a micromixer at an early stage, having an initial measurement time of 100 ms. The distance between the micromixer and the SAXS flow cell was changed from 19 cm to 10 m, corresponding to residence times from 100 ms to 136 s. The study revealed two stages within the first second of the synthesis by detecting the size of particle clusters. In the first stage within 200 ms, few-atom clusters were formed and coalesced into nuclei with sizes below 1.7 nm. This was observed together with a decrease in the number of particles. The second stage consisted of considerably slower growth from 2 s to 180 min...
of the reaction. Both works fully utilized the advantage of a flow system where the reaction system can be accessed at early stages, i.e., short initial measurement times. More examples involving in situ X-ray characterization can be found in Table 3.

Concerning lead-halide perovskites, a range of in situ monitoring in flow reactors provides a mechanistic understanding of the phenomena taking place during their synthesis with a full list of examples in Table 3. Maceiczky et al. synthesized FAPb(Br/I)\(_3\) NCs in flow with in situ spectroscopy, showing that FAPbI\(_3\) NCs are first formed followed by incorporation of the Br anion during growth, in contrast with simultaneous Br and I ion lattice formation.\(^{[291]}\) Lignos et al. studied the shape evolution and halide segregation within 7 s in mixed halide perovskites using a microfluidic platform equipped with in situ PL measurements (time resolution of 100 ms).\(^{[322]}\) Stable emission between 465 and 520 nm was achieved by FAPb(Cl\(_{1−x}\)Br\(_x\))\(_3\) NCs, though the challenge behind producing stable blue emission (420–450 nm) from mixed Br/Cl perovskites remained. When the Cl content is over 60%, the FWHM of the PL peak nearly doubled to over 40 nm and the PLQE decreased significantly from 26% to 1%. The group also studied the fluorescence lifetime dependency of lead-halide perovskite NCs by parameter screening, during which the fluorescence lifetime was tracked along the synthesis process using a customized optical setup.\(^{[322]}\) Apart from the well-known temperature and composition dependence, it was first discovered that the lifetime is also dependent on the feed Pb-to-Cs ratio. Similarly, Abdel-Latif et al. proposed a “halide exchanger” for halide perovskites using in situ optical spectroscopy, where the time of completing halide exchange ranged from 0.5 to 9 s depending on the flow rate ratio of the perovskite NC and the halide salt stream.\(^{[324]}\)

In situ characterization in flow reactors can also provide data at longer time scales from minutes to tens of minutes. For intermediate reaction times, Abolhasani et al. set up an oscillatory microprocessor to study the growth of semiconductor NPs (CdSe, CdTe, and InP) for up to 10 min.\(^{[325]}\) The oscillatory motion of the droplet allowed monitoring over 10 min residence time at a time resolution of 3 s in a 12 cm reactor; this approach avoided the need for a 24 m tube in a continuous flow to achieve such residence time. A range of temperatures from 160 to 220 °C was explored using small amounts of reactants. In an alternative approach to achieving longer residence times, Pinho and Torrente-Murciano connected multiple microreactors in series with flow cells between them.\(^{[70]}\) In this way and by using distributed feeds, 80 nm Ag NPs were synthesized with a total residence time of ≈40 min. The authors also reported seed-mediated growth of Ag NPs using a similar setup with automated control.\(^{[62]}\) The seeds were synthesized in the first reactor, growing in consecutive reactors under different conditions in a successful attempt to separate seed formation from growth. Even longer residence times can be monitored in flow reactors as illustrated by Watt et al. who reported the effect of seed age on the synthesis of Au nanorods under Ostwald ripening, using a microfluidic reactor equipped with in situ SAXS and UV–vis.\(^{[326]}\) The activity of ultrasmall gold seeds decreases with aging up to 90 min. Similarly, Shen et al. studied the ligand exchange dynamics of CdSe QDs using an oscillatory flow reactor.\(^{[326]}\) The oscillating motion in a U-shaped flexible tubing enabled continuous monitoring of UV–vis absorbance over a long reaction time of 200 min, the time at which the ligand exchange process continued for phosphonate-capped CdSe QDs.

An alternative to static multipoint in situ analysis is the moving multipoint in situ analysis, where a single probe/cell is moved at various positions along the reactor to obtain time-resolved data with an enhanced time resolution, exploiting the steady-state regime of flow reactors. Yao et al. studied the kinetics of CdTe QD synthesis using fluorescence imaging along a microfabricated serpentine reactor where the change in color gave indirect information on particle growth.\(^{[327]}\) Under steady state, the residence time increases as the length of the reactor increases, being possible to obtain in this way time-resolved information. Using a high total flow rate at 40 μL h\(^{−1}\) (water phase 10 μL h\(^{−1}\) and organic phase 30 μL h\(^{−1}\)), the time resolution was 8.1 ms between droplets. The effect of temperature on the size and distribution of synthesized CdTe QDs was studied; when the temperature is increased from 81.5 to 91 °C by a 1 °C interval, the emission peak was observed to shift significantly from 531 to 619 nm, demonstrating fine control of emission wavelength by temperature. This work showed the unique advantages of using a flow reactor for the synthesis of fluorescent CdTe QDs, that is, the precise control of temperature by a slight change of 1 °C with minimum variation across the entire platform, which could not be realized in batch flasks. Such accuracy in temperature was critical to obtaining the desired emission of synthesized CdTe QDs. Another advanced example is the work of Lignos et al. monitoring the synthesis of PbS QDs in a biphasic system consisting of reactive phase (Pb and S precursors) separated by inert perfluorinated fluid with in situ PL with a time resolution of 100 ms.\(^{[89]}\) The synthesis took place in a transparent polymer tubing coiled around a motorized heating rod, so the moving droplet is kept under probe beam focus. Continuous detection was achieved by moving the sampling point along the reactor and keeping the focus on one droplet. The NP sizes were estimated using PL and the absorption peak energy. The initial measurement time of 100 ms detected emissions from ultrasmall seeds (diameter less than 2.8 nm) that have not been detected before using conventional batch synthesis. As a result, it was revealed that the synthesis of PbS QDs consists of a two-stage process, with more distinctive rates at elevated temperatures (Figure 5A). At the studied conditions, the nucleation stage takes place during the first second of the reaction when the concentration of particles bursts to a maximum, indicating that new particles with diameters of 2.94 nm form rapidly as the precursor concentration reaches a minimum threshold value. In the second stage (from 2 s onward), the particle concentration decreases, while the particle size increases due to growth. This was the first kinetic study of the synthesis of PbS QDs, highlighting the advanced capabilities of flow systems coupled with in situ characterization for kinetic studies within the first second of the reaction, and the possibility to apply the same methodology to explore other materials that have similar reaction timescale. Similarly, this two-stage nucleation and growth mechanism, in accordance with the La Mer model, was confirmed for CdSe QDs using a serpentine reactor coupled with online UV–vis and PL.\(^{[323]}\) Reaction parameters such as temperature, time, and precursor ratio were fitted into a first-order kinetics model for the
nucleation stage, and the growth stage was found to be strongly temperature-dependent. The conclusion was extended to ZnSe QDs using droplet flow in a helical reactor, where the nucleation and growth stages were clearly distinguished by in situ UV–vis absorption measurements at different temperatures.\[^{328}\]

In conclusion, flow reactors coupled with in situ X-ray diffraction, scattering, and spectroscopy techniques have enabled rapid data acquisition from the early stages of the reaction to the growth and evolution of the material at considerably longer reaction times, able to resolve the reaction kinetics for fast reactions within a few seconds and slow phenomenon over tens of minutes.

### 4.4. Limitations of Understanding Material Synthesis Kinetics in Flow Reactors

Kinetic studies need, by definition, time-resolved data during the synthesis of nanomaterials. Although flow microreactors open the door to the understanding of the early synthetic stages, with very small initial reported times, ex situ and single-point in situ measurements do not offer time-resolved capabilities to extract kinetic information across the synthesis. A common way of resolving this limitation is by varying the initial flow rates of precursors fed into the microreactors, consequently varying the residence time at any given point in the reactor. However, varying the initial flow rates influences the fluid dynamics of the system, affecting the initial measurement times, defined as the residence time to achieve homogeneous conditions in the microreactor. This aspect is particularly important in fast reactions where mixing time is comparable, if not longer, than reaction times. In many kinetic studies, mixing efficiency and reaction times are not properly assessed.\[^{200,293}\] As an example, the effect of flow rate on a particular size was investigated in the synthesis of CdSe QDs using a microchannel chip reactor.\[^{305}\] By decreasing the flow rate from 10 to 0.25 µL, the size increased from 1.05 to 1.52 nm. However, this might not be only due to longer reaction times, but also the effect of mixing on the early stage nucleation rates. To decouple both effects, the reaction time could be varied by varying the length of the reactor using fixed flow rates.\[^{294}\]

Directly related, it is the importance of quantifying the reactant concentrations during the nanomaterial synthesis as part of the kinetic studies. For this, it is important to ensure that the microreactor design promotes mixing, leading to very low initial measurement times (typically in the range of milliseconds), to the point of being negligible in comparison to the early stage synthetic reaction times.\[^{200,293}\] If this is not the case, the kinetic data are inaccurate until the initial measurement residence time is achieved. To tackle this issue, Epps et al. built a braided tube micromixer able to achieve homogeneous conditions within 53 ms.\[^{300}\] This initial measurement residence time was quantified using a fluorescein quenching reaction where the time for the total disappearance of the fluorescence tracker is considered as the mixing time. In this way, the mixing times can be recorded for a wide range of flow rates. When the braided mixer is used to synthesize CsPbBr\(_3\) NCS, it was found that the mixing time has an effect on the size. Increasing the mixing time from 0.3 to 6.3 s leads to a redshift in the emission peak (2.53–2.46 eV) as well as a broader absorption peak. Having said this, one of the main advantages of flow reactors to measure kinetics is that they operate at steady state, and thus, mixing nonhomogeneities do not lead to the lack of reproducibility observed in batch reactors.

Despite current efforts to monitor the kinetics of the synthesis of lead-halide perovskites, the fast kinetics require initial measurement times (i.e., mixing times) below 100 ms.\[^{87,179}\] In addition, such kinetic studies are particularly complex due to the formation of multiple morphologies (e.g., nanocubes or nanoplatelets) and perovskite-inspired structures (e.g., CsPb\(_5\)Br\(_5\) and Cs\(_3\)PbBr\(_7\)).\[^{300}\] Therefore, further research with a focus on enhanced mixing reactors and in situ monitoring is required.

The use of in situ optical spectroscopy techniques is facile in terms of both equipment setup and data interpretation in studies of kinetics for optoelectronic materials. However, these techniques (UV–vis, PL) have a limited size-related response range; when the few-atom clusters or ultrasmall nuclei are formed, the spectral response for the very small species is not detectable. For example, the PbS QDs synthesized using droplet flow microreactor showed PL response from particles with sizes from 2.9 to 3.5 nm.\[^{89}\] However, it is likely that smaller QDs are formed, however, the PL threshold sensitivity is ≈2.9 nm for these materials. The same case is observed for CdTe QDs, where the first 25% of the total reactor length did not show detectable photoluminescence.\[^{127}\] Therefore, alternative characterization techniques should be considered for optoelectronic materials in cases where optical spectroscopy gives limited information on very small clusters.

In addition, it is important to note that the kinetic of different nanomaterial synthetic steps (e.g., growth) can be affected by the presence and nature of ligand and stabilizer.\[^{92,321,332}\] Indeed, it has been demonstrated that the rate constants can vary in orders of magnitude, especially in fast reactions of optoelectronic quantum dots such as lead-halide perovskites.\[^{326}\] To add to the complexity, the presence of ligands can also promote anisotropic growth such as in the case of lead-halide perovskites where the shape is determined by the ligand combination.\[^{223}\]

### 4.5. Limitations in Integrating In Situ Characterization Techniques into Flow Reactors

To date, many characterization techniques have been implemented for in situ and/or online measurements in flow reactors, including UV–vis,\[^{70,240}\] PL,\[^{302,327}\] XAS,\[^{140,144}\] Raman,\[^{155}\] SAXS,\[^{254,312}\] TEM\[^{131}\] and NMR.\[^{275}\] Fast data acquisition in the millisecond time range enables access to processes occurring in the early stage of the synthesis of nanomaterials, which is especially important for optoelectronic materials, which are formed within a few seconds.\[^{89}\] However, a range of characterization techniques (see details in Table 1) have not yet been applied for in situ or online monitoring due to the time required to obtain reliable data. In situ XRD has been implemented in stopped-flow devices;\[^{212,254}\] however, it suffers from the low resolution required to monitor the synthesis of small species such as nuclei. Similarly, the in situ adaptation of the
particles would be masked and affected by their flow motion in continuous reactors. Despite this, a flow-connected DLS instrument has been proposed, but has yet to gain widespread use. Although in situ NMR measurements have not been applied for the synthesis of nanomaterials, its deployment to monitor organic reactions demonstrates its potential feasibility. Microfluidic chips have been placed inside the magnetic chamber with a planar coil placed on top of the channel to generate and receive radio-frequency signals. Mass spectroscopy is intrinsically incompatible with in situ measurements as it is a destructive technique and requires meticulous sample preparation (washing, digestion, etc.). Another optical technique that has been proved challenging to be integrated for in situ time-resolved monitoring of nanoparticle synthesis is transient absorption spectroscopy (TAS). TAS is a powerful method to track the kinetics of photoexcited charge carriers, providing insights into the types of carriers formed after excitation, and how these are transported in the material and lost due to nonradiative recombination. Monitoring the evolution of these properties during synthesis will show, for example, how the ligands attach to the surface of the NCs over time and influence the density of surface traps. The challenge with TAS is that the differential absorption usually takes several minutes to take because of the need to obtain a sufficient signal-to-noise ratio, and the spectra at different pump–probe delays need to be sequentially acquired. Recently, the latter challenge was addressed through single-shot TAS. In this method, the different pump–probe delays are achieved by having the probe beam at an angle to the sample, while keeping the pump beam normal to the sample. The pump–probe delay therefore varies across the width of the measurement spot, enabling the entire kinetics of the TA spectra to be taken at once. While this substantially reduces the time to acquire TA spectra from minutes to seconds (for MAPbI₃ colloidal nanocrystals), it is still not sufficiently short to probe the rapid kinetics of halide perovskite systems and other optoelectronic and plasmonic materials. Furthermore, single-shot TAS requires uniform pump/probe beams, as well as nonchanging samples over the entire measurement spot.

4.6. Reproducibility

In contrast to the batch-to-batch variation associated with the batch system, flow reactors offer high reproducibility as they operate under steady state. However, this can be altered by perturbations such as the fouling of the reactor walls. Nakamura et al. reported the synthesis of CdSe QDs using a silica capillary flow reactor, where the reactions were conducted 3 times with a 1 h interval. The ex situ PL measurements were nearly identical in the repeated experiments. Moreover, Toyota et al. analyzed the reproducibility of helical reactors connected in series by running the same CdSe synthesis reaction over 6 times, and the result showed only a 0.05 nm standard deviation in particle size. Panariello et al. reported high reproducibility on the synthesis of 50 nm Au NPs with just 1% variation in the average size of 53 ± 0.6 nm over three independent runs. Pinho and Torrente-Murciano systematically quantified the repeatability of flow reactors by running the synthesis of Ag NPs 100 times at various target sizes. The relative deviation of particle size was 13% over a wide range of target sizes.

In summary, the use of flow reactors provides several advantages with respect to batch reactors in the understanding of the synthesis kinetics of nanomaterials: 1) shorter initial measurement times, 2) higher reproducibility, and 3) minimal mass transfer limitations. Abundant examples for a wide range of materials are presented in Table 3. Current limitations are more associated with the integration of a wider range of in situ characterization techniques.

5. Conclusions and Outlook

Understanding the synthesis mechanisms of plasmonic and optoelectronic materials is at the core of their development and discovery. It is only by inspecting time-resolved data during synthesis, revealing the different mechanistic stages taking place, and measuring their relative rates, that one can design the synthesis of size-controlled nanomaterials to move away from trial-and-error. However, this objective is particularly complex due to the fast nature of the reactions: for example, coprecipitation of lead-halide perovskite nanocrystals is known to take place within ms, similar to the nucleation stage of some plasmonic nanoparticles (e.g., Au). Traditionally batch reactors, and more recently flow reactors, have been extensively used for the discovery and synthesis of new nanomaterials. In both cases, conventional ex situ characterization (mainly spectroscopy and imaging) enables the understanding of the physical properties of the resulting materials. This approach can be used to successfully study the effect of synthetic parameters, such as temperature, concentration of reactants, presence of capping ligands and their nature, etc. However, ex situ characterization can only provide discrete time-resolved synthetic information, either by taking periodic samples in batch reactors or by varying the residence time in flow system. Thus, it suffers from a number of disadvantages associated with postsynthesis stabilization, which is problematic due to the inherent instability of these nanomaterials. To mitigate this, samples need to be rapidly quenched and stabilized. Yet, this is not easy to accomplish as proved by Koerner et al. Additionally, there are no established quenching protocols or standardization in place leading to large sampling times and a general lack of repeatability. In any case, samples need to be collected, in most cases at times in the millisecond scale to reveal information about the early synthetic stages, which is in most cases unattainable when using ex situ characterization. Several researchers have tackled this issue by slowing down the synthesis through the reduction of the reaction temperature, the addition of mild reducing agents, interfering capping ligands, etc. (refer to Table 2). For ex situ characterization, it is only in this way that synthetic stages such as nuclei burst, coalescence of nuclei, and subsequent growth have been successfully identified and separated.

In situ monitoring of nanomaterial syntheses using a range of optical fibers, optical cells, and different probes overcomes the problem of experimental error associated with sample collection and stabilization effects, resulting in lower measurement time resolution (Δtₑ, millisecond timescale). In situ characterization can provide early stage synthetic information, assuming
that the mixing time is minimized so the initial measurement
time can be reduced to capture early kinetic information (e.g.,
when applied to flow reactors or stopped-flow devices). This
point highlights the importance of mixing and therefore,
reactor design, during the development of materials – an aspect
overlooked and responsible for the lack of consistent and repro-
ducible data in the literature, especially for batch systems. Con-
ventional strategies to maximize the mixing efficiency in batch
reactors consist of the use of vigorous stirring and on very few
occasions, the use of baffles. Nevertheless, the mixing time in
batch reactors is often in the range of a few seconds. The time
required for mixing and heating in batch reactors is at the core
of their characteristic batch-to-batch variations and can impede
access to important time-resolved data, even when using in situ
analytics. Attempts to improve mixing come at the cost of pro-
moting agglomeration of the crystals during their synthesis,
especially in the early stages, making equally traditional the use
of capping and stabilizing ligands. The effect of such additives
on the mechanism and kinetics of the system is another often
overlooked aspect and is probably responsible for some of the
discrepancies in the literature kinetic data.

The adoption of flow microreactors (conventionally used
in fast organic transformations) for material synthesis usu-
ally overcomes the issue of reproducibility due to their steady-
state operation combined with higher control over mixing and
shorter mixing times (i.e., higher mixing efficiencies) than
batch system counterparts. According to studies discussed in
this review, microfluidic reactors with in situ characterization
can achieve initial reported times as low as 6 ms. Neverthe-
less, they present several challenges such as fouling, blockage,
etc., that should be taken into consideration during the data
processing. While it is commonly accepted that microreactors
present high mass and heat transfer due to their small char-
acteristic diameters (within a few millimeters), mixing is
dominated by diffusion under their laminar flow so again, one
should consider the relation between synthesis and mixing
times when using microreactors for kinetic studies. Although
a number of studies in the literature clearly present the
differences in the physical properties (mainly in terms of size
distribution) of the nanomaterials during batch and flow syn-
theses, only a fraction of studies properly assessed the
effect of radial and axial mixing in microreactors. When done,
the potential diffusion limitations are tackled using biphasic
systems (to promote Taylor flow) or 3D microreactor
configurations (to promote Lagrangian turbulence, Dean vor-
tices, or similar). It is noteworthy, that only the use of in
situ characterization in well-designed flow reactors can enable
the real monitoring and understanding of the early stages
of nanoparticle formation, especially during fast syntheses (few
seconds to reach completion, and nucleation below ~100 ms)
in a reproducible and reliable manner. As reviewed in this
article, most of the in situ monitored flow syntheses have ini-
tial reported times within 100 ms, which is the core advantage
offered by flow reactors in investigating kinetics. In situ char-
acterization in flow reactors requires the design and construc-
tion of sampling points, with research focused on the design
of optical cells with minimum flow and conditions (e.g., tem-
perature) disruption. The field should adapt any state-of-the-
art progress focused on the monitoring of organic reactions in
flow, such as the development of novel optical fiber configu-
rations to enhance sensitivity or even carrying out reactions
within the optical fiber themselves. Another important
aspect should be the expansion of the characterization tech-
niques adopted in flow material synthesis to other spectro-
scopic techniques such as Raman, broadening the accessible
data.

5.1. Potential of Real-Time Material Synthesis Monitoring:
On-Demand Material Synthesis and Discovery

The state-of-the-art real-time monitoring of material synthesis
in flow reactors is not only able to provide kinetic data within
the relevant reaction time range but also invaluable kinetic data
via fixed multipoint (discrete data) or moving multipoint (con-
tinuous) in situ analyses (Figure 6). This approach presents a
number of advantages versus single-point monitoring, where
variations in residence times will only be possible by varying
the fluid dynamics of the system (e.g., varying the flow rates),
potentially affecting the mixing times. Time-resolved moni-
toring of the nanomaterial synthesis provides unique informa-
tion which can be used beyond a material development and
mechanistic understanding tool into quality control in real
time, as it has been successfully demonstrated over the last

![Figure 6](https://www.advancedsciencenews.com)
years for plasmonic nanoparticles and optoelectronic materials \[346,347\] (make-a-particle approach). Current state-of-the-art research goes one step further by linking both aspects together, mechanistic understanding and quality control, to develop advanced feedback closed-loop algorithms for the synthesis of materials on-demand in self-regulated systems (dial-a-particle approach). By understanding the kinetics of the different mechanistic stages, algorithms can control the final nanoparticle size, adapting conditions, and/or flow rates to achieve the desired material properties \[347\]. For example, Bezinge et al. compiled an algorithm to synthesize mixed-cation, mixed-halide perovskite NCs at user-defined photoluminescence wavelength by adjusting the flow rates of the precursors \[347\].

The rapid online PL data acquisition provided feedback information so that after multiple iterations, the target emission can be achieved in a short amount of time. Similarly, Lignos et al. have used an automated platform to explore the composition of mixed-halide, mixed-cation lead-halide perovskites with near-infrared emissions between 700 and 800 nm \[378\]. The setup allowed rapid iterations of precursor input, hence obtaining continuous spectra covering the target range. Pinho and Torrente-Murciano reported a novel dial-a-particle system where Ag NPs can be produced with a target size between 4 and 80 nm \[62\]. Such size tunability was achieved by a combination of multiple flow reactors with distributed feed using in situ absorption measurements between reactors, and a customized algorithm to relate early growth rates to final sizes. In this way, the desired size can be obtained by automatically adjusting the precursor ratio and flow rates based on feedback from absorption spectra. The implications of the dial-a-particle capabilities will be numerous in the near future from the development of manufacturing processes for the synthesis of plasmonic and optoelectronic materials to their fast deployment from the lab to real-world applications. Self-regulated autonomous synthetic platforms are particularly important during the synthesis of nanomaterials when small, uncontrollable perturbations (such as the quality or aging of the precursors) are known to have a large effect on the kinetics of the early stages of the synthesis, and consequently the resulting nanoparticle size and distribution. We believe that in the future, the combination of detailed mechanistic and kinetic understanding of the formation of plasmonic and photoelectronic materials at the nanoscale will enable the building of surrogate models, underpinning the design of novel materials in an autonomous manner (design-a-particle). Such models could be used by machine learning algorithms to predict the properties of other materials including composite ones in a future autonomous discovery of materials driven by application needs.

**Acknowledgements**

B.P., K.Z., and L.T.-M. would like to acknowledge the UK Engineering and Physical Science Research Council (EPSRC) for funding through project Grant No. EP/V025759/1. K.Z. acknowledges a studentship from the EPSRC Centre for Doctoral Training in Graphene Technology (Grant No. EP/L016087/1). R.L.Z.H. acknowledges support from the Royal Academy of Engineering under the Research Fellowship scheme (Grant No.: RF/201718/1701).

**Conflict of Interest**

The authors declare no conflict of interest.

**Keywords**

in situ/ex situ/online characterization, microreactors, optoelectronic materials, perovskites, plasmonic nanoparticles, quantum dots

Received: March 6, 2022
Revised: April 8, 2022
Published online: June 16, 2022

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