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Evolution of Particle Characterization: Past, Present, and Future†

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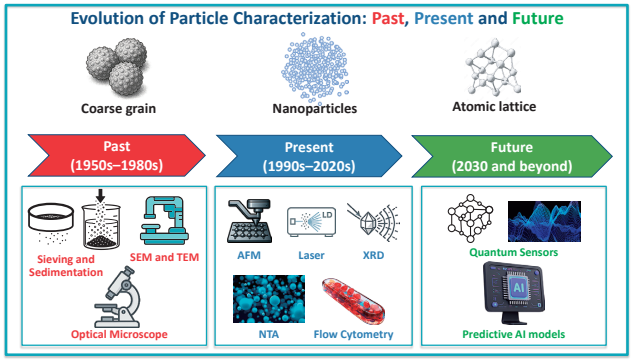
Particle characterization underpins a wide range of fields, including mineral processing, materials science, nanotechnology, pharmaceuticals, food processing, agriculture, and environmental applications, by providing essential information on particle size, shape, surface properties, and size distribution within material systems. Particle characterization techniques have undergone a significant transformation over the last 70 years, moving from simple instruments like sieving and sedimentation to AI-driven analytics and novel imaging technologies that examine structures at the nanoscale and even atomic scale. Because they relied on fundamental physical principles and diffraction limitations, early characterization techniques in the 1950s, like gravity sedimentation and optical microscopy, provided limited results. The introduction of light scattering techniques in the 1970s, such as dynamic light scattering (DLS) and laser diffraction, significantly improved accuracy and efficiency of particle size analysis. The development of atomic force microscopy (AFM), electron microscopy techniques including scanning electron microscopy (SEM) and transmission electron microscopy (TEM), X-ray diffraction (XRD), and nanoparticle tracking analysis (NTA) increased the capacity to analyze complex and ultra-small particles precisely. These innovations are driving groundbreaking applications across various domains, including drug delivery systems, sustainable materials development, and environmental monitoring. Despite these technological advancements, challenges such as scalability in industrial plants, environmental interference, and computational accuracy still pose significant hurdles that must be overcome to fully unlock the potential of next-generation characterization techniques. The ongoing convergence of nanotechnology, AI-driven analytics, and cutting-edge imaging technologies hold immense promise for the future of particle characterization and plant-scale applications. This review traces the historical evolution of particle characterization, highlights key technological milestones over different periods, and explores its future as a driving force for innovation in science and technology.



Keywords: particle characterization, nanoparticle, microbe, resolution, size

1. Introduction

Particle characterization is a fundamental aspect of materials science, nanotechnology, food processing, agriculture, pharmaceuticals, and environmental science. Understanding particle size, shape, surface properties, and distribution is crucial for optimizing materials and improving product performance. Over the past seven decades, this discipline has charted an extraordinary evolution, transitioning from the rudimentary tools of the mid-20th century to sophisticated technologies that pierce the nanoscale frontier and beyond. Early techniques, such as sieving and sedimentation, which depended on gravitational settling and mechanical separation; however, they failed when faced with fine or polydisperse particles due to their reliance on elementary physical principles (Barth and Sun, 1989; Skoog et al., 2018). Optical microscopy offered a window into particle morphology, but it is limited by the diffraction limit (~200 nm), leaving submicron domains elusive until breakthroughs like phase-contrast and electron microscopy illuminated the way (Goldstein et al., 2003; Malvern, 2002). Today, the field utilizes high-precision instruments such as atomic force microscopy (AFM), X-ray diffraction (XRD), nanoparticle tracking analysis (NTA), and AI-driven analytics delivering atomic-scale resolution, real-time data, and automated insights that overcome earlier barriers related to scale, speed, and complexity (Binnig et al., 1986; Bishop, 2006). These cutting-edge tools stand on the shoulders of foundational methods that harness simple separations, now amplified by advanced imaging and computational power to explore nanoscale phenomena (Allen, 1997). This review explores the transformative journey of the field of particle characterization, highlighting key technological advancements spanning from traditional sieving methods to artificial intelligence-driven sensors. It also projects a future in which particle characterization will deepen our understanding and

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spur groundbreaking scientific and technological progress.

2. Past: early methods (1950–1980)

In the mid-20th century, particle characterization relied on relatively simple techniques, such as sieving and sedimentation, to determine particle size distribution. Sieving was widely used for larger particles (>50 μm), employing mesh screens of varying pore sizes to separate particles based on size. These screens were often handmade or mechanically woven to sort particles with hand-shaken or vibratory sieve shakers like the Ro-Tap or industrial setups from manufacturers like Hosokawa Micron Powder Systems, who contributed significantly to early powder classification and processing systems (Barth and Sun, 1989). However, fine particles can also stick to each other, to coarser particles, or to the sieve due to cohesive forces (van der Waals interactions), especially if they are dry or irregularly shaped. This effect is particularly pronounced in dry samples due to the lack of moisture that might otherwise mitigate adhesion. In wet systems, capillary forces can also contribute significantly to particle agglomeration, hindering accurate separation, especially in humid environments or slurries with fine, irregularly shaped particles. Sedimentation techniques measured particle settling velocities in liquid media based on Stokes' Law, allowing for the determination of particle size distribution for smaller particles. Sedimentation used glass settling tubes or the Andreasen pipette, a manual sampling device, to measure particle settling rates in liquids, though setups like hydrometers or sedimentation balances offered rudimentary automation (Skoog et al., 2018). Sedimentation struggled with fine particles, where gravitational effects were overshadowed by Brownian motion and fluid drag, resulting in impractically slow settling times, as described by Stokes' Law. Although this law provides a foundational model for sedimentation, it is only valid under idealized conditions assuming spherical particles and laminar flow, making it increasingly inaccurate for submicron particles. Moreover, the size determined via sedimentation is a hydrodynamic diameter, rather than the actual physical diameter. This value reflects a combination of factors, including particle shape, density, and surface roughness, as well as the viscosity and density of the suspending fluid.

Different techniques are inherently associated with different size definitions: sieving measures geometric (mesh) size, sedimentation yields an equivalent hydrodynamic diameter, and microscopy offers an equivalent projected area diameter. The choice of method and, thus, the definition of "size" must align with the specific application. For example, pharmaceutical dissolution studies often rely on surface area-relevant measurements, whereas material compaction in ceramics may depend on volume-based size distributions. A clear understanding of these distinctions is crucial for selecting the appropriate characterization tools and interpreting data accurately.

These considerations are particularly important in industrial applications. For instance, designing a pneumatic conveying system requires accurate knowledge of a particle's aerodynamic behavior, which is best captured through equivalent spherical diameters measured via laser diffraction or time-of-flight techniques (Merkus, 2009). On the other hand, optimizing a high-shear mixer or ribbon blender depends on particle shape, cohesion, and packing behavior—parameters more accurately characterized using optical microscopy or image-based particle analysis techniques (Muzzio et al., 2002). Selecting an inappropriate sizing method can lead to inefficient processing, equipment wear, or inconsistent product quality, underscoring the importance of application-specific technique selection.

Furthermore, both sieving and sedimentation were particularly ineffective for polydisperse mixtures, which feature a wide range of particle sizes, as they lacked the precision and flexibility to resolve overlapping size populations or isolate specific fractions with high fidelity.

Fig. 1 illustrates the sedimentation process, which relies on the principle that particles of varying sizes and densities settle at different rates in a fluid. Larger and denser particles sediment more rapidly under the influence of gravity, while finer particles remain suspended for longer periods. This method is effective for measuring particle size distribution in suspensions and colloids, and its behavior is governed by Stokes' Law. On the right of the figure (**Fig. 1(d)–(e)**), the graphs depict the various interaction potentials that influence sedimentation at the nanoscale, including van der Waals, electrostatic, Born, osmotic, and elastic forces. These forces influence particle aggregation, stability, and dispersibility in solvents such as water and ethanol. For example, van der Waals attraction dominates at short interparticle distances, which can lead to agglomeration unless counteracted by repulsive forces such as electrostatic or steric interactions. These foundational techniques were crucial precursors to modern analytical methods, offering early insights into particle behavior, stability, and interactions in both industrial and research settings.

Optical microscopy was a widely used and foundational method for analyzing particle morphology, leveraging visible light and magnifying lenses to enable direct two-dimensional visualization and measurement of particle shape and size. Optical microscopes from various manufacturers such as Zeiss, Leitz (later Leica), Nikon, and Olympus were commonly equipped with glass objective lenses and manual stages, often requiring meticulous sample preparation on slides and the use of ocular micrometers for dimensional measurements (Murphy and Davidson, 2012). However, its effectiveness was limited by the diffraction limit of light, approximately 200 nm, as defined by Abbe's resolution formula:

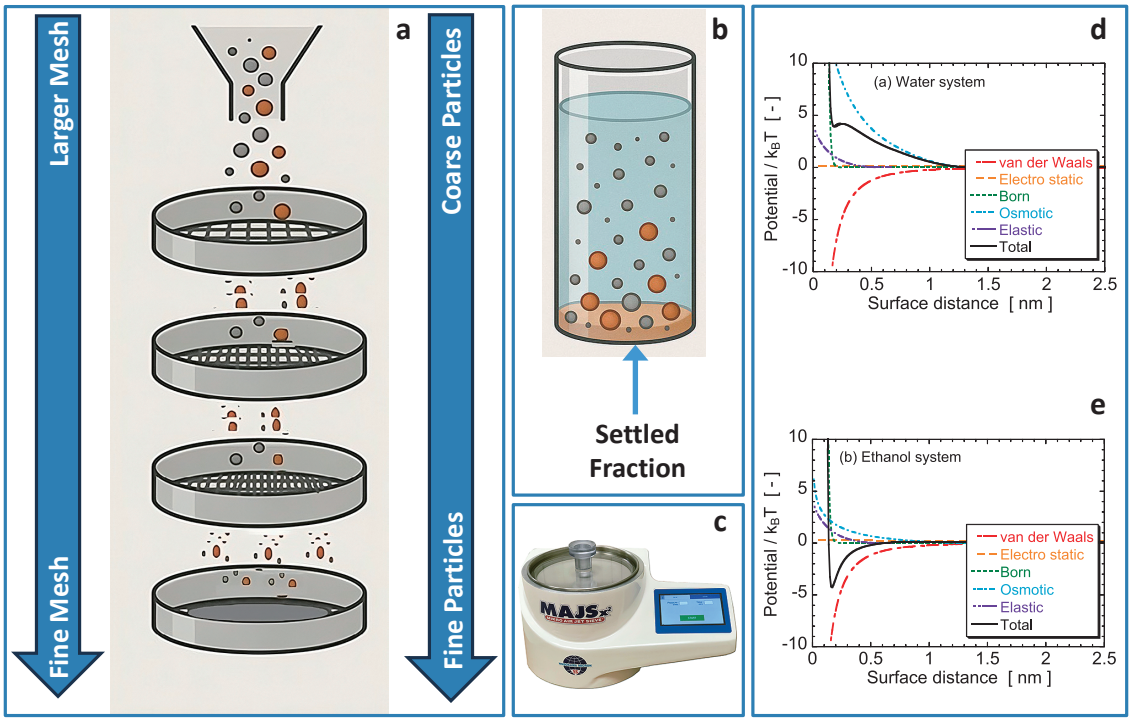

Fig. 1 **(a)** Sieving techniques used for particle size separation, where coarse particles are retained on larger mesh screens while finer particles pass through to finer mesh levels; **(b)** Sedimentation technique showing particle size-based settling in a fluid medium; larger particles settle at the bottom faster than finer ones; **(c)** Hosokawa's MIKRO Air Jet Sieve® system used for precision particle size analysis. **(d)** and **(e)** Interaction potential vs. surface distance in water-based and ethanol-based systems showing contributions from van der Waals, electrostatic, Born, osmotic, and elastic forces. **(d)** and **(e)** Reprinted from Ref. (Mori, 2015) under the terms of the CC-BY 4.0 license. Copyright: (2015) The Authors, published by Hosokawa Powder Technology Foundation.

$$d = 0.612\lambda / (n \sin \alpha) \quad (1)$$

where:

d is the resolution,

λ is the wavelength of light,

n is the refractive index of the medium between the lens and the sample, and

α is the half-angle of the light cone from the specimen plane accepted by the objective.

This limitation rendered conventional optical microscopy inadequate for resolving fine colloids or nanoparticles, which fall well below the diffraction limit. Moreover, standard brightfield microscopy struggled with low-contrast or transparent samples, particularly biological particles such as microbes (e.g., bacteria, protozoa), protein aggregates, and virus-like particles, as well as polymeric microspheres and hydrogels. These samples often lack sufficient inherent contrast due to weak light absorption and suffer from a shallow depth of field, which restricts accurate 3D visualization. To address these issues, phase-contrast microscopy was introduced in the 1930s and widely commercialized by the 1960s. This technique converted phase shifts caused by refractive index variations into visible contrast, enhancing visibility of transparent specimens. Similarly, differential interference contrast (DIC) microscopy, refined in the 1950s and adopted in the 1960s, used polarized light interference to generate pseudo-3D images, improving surface detail resolution in low-contrast biological and polymeric samples, such as microbial cells, polymer films, or thin tissue sections. DIC systems were developed and distributed by several major instrument makers, including Leitz (later Leica), Zeiss, and Olympus, all of whom contributed to the widespread adoption of these enhanced contrast techniques (Pluta, 1988). Despite these innovations, both phase-contrast and DIC remained limited by the fundamental diffraction barrier of optical systems. It was not until the advent of electron and laser-based methods—such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), and confocal or super-resolution microscopy—that researchers gained access to nanoscale features in three dimensions with significantly higher resolution and contrast.

A major breakthrough in the 1970s came with the development of light scattering techniques, such as dynamic light scattering (DLS) and laser diffraction. Instruments such as laser diffraction analyzers, developed and distributed by companies including Hosokawa Micron Powder Systems, have made significant contributions to modern particle size analysis across dry and wet sample applications. This method enabled more accurate and rapid particle size analysis by analyzing the scattering pattern of laser light as it interacted with particles in suspension (Barth and

Flippen, 1995). DLS was particularly valuable for characterizing nanoparticles, as it provided a non-invasive, high-throughput method for determining equivalent hydrodynamic diameter based on Brownian motion. Meanwhile, laser diffraction allowed for real-time particle size distribution measurements across a broad size range (Xu, 2002).

The late 1970s and early 1980s ushered in electron microscopy techniques like SEM and TEM, transforming particle analysis with unprecedented resolution down to the nanometer scale. SEM harnessed a scanning electron beam to generate detailed, high-magnification images of surface topography, offering magnifications up to 100,000x and resolutions of 1–10 nm, ideal for mapping particle textures and shapes. Leading SEM systems were developed by manufacturers such as JEOL, Hitachi, Zeiss, and later FEI (now part of Thermo Fisher Scientific). TEM, by contrast, transmitted electrons through ultrathin samples to reveal internal structures, crystallinity, and, in advanced cases, atomic arrangements, achieving sub-nanometer precision (e.g., 0.1–0.2 nm) by the early 1980s (Goldstein et al., 2003). Prominent TEM instrument makers included JEOL, Philips, Hitachi, and FEI, each contributing to the evolution of high-resolution imaging technologies. These powerful imaging techniques enabled the visualization of nanoparticles, crystal defects, and a range of biological particles with remarkable clarity (Binnig et al., 1986). For instance, SEM has been extensively used to image bacterial surfaces (e.g., pili and flagella of *Escherichia coli*), fungal spores, and pollen grains, while TEM has allowed researchers to study internal ultrastructures of viruses (e.g., influenza and adenoviruses), protein complexes, lipid vesicles, and cellular organelles (e.g., mitochondria and endoplasmic reticulum). These biological specimens, which were often well below the resolution limits of optical microscopy, became accessible for detailed investigation through the invention of electron microscopy.

However, several limitations tempered the versatility of electron microscopy. SEM required conductive coatings for non-metallic samples such as biological tissues, polymers, or ceramics, which risked introducing artifacts, and required a vacuum environment, thereby excluding wet materials. TEM demanded painstaking preparation of ultrathin sections, which often altered delicate particles. Both techniques risked beam-induced damage to fragile samples. Despite offering revolutionary resolution and insights, high costs, small fields of view, and the complex image interpretation further restricted their use to specialized laboratories. Nonetheless, these advancements laid the foundation for modern particle characterization, paving the way for high-resolution techniques that would emerge in the following decades.

During this period, the size and shape measurements of biological particles such as microbes relied on basic optical tools and manual techniques tailored to biological samples. Optical microscopes, such as the Nikon or Olympus models with brightfield illumination, were the workhorses, with glass slides and stains (Gram staining) to improve contrast for bacteria or yeast. These instruments could usually resolve shapes of larger microbes like *Escherichia coli* (1–2 μm), but not viruses (Alberts et al., 2002). Sedimentation via centrifugation with simple benchtop units (e.g., Sorvall models) separated cells by size and density in liquid gradients, though quantitative shape data required laborious ocular micrometer measurements or photographic analysis (Skoog et al., 2018). Phase-contrast microscopy, popularized in the 1960s, improved the visualization of transparent microbes like amoebae without staining, yet the diffraction limit and shallow depth of field hindered precise 3D shape analysis of smaller biological particles (Murphy and Davidson, 2012). These methods provided a foundational framework for biological imaging but struggled with nanoscale precision and automation.

Fig. 2 illustrates how various microscopy techniques enable the visualization and characterization of microbes and particles at different scales. In **Fig. 2(a)**, optical microscopy, such as fluorescence microscopy, allows for the visualization of microbes using fluorescent dyes that bind to specific biological components, with red and green dyes differentiating microbial populations. **Fig. 2(b)** shows TEM, which reveals fine structural details of bacteria through contrast generated by electron density differences, allowing observation of intracellular features like membranes and ribosomes. **Fig. 2(c)–(f)** present SEM, which provides detailed 3D surface morphology of particles, highlighting precise topographical features of tin particles and microbes. Finally, AFM provides topographical data at the nanometer scale through mechanical probing. In **Fig. 2(f)**, a tin particle is attached to an AFM cantilever tip, enabling the study of nanoscale surface interactions.

3. Present: high-precision techniques (1990–2020)

The 1990s marked the beginning of a high-precision era in particle characterization, facilitated by the development of atomic force microscopy (AFM) and X-ray diffraction (XRD). AFMs, such as the Digital Instruments Nanoscope, later acquired by Bruker, utilize piezoelectric scanners and sharp cantilever tips to map surfaces with atomic resolution, controlled by sophisticated software that provides real-time topography data. AFM, pioneered by Binnig et al. (1986), enables nanoscale imaging with a vertical resolution approaching 0.1 nm, offering detailed insights into surface morphology, mechanical properties (e.g., stiffness, elasticity), and a range of molecular interactions, including hydrogen bonding, van der Waals forces, and electrostatic interactions. In addition to Bruker, other prominent AFM system manufacturers—such as Park Systems, Asylum Research (later acquired by Oxford Instruments), and

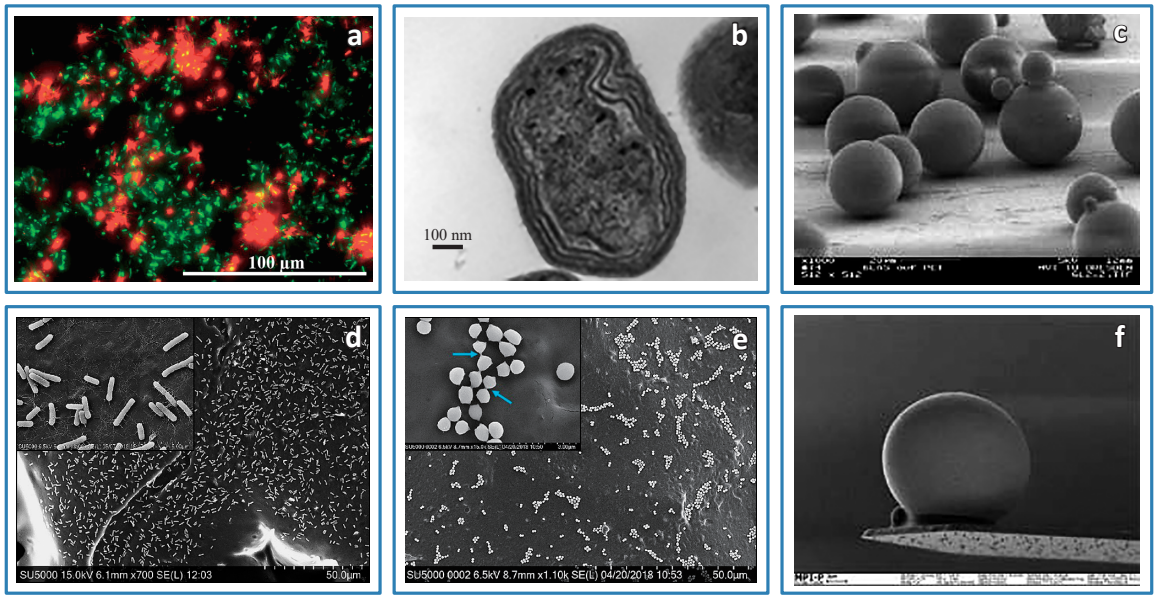

Fig. 2 **(a)** Fluorescence microscopy image showing live (green) and dead (red) *Escherichia coli* cells; **(b)** Transmission electron microscopy (TEM) image of a single *Nitrosomonas europaea* bacterium revealing internal structural detail; **(c)** Scanning electron microscopy (SEM) image of spherical tin particles with varying diameters; **(d)** SEM image of *E. coli* bacteria, with inset showing magnified rod-shaped morphology; **(e)** SEM image of *S. aureus* bacteria, with inset indicating spherical shape and clustering behavior (blue arrows); and **(f)** SEM image of a tin particle attached to the end of an AFM cantilever for force measurements or manipulation studies. **(a)**, **(d)**, and **(e)** Reprinted from Ref. (Nandakumar, 2018) under the terms of the CC-BY 4.0 license. Copyright: (2018) The Author, published by University of Florida. **(b)** Reprinted from Ref. (Somasundaran et al., 2010) under the terms of the CC-BY 4.0 license. Copyright: (2010) The Authors, published by Hosokawa Powder Technology Foundation. **(c)** and **(f)** Reprinted from Ref. (Ripperger and Hein, 2004) under the terms of the CC-BY 4.0 license. Copyright: (2004) The Authors, published by Hosokawa Powder Technology Foundation.

NT-MDT—have contributed significantly to broadening the technique's applications. AFM has become particularly valuable for studying biological materials such as DNA strands, protein aggregates, bacterial cell walls, and lipid bilayers, especially in near-physiological conditions without requiring staining or vacuum environments. However, the technique was not without limitations: its relatively slow scanning speed, susceptibility to tip-induced artifacts, and limited field of view restricted its utility for high-throughput or large-area analyses. Complementing AFM, X-ray diffraction (XRD) provided powerful insights into internal crystallographic structures. In XRD, X-rays are directed at a crystalline sample, and the rays diffract off atomic planes according to Bragg's Law:

$$n\lambda = 2d \sin\theta \tag{2}$$

where:
n is an integer,
λ is the wavelength of the X-rays, and
θ is the angle of incidence producing a pattern that reveals lattice spacing and crystal structure.

Here, *d—the interplanar spacing*—is the key variable measured to determine the sample's structural fingerprint. X-ray diffraction (XRD) instruments—from Rigaku, Bruker, PANalytical (now Malvern Panalytical), Shimadzu, and Thermo Fisher Scientific—employed high-intensity X-ray tubes and advanced digital detectors (e.g., CCDs and silicon strip detectors) to probe crystallographic structures with high sensitivity. Automated goniometers and improved control software significantly enhanced angular precision and throughput. By the 1990s, improved detectors and software had made it a workhorse for particle analysis, particularly in decoding crystallographic structures critical for pharmaceuticals and nanotechnology. However, the technique struggled with amorphous materials and bulk averaging, and its resolution (typically < 10 nm) is limited by peak broadening, complicating precise sizing (Cullity and Stock, 2001).

In the 2000s, nanoparticle tracking analysis (NTA) and field-flow fractionation (FFF) emerged for liquid-phase precision. NTA uses a laser to illuminate nanoparticles in suspension, capturing their Brownian motion via a microscope and camera. NTA systems like Malvern's NanoSight combine laser illumination with high-speed cameras and tracking software to measure particle size in liquids. Software tracks individual particle trajectories via Brownian motion, calculating size via the Stokes–Einstein equation:

$$D = kT/(6\pi\eta r) \tag{3}$$

where:
D is the diffusion coefficient,
k is Boltzmann constant,
T is absolute temperature,
η is the viscosity of the fluid, and
r is the radius of the particle.

This equation is central to NTA, as it enables the estimation

of particle size from observed motion in a fluid medium. NTA visualized nanoparticle size distributions (typically 10 nm to 1 μm), which is vital for polydisperse systems, although it struggled with extreme concentrations or low-contrast particles (Griffiths et al., 2020). FFF units such as Wyatt Technology's Eclipse used programmable pumps and flow channels for hydrodynamic separation. An external field (e.g., flow, centrifugal, thermal) is applied perpendicular to a laminar flow in a channel, separating particles by size, mass, or hydrodynamic properties. Smaller particles elute faster due to differential positioning in the flow profile. FFF separated particles by hydrodynamic properties without stationary phases, excelling for delicate samples, though its complexity and resolution limits posed challenges (Giddings, 1993).

The 2010s fused artificial intelligence (AI) and multimodal techniques into particle characterization, amplifying precision and scalability. Deep learning algorithms analyze microscopy images or scattering data, segmenting particles, recognizing patterns, and predicting properties. Convolutional neural networks (CNNs) excel at identifying shapes or sizes from noisy datasets (Bishop, 2006). AI automated tedious tasks—for example, counting particles in SEM images—thereby boosting throughput and reducing human error. It enhanced morphology analysis (e.g., distinguishing rods from spheres) and even predicted particle behavior (e.g., stability) from limited data. However, training set models require large, labeled datasets, poorly tuned algorithms may misinterpret noise as signal, and their decision-making lacks transparency, challenging validation in regulated fields like pharmaceuticals. Additionally, combining spectroscopy, microscopy, and real-time processing offered comprehensive insights, revolutionizing applications from drug design to materials engineering, albeit at the cost of complexity and expense.

Biological particle characterization progressed between 1990 and 2020 due to high-resolution tools that could probe the size and structure of microbes at the cellular and molecular levels. SEM and TEM, using systems like the JEOL JSM or Hitachi HT7700, delivered nanometer-scale imaging. SEM mapped bacterial surface morphologies (e.g., pili on *Staphylococcus*), while TEM revealed viral capsid structures (~20–100 nm) after ultrathin sectioning or negative staining (Goldstein et al., 2003). Flow cytometry instruments, such as the BD FACSCalibur, enabled high-throughput analysis of microbial populations by measuring size and shape indirectly through forward and side light scattering, along with fluorescence labeling. These systems could process thousands of individual cells per second, generating population-level data on size, granularity, and biomarker expression. While not providing direct imaging, flow cytometry typically detects particles in the range of ~200 nm to 50 μm, with effective resolution depending on the optical setup and sensitivity of the detectors (Shapiro, 2003). AFM, such as Bruker's BioScope, offers complementary high-resolution imaging by generating three-dimensional topographic maps of living microorganisms, including bacteria and yeast, under in vitro and physiological conditions. These conditions refer to controlled environments (e.g., temperature, pH, and buffer composition) that mimic the natural biological settings but are maintained outside living organisms, for example, using liquid imaging chambers on the AFM stage. This tool allows researchers to observe biological structures in their native hydrated state without requiring fixation or dehydration. However, the technique's slow scan speeds and limited field of view constrained its throughput (Binnig et al., 1986). Together, flow cytometry and AFM provided complementary insights into microbial cell morphology but required complex sample preparation and specialized expertise.

4. Timeline of particle characterization evolution

1950—Foundations of Measurement:

Sieving and sedimentation used for basic particle size distribution.

1960—Morphological Insights:

Optical microscopy employed to analyze particle morphology.

1970—Precision in Size Analysis:

Dynamic light scattering (DLS) and laser diffraction introduced for improved particle size analysis.

1980—Nanoscale Imaging Revolution:

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) revolutionize nanoscale imaging.

1990—Surface and Structural Characterization:

X-ray diffraction (XRD) and atomic force microscopy (AFM) enhanced crystallographic and surface characterization.

2000—Advancements in Nanoparticle Analysis:

Nanoparticle tracking analysis (NTA) and field-flow fractionation (FFF) improved precision in nanoparticle characterization in liquids.

2010—AI-Powered Automation:

Artificial intelligence (AI) and machine learning integrated for automated image and data analysis.

2020—Multi-Modal Synergy:

Multi-modal approaches combining spectroscopy, microscopy, and deep learning refine accuracy and efficiency.

5. Future: emerging innovations (2030 and beyond)

5.1 Revolutionizing resolution: the rise of quantum imaging tools

The rise of quantum-based particle characterization promises a seismic shift in precision, targeting atomic and

subatomic scales with techniques unattainable by classical methods. Quantum-enhanced imaging, harnessing phenomena like quantum entanglement and squeezed light, exploits the quirky properties of quantum mechanics where photons or electrons are correlated in ways that amplify signal-to-noise ratios to break past the diffraction limit (~200 nm) of traditional optical microscopy.

This could yield resolutions approaching picometers, enabling visualization of individual atomic orbitals or molecular bonds in nanoparticles, as theorized by Dowling and Milburn (2003). Quantum sensors, such as those based on nitrogen-vacancy (NV) centers in diamond, could measure mass, force, and electromagnetic fields with exquisite sensitivity down to yoctonewtons (10^{-24} N) or attograms (10^{-18} g), offering unparalleled insights into nanoscale interactions like protein folding or van der Waals forces. For fields like quantum computing, biophysics, and materials engineering, this could unlock precise tailoring of particle properties at their most fundamental level (Degen et al., 2017).

5.2 Real-time insight: deep learning in particle science

Artificial intelligence and deep learning will cement their dominance in particle characterization, driving real-time monitoring and predictive insights by 2030 and beyond. AI-powered automation could monitor particle properties such as size, shape, charge, or aggregation instantaneously, slashing the hours or days once needed for manual data crunching. Advances in predictive modeling, rooted in deep learning frameworks like those pioneered by LeCun et al. (2015), could simulate particle behavior in dynamic systems—for example, forecasting how a drug carrier disperses in blood or how pollutants clump in air. This speed and foresight would supercharge applications: optimizing drug delivery in real time, accelerating material synthesis for 3D printing, or tracking environmental nanoparticles during pollution events. Moreover, the fusion of AI with multi-modal data (e.g., microscopy, spectroscopy) could even reveal hidden correlations and driving discoveries in complex systems. However, the reliance on robust datasets, opaque algorithms, and heavy computing resources raises red flags. Accuracy may falter with poor inputs, and over-automation might miss subtle anomalies—tempering AI's promise with practical caveats.

5.3 Lab on a chip: seeing particles in action

The integration of miniaturized, portable characterization devices is set to enable real-time *in situ* monitoring of particles in complex environments. Advances in miniaturized sensors such as lab-on-a-chip platforms with optical or electrochemical detection (Whitesides, 2006) along with non-invasive probes like Raman scattering in flow systems such as next-generation microfluidic platforms (Scholtes-Timmerman et al., 2014), might track particle size, shape, and chemistry without disrupting the system. This could revolutionize process control in manufacturing, enable real-time environmental monitoring (e.g., aerosol mapping), and enhance biomedical research (e.g., drug particle uptake in tissues), offering a live window into particle behavior.

5.4 Modeling the invisible: the power of simulations in particle analysis

The application of high-performance computing and simulation-driven characterization will enhance the understanding of particle interactions at molecular and atomic scales. Supercomputers or quantum computing may

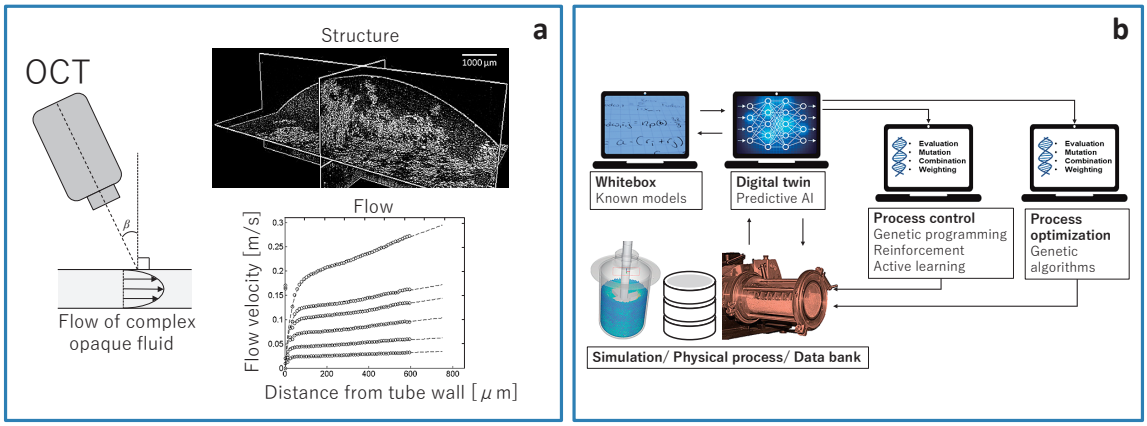

Fig. 3 Key emerging trends poised to redefine particle technology by 2030 and beyond. **(a)** Optical Coherence Tomography (OCT) enables non-invasive visualization and flow profiling of complex opaque fluids, offering both structural imaging and velocity field mapping inside microchannels; **(b)** Artificial Intelligence (AI)-driven digital twins integrate unit operations models with predictive AI, facilitating advanced process control and optimization through reinforcement learning, genetic programming, and simulation-guided decision-making. **(a)** Reprinted from Ref. (Koponen and Haavisto, 2020) under the terms of the CC-BY 4.0 license. Copyright: (2020) The Authors, published by Hosokawa Powder Technology Foundation. **(b)** Reprinted from Ref. (Thon et al., 2024) under the terms of the CC-BY 4.0 license. Copyright: (2024) The Authors, published by Hosokawa Powder Technology Foundation.

Table 1 Evolution of characterization techniques at laboratory and plant scale.

Era	Lab-scale				Plant-scale (in-line/on-line)			
	Techniques	Size range measurement	Advantages	Limitations	Techniques	Size range measurement	Advantages	Limitations
1950s–1960s	*Sieving*	20 μm–125 mm	Simple, inexpensive, widely used	Limited to coarse particles, low precision	*Manual sampling and offline analysis*	1 μm–10 mm	Basic quality control	Time-consuming, lacks real-time monitoring, limited to bulk biological particles
	Sedimentation (Bittelli et al., 2019)	1 μm–200 μm	Useful for fine particle distribution	Slow, ineffective for polydisperse samples				
	Optical microscopy (Chen et al., 2011)	~200 nm–0.2 mm	Direct visualization of morphology (microbe, tissue)	Diffraction limit (~200 nm), low throughput				
1970s–1980s	*Dynamic light scattering (DLS)* (Stetefeld et al., 2016)	1 nm–10 μm	Rapid, non-invasive measurement, effective for vesicles and bio-nanoparticles	Poor accuracy for polydisperse systems	*Basic on-line particle size monitors*	1 nm–100 μm	Faster in-line analysis, better process control, effective for colloidal biological particles	Limited real-time precision, calibration issues, limited for complex biological particles
	Laser diffraction (Grubbs et al., 2021)	0.1 μm–3 mm	Broad size range, fast analysis, provides size distribution of biological particles	Assumes spherical shape, resolution limits				
	Scanning electron microscopy (SEM) (Brown et al., 2010)	1 nm–50 μm	High-resolution imaging, (bio-surfaces)	Requires conductive coating, vacuum environment	*Laser diffraction sensors*	1 nm–100 μm		
	Transmission electron microscopy (TEM) (Brown et al., 2010)	0.1 nm–100 nm	Atomic-scale resolution (bio-internal structures)	Difficult sample preparation, beam damage				
1990s–2000s	*X-Ray diffraction (XRD)* (Brown et al., 2010)	0.1 nm–10 μm	Structural information, non-destructive, structural analysis of bio-crystals (gout, $CaCO_3$)	Requires crystalline samples, bulk averaging	*Automated in-line particle analyzers*	0.1 nm–10 μm	Continuous monitoring, automated adjustments, bio-molecular structure analysis	Costly implementation, maintenance challenges
	Atomic force microscopy (AFM) (Brown et al., 2010)	0.1 nm–10 μm	Atomic-scale resolution, 3D mapping, molecular-level imaging of bio-matter	Limited throughput, tip artifacts	*In-line rheometers*	0.1 nm–10 μm	Viscosity and bio-polymer analysis, process optimization	Complex interpretation, high cost
	Nanoparticle tracking analysis (NTA) (Filipe et al., 2010)	10 nm–1 μm	Individual particle tracking, Tracking individual bio-nanoparticle	Affected by concentration, limited throughput	*On-line flow cytometry*	10 nm–1 μm	Single bio-cell and exosome detection, high-throughput single-cell analysis	Expensive, requires specialized training
2010s–2020s	*AI-enhanced imaging* (Najjar, 2023)	Sub-nm–10 μm	Automated image recognition, efficiency, AI-driven recognition of bio-structures	Data processing challenges, computationally intensive	*Real-time process analytical technology (PAT)*	Sub-nm–10 μm	Highly precise, predictive maintenance, AI-assisted bio-molecular analysis	Complexity, dependence on AI training data
	Multi-modal spectroscopy (Zhu and Barker, 2011)	Sub-nm–10 μm	Comprehensive characterization (biological particles)	Integration complexity, expensive equipment	*Real-time spectroscopic monitoring (Raman, FTIR)*		Bio-chemical structure identification, continuous process monitoring	Complex data interpretation
2030 & Beyond (Predictions)	*Quantum-based sensing* (Wang et al., 2024)	Near-atomic resolution	Ultimate precision, real-time nanoscale tracking, subatomic bio-sensing potential	Expensive, still in development	*Fully automated, AI-integrated smart factories*	Near-atomic resolution	Fully autonomous, optimized material processes, bio-molecular subatomic characterization	High setup cost, ethical & regulatory concerns
	AI-driven real-time analysis (Sarker, 2021)	Near-atomic resolution	Instantaneous monitoring and predictions (bio-data monitoring)	Heavy computational requirements, data bias				

simulate how nanoparticles assemble, diffuse, or react at atomic scales, thereby dramatically reducing development timelines for advanced materials like battery electrodes or photonic crystals (Dowling and Milburn, 2003). Next-generation computational tools, including quantum computers and high-performance computing clusters running molecular dynamics software (e.g., LAMMPS - Large-scale Atomic/Molecular Massively Parallel Simulator successors), could simulate particle interactions at unprecedented scales, supported by vast memory banks and AI accelerators. Virtual testing could guide experimental design, optimize particle synthesis, or even predict long-term stability under extreme environments (e.g., outer space or deep-sea conditions). Techniques like molecular dynamics (MD) simulations and density functional theory (DFT) calculations will complement experimental techniques, allowing researchers to predict particle behaviors across diverse conditions (Frenkel and Smit, 2002). As computational modeling matures, it will become a cornerstone of next-generation particle science and engineering.

Fig. 3 highlights several pivotal trends poised to redefine the field by 2030 and beyond: optical coherence tomography (OCT) and AI-driven digital twins in particle technology. Collectively, these technologies indicate a data-centric, model-informed, and intelligent future for particle science, where complex dynamics are simulated, predicted, and controlled with unprecedented accuracy. As innovation accelerates, the synergy between imaging, simulation, and AI will become the cornerstone of next-generation particle design and manufacturing.

Beyond 2030, measuring biological particle size and shape is expected to leverage quantum and real-time technologies to capture microbial dynamics at unprecedented scales. Quantum-enhanced microscopy, potentially employing NV-center diamond probes or entangled photon systems, may resolve sub-nanometer features like viral protein conformations or bacterial membrane fluctuations in living states as biomarkers, bypassing fixation artifacts (Glenn et al., 2015). *In situ* techniques, such as lab-on-a-chip platforms integrated with Raman spectroscopy (e.g., next-generation Horiba systems), could monitor microbial size and shape in real time within biological fluids, tracking changes during infection, growth, or treatment (Scholtes-Timmerman et al., 2014; Whitesides, 2006). Although data fidelity and computational demands are still obstacles, AI-driven image analysis based on deep learning frameworks may analyze these complex datasets immediately, reconstructing 3D microbe models from multi-modal inputs (e.g., fluorescence and scattering signals) (LeCun et al., 2015). These innovations promise a leap in biological particle analysis, potentially revolutionizing diagnostics and microbial engineering.

6. Conclusion

The evolution of particle characterization, as charted in this paper, reveals a field propelled by continuous innovation yet continually challenged by the complexity of particulate systems. As shown in **Table 1**, from the 1950s' reliance on sieving and sedimentation effective for coarse particles but faltering with fines to the nanoscale revolutions of SEM, TEM, AFM, and AI-enhanced analytics of the present, each era has built on its predecessor to overcome limitations in resolution, contrast, and throughput (Binnig et al., 1986; Bishop, 2006; Ruska, 1987). Today's state-of-the-art tools offer unprecedented detail and automation; however, struggles with sample preparation, cost, and data interpretation persist. Looking toward 2030 and beyond, quantum-based sensing, *in situ* monitoring, and computational simulations signal a future where atomic-scale precision and dynamic, real-world insights become routine (Frenkel and Smit, 2002; Giovannetti et al., 2011). These advancements have the potential to revolutionize diverse fields—such as drug delivery, sustainable materials, and environmental control—provided challenges related to scalability, environmental interference, and computational accuracy are effectively addressed. Beyond expanding our knowledge of particles, the continued advancement of particle characterization techniques will reinforce their function as a driving force behind future research and development.

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