Overview of modern methods for nanoparticle production

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Abstract

Nanoparticles, typically ranging from 1–100 nm, possess unique physical, chemical, and biological properties that make them indispensable across medicine, electronics, energy, and advanced materials. Their growing importance has driven the development of diverse production methods, each with distinct advantages and limitations. This review provides an overview of modern nanoparticle synthesis technologies, including Flame Spray Pyrolysis (FSP), Continuous Hydrothermal Flow Synthesis (CHFS), Spark Discharge Generation (SDG), classical chemical synthesis, and Pulsed Laser Ablation in Liquid (PLAL). FSP enables large-scale production with high throughput and uniformity, but faces challenges of aggregation and high infrastructure costs. CHFS offers continuous, "green" synthesis in aqueous environments with fine control over particle properties, though it requires complex post-processing to ensure purity and sterility. SDG produces highly pure nanoparticles directly from conductive materials using compact equipment, yet its productivity remains limited. Traditional chemical synthesis excels in shape and size control and is cost-efficient, but sterility issues and organic residues hinder biomedical translation. By contrast, PLAL combines simplicity, compact instrumentation, and the ability to generate sterile, ligand-free colloidal nanoparticles in solution, eliminating many post-synthesis steps. Comparative analysis demonstrates that no single approach is universally optimal; instead, method selection must balance scalability, cost, sterility, and application-specific requirements. Among these, PLAL emerges as a particularly promising technique for biotechnology and medicine, where rapid, clean, and scalable nanoparticle production is critical. The review highlights how aligning synthesis methods with end-use needs can accelerate translational applications in diagnostics, therapeutics, and advanced material technologies.

Significance statement

Modern nanoparticle production methods strike a balance between scalability, purity, and sterility, key factors for advancing biotechnological and medical applications. Among these methods, PLAL combines ligand-free purity, inherent sterility, and inline UV–Vis/DLS monitoring to deliver ready-to-use biomedical colloids with minimal post-processing—shortening the bench-to-bottle path.

Introduction

Nanoparticles are super tiny particles, usually between 1 and 100 nanometers in size, with unique physical, chemical, and biological properties that are different from bulk materials. Due to their high surface-to-volume ratio and the ability to control their composition, they are widely used in biomedicine for drug delivery, imaging, diagnostics, etc., as well as in electronics, energy, and materials science. In recent decades, several sustainable approaches have emerged: gas-phase methods such as Flame Spray Pyrolysis (FSP), Continuous Hydrothermal Flow Synthesis (CHFS), Spark Discharge Generation (SDG), classical chemical synthesis in solution, as well as physical approaches based on laser ablation. Each of these solutions has its own advantages and limitations related to scalability, economics, logistics, equipment, facility, and environmental requirements, personnel qualifications, and the degree of purity and sterility of the final product. Laser Ablation is a modern method that opens up enormous prospects in biotechnology, research, and medicine. The purpose of this review was to compare nanoparticle production methods, weighing their advantages and limitations to identify options best suited for biotechnological and medical use.

1. Flame Spray Pyrolysis

Chemical synthesis is still widely used in laboratories due to its simplicity and low temperature requirements. However, FSP was actively developed in the early and mid-2000s as an industrially applicable alternative to wet chemistry[1] that stands out for the production of nanoparticles on an industrial scale in a single step due to its speed, scalability, and ability to produce highly uniform nanoparticles[2]. This method uses a sprayed precursor, often a solution of organometallic or salt origin, which is then ignited in a flame, resulting in the formation of nanoparticles[2,3]. The process is characterized by a single-stage, fast-flowing reaction with a short particle formation zone ranging from 10 to 50 nm[1,4], with a dispersion depending on conditions and reagents, and for the Liquid-Feed FSP (LF-FSP) method, the spread is already from 15 to 100 nm on average[2]. However, the high concentration of the precursor (0.05–0.5 mol/L) leads to rapid agglomeration in the aerosol, forming fractal structures larger than 100 nm[5,6]. FSP is a gas-phase process, so nanoparticles are formed immediately without organic stabilizers (ligands)[3,7]. LF-FSP particularly emphasizes the absence of toxic products, such as HCl. The use of organometallic precursors instead of chlorides eliminates the need for costly equipment protection and waste neutralization[8]. Carbonate or carbon contamination is possible, but it can usually be removed by settling and drying. This method is highly sterile, as it involves very high temperatures up to ≈2000°C[9]. Sterility is ensured by the thermal destruction of organic contaminants. However, for biomedical applications, the need for secondary processing (separation, sterilization) must be taken into account, which leads to longer logistics and increased costs from precursors to the final product[4,10]. The positive qualities of the method include scalability and high productivity; flexibility in terms of materials; and relative “purity” (no ligands)[11]. There are also negative qualities, such as aggregation into agglomerates larger than 100 nm; high dispersion; significant capital and operating costs for reactors, filters, gases, automation, and safety systems; and contamination with carbon/carbonates.

Thus, Flame Spray Pyrolysis is a powerful industrially applicable method for producing nanoparticles. It provides high productivity (grams → kilograms per hour)[11], stable yield, and relative product purity. FSP is suitable for a wide range of materials, from simple oxides to complex compositions used in sensors for gas detection, fuel processing, environmental remediation, battery electrodes, fuel cells, and allows for the production of homogenous Y_2O_3–MgO nanopowders, biomedical ceramics, and transparent armor for lightweight ballistic protection[12-14]. Its main competitive advantage is its environmental sustainability and cost-

effectiveness compared to traditional chemical methods. However, the method requires significant investment in equipment, precise process control to avoid aggregation, and complex engineering infrastructure. Conclusive sentence. Translational significance. Therefore, for use in biotechnology or sterile areas, additional processing will be required for cleaning and particle control, as well as sterility.

2. Hydrothermal Flow Synthesis

Hydrothermal Flow Synthesis (HFS) is one of the most widely used methods for producing nanoparticles due to its simplicity and versatility[15,16]. However, Continuous HFS offers a unique advantage: continuous production with high throughput and precise control, making it attractive for industrial production of nanomaterials and catalytic ceramics for the production of nanostructured oxides for solid oxide fuel cells, growing synthetic quartz and gemstones, photocatalysis, and green chemistry[17-20].

The first hydrothermal crystal growth dates back to 1845, when Karl Emil von Schafhautle grew microscopic quartz in a pressure cooker. Bunsen and others then refined this technique using sealed environments. During World War II, a shortage of natural quartz prompted Bell Labs to develop commercial hydrothermal quartz growth technology in the 1950s[21]. Since the 2000s, CHFS methods using supercritical water have transformed hydrothermal synthesis into a sought-after method for the continuous production of nanomaterials[22,23]. High reaction speed and very short nucleation and growth times allow nanoparticles of uniform size to be obtained without the many hours of synthesis typical of wet chemistry. The flow process for obtaining nanoparticles can be scaled up by increasing the flow rate of the pumps and the configuration of the mixers[24]. Laboratory installations have demonstrated tens of grams per hour, while pilot installations have demonstrated hundreds[25].

HFS is a synthesis method in which a jet of precursor solution is instantly mixed with a jet of supercritical water (temperature above 370 °C and pressure of about 20–25 MPa), ensuring ultra-fast nucleation and crystallization of nanoparticles in the aqueous phase[17,26]. A typical CHFS assembly includes pumps, heaters for water to SCW, mixers, and a reactor zone. The use of water as a reagent/solvent avoids the need for organic solvents, and short residence times and immediate cooling limit crystal growth/aggregation, improving uniformity[27,28]. The method also allows the properties of nanoparticles, such as size, phase, and morphology, to be finely adjusted by changing the temperature, pressure, pH, and mixing speed[23]. However, there are high capital costs for preparing the premises, high-pressure pumps, heaters, and thick-walled pipe fittings made of nickel-containing corrosion-resistant alloys. The same applies to operating costs: electricity and pressure maintenance costs, pump maintenance, seal replacement, salt deposit flushing, and end product filtration[29]. This, in turn, poses risks to sterility.

This method allows for the synthesis of a wide range of nanomaterials: oxides (TiO_2, ZrO_2, CeO_2), hydroxyapatites and other calcium phosphates for biomedicine, sulfides, phosphates, and even MOF structures, and ensures purity in terms of organics and organic solvents, so there are no toxic residues characteristic of colloid chemistry[17]. [30]. However, high pressures and temperatures, as well as alkalis for pH/hydrolysis control, lead to corrosion and leaching of structural materials, as well as the need for mandatory washing, centrifugation, and lyophilization to remove ions and side salts[31]. The process is initially “clean” in terms of organics and can produce nanoparticles without ligands and surfactants; however, mineral ions/alkali salt residues and metal traces from equipment require subsequent washing and sterilization. Biocompatible materials (carbonate/silicate HA) are successfully produced and positioned for medical applications, but regulatory “sterility” is always a matter of post-reaction chain validation[32,33]. Together with excessively long logistics from the

point of synthesis to the finished product, including cooling, pressure relief, filtration, washing, drying, sometimes calcination, and sterilization, this lengthens the path from the reactor to application.

3. Spark Discharge Generation

In the 1960s–1970s, spark discharges were used in physics to obtain metal particles in the gas phase (mainly as model aerosols for aerial research in the field of health and air pollution). The technology is based on passing high-voltage spark discharges between two electrodes made of the target material in a flow of inert gas (usually Ar, N_2, or their mixtures)[34,35]. As a result of a microexplosion and local evaporation from the surface of the electrodes, plasma is formed, condensing into nanoparticles. The particles are carried away by the gas flow and can be collected by filters, impactors or introduced directly into gas-aerosol systems[34,36]. The method is widely used in sol studies and for obtaining "reference nanoparticles", as well as a particle generator for toxicological, medical, and logistical experiments[37].

Typical nanoparticle sizes are usually in the range of 1 to 100 nm, with the most common distribution modes being those with maxima in the 5 – 20 nm region[38,39]. Some studies indicate that particles from 3 to 12 nm can be obtained and their size can be controlled through spark energy, circuit parameters (capacitance, voltage, discharge frequency), gas flow, and distance between electrodes[34]. The productivity of such installations is relatively low: in standard configurations, it is milligrams per hour[40]. The method is suitable for obtaining nanoparticles of virtually any conductive material — metals (copper, nickel, iron, silver, gold), their alloys, and some conductive oxides, depending on the available electrodes. The purity of the particles is very high and is mainly determined only by the quality of the electrodes used and the purity of the supplied gas[41].

The main advantage of spark ablation is the production of high-purity nanoparticles. Since the process is completely physical, [40]. The equipment is compact and relatively inexpensive, which makes the method attractive for laboratories. In addition, the high plasma temperature ensures sterility at the time of synthesis, destroying organic matter and microorganisms in the chamber[42]. In terms of costs, capital investments can be estimated as low to medium: only a source of high-voltage pulses, a gas supply system and a chamber for generating and transporting an aerosol, and a filtration system are needed[43]. Operating costs consist mainly of the cost of inert gas (argon or nitrogen), electrode consumption, and electricity costs[40]. However, low productivity compared to Flame Spray Pyrolysis, Hydrothermal Flow Synthesis, and Laser Ablation is a serious limitation. In addition, the particles have a wide size distribution. The diameter can vary from units to hundreds of nanometers, and the average values change depending on the stability of the discharge[40,44]. Electrode erosion over time worsens reproducibility as the shape and composition of the electrodes change[45]. A separate problem is the delivery of nanoparticles. The product is formed as an aerosol, so to obtain a stable powder, it is necessary to go through filtration, sedimentation, washing, and drying. Each of the processing stages introduces the risk of sterility violation, despite the fact that the plasma itself initially provides clean conditions, and this lengthens the path from the reactor to the finished material[46].

4. Chemical synthesis

The first examples of chemical synthesis of nanomaterials can be traced back to the 14th–13th centuries BC, when the Egyptians and Mesopotamians produced colored glass using metal nanoparticles—for example, red glass was colored by the presence of copper on the surface, which emitted plasmon resonance[47]. Analyses confirm that artificial nanoparticles (e.g., lead sulfide PbS with a size of about 5 nm) were already used 4,000 years ago to dye hair[48]. Chemical methods,

such as the Stöber process, are classic for the synthesis of spherical silicon nanoparticles with a distribution of 50 to 2,000 nm[49]. [50]. They allow the size, shape, composition, and morphology of nanoparticles to be precisely specified, apply to a wide range of materials, and are easily scalable from laboratory conditions to industrial applications.

In the chemical synthesis of nanoparticles, one of the key tasks is to control their size, shape, and colloidal stability. To do this, organic molecules—ligand stabilizers—are used, which adsorb onto the surface of nascent and growing nanoparticles and prevent aggregation. Since ligands bind to specific crystallographic faces, slowing or accelerating growth in different directions, this allows cubes, rods, octahedra, or more complex morphologies to be obtained[51]. Despite their important role in synthesis, the presence of organic stabilizers creates a number of problems associated with organic residues on the surface. Even after washing, ligands remain on the particles, which prevents their use in biomedicine, where a "clean" surface is required for interaction with cells or proteins. Such organic stabilizers have low sterility and biocompatibility[52]. Therefore, nanoparticles obtained by chemical methods are mainly used in the manufacture of optics and sensors, in energy, and in the production of catalysts and polymer materials. At the same time, capital costs are relatively low: unlike spark or supercritical installations, chemical synthesis requires only standard laboratory equipment and time[53]. However, sterility remains an important issue: reactions usually take place at moderate temperatures and in the presence of organic matter, which does not destroy the microbiota. Therefore, the products obtained require additional sterilization — autoclaving, filtration, or gamma irradiation[54]. Finally, chemical synthesis involves lengthy purification logistics. Removing by-products requires multiple centrifugation, washing, and dialysis steps, which lengthens the path from synthesis to finished product and increases the risk of contamination at each stage.

5. Laser Ablation

Laser ablation is an amazingly simple and versatile tool for quickly producing high-quality nanoparticles[55,56]. Lasers were first used in pulsed laser deposition (PLD) to produce thin films in 1960. In 1995, R. Smolli's team (Rice University) first used laser ablation to synthesize carbon nanotubes—first multilayer, then single-layer—using cobalt/nickel as a catalyst. Later, the method of Pulsed Laser Ablation in Liquid (PLAL) appeared — a clean, physical method of obtaining nanoparticles without the use of chemical precursors or stabilizers[57]. In its modern form, the PLAL method has established itself as a "green method"[58] of nanoparticle synthesis since the 2000s. In contrast to complex installations requiring vacuum, high temperatures, or chemical reagents, PLAL requires only a standard pulsed laser, simple optics, and a conventional cuvette with a liquid medium[59]. Such equipment is compact and can be used in a normal laboratory room without the need for expensive ventilation or protective structures. At the same time, it provides access to sterile, biocompatible nanoparticle preparation—without post-processing, filtration, or additional purification[55,60]. A particular advantage of the method is the ability to obtain nanoparticles ranging in size from 1 to 100 nm directly in a working solution of the desired concentration, suitable for use[58,61].

Today, the PLAL method is a fast and economical solution for synthesizing nanoparticles, combining ease of installation with high quality, purity, and sterility of the finished product. It allows you to obtain pure, sterile, and biocompatible colloidal solutions with controlled concentration and size, without complex post-processing[62]. This promising technology is still evolving, but its areas of application and bright prospects are already clear. It is suitable for the production of materials for creating quantum dots, nanowires, carbon nanostructures, and for creating complex oxide films and conductors in photonics and electronics. However, the best areas

for PLAL application are undoubtedly medicine and biotechnology[59,63-65]. It is in these areas that the laser ablation method can fully realize its potential. [66]. The production of high-purity nanoparticles of the required concentration directly in a functional solution ensures very short logistics, eliminating additional stages of filtration, purification, distillation, and drying, as well as sharply reducing the risks of biological and toxicological contamination and ensuring high sterility[55]. Preliminary design shows the possibility of manufacturing a compact desktop PLAL unit with in-line control of nanoparticle size, dispersion, and concentration, which in turn opens up wide access to biotechnology and medical centers, educational laboratories, as well as manufacturers of electronics, optics, and nanomaterials[62].

Conclusion

A comparative analysis of synthesis methods demonstrates that there are no universal solutions yet: each technology is optimized for its own set of parameters. Gas-phase processes such as FSP offer record productivity and industrial scalability, but require significant capital investment and complex engineering infrastructure. CHFS allow the synthesis of a wide range of biocompatible materials in an aqueous environment and provide high uniformity, but are accompanied by lengthy post-processing logistics and contamination risks. SDG is simple and produces a clean product, but has low productivity. Classic chemical synthesis remains the leader in shape control and scaling, but suffers from ligand contamination and sterility issues. PLAL stands out for its combination of simple equipment, no need for special facilities, complete biocompatibility, and the ability to obtain sterile colloids of the desired concentration directly in the working solution without additional purification. It is this feature that makes PLAL particularly attractive for personalized medicine and pharmaceutical applications, where speed and purity are critical. Furthermore, laser ablation in liquid represents a highly promising nanotechnology, with the potential to drive breakthroughs not only in personalized medicine but also in advanced materials science, offering new opportunities for diagnostics, therapeutics, and innovative technological applications.

Figures

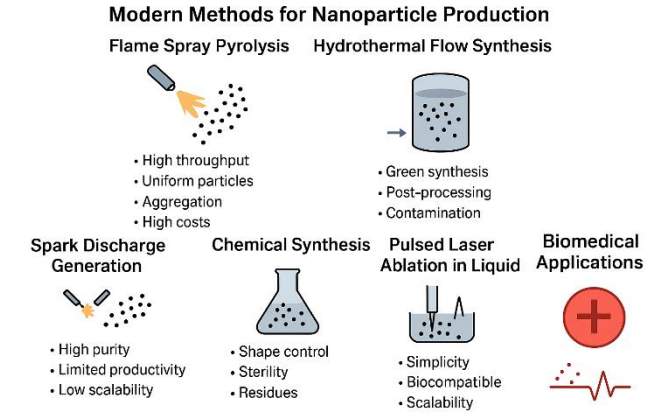

Figure 1. Graphical abstract of methods of nanoparticles production

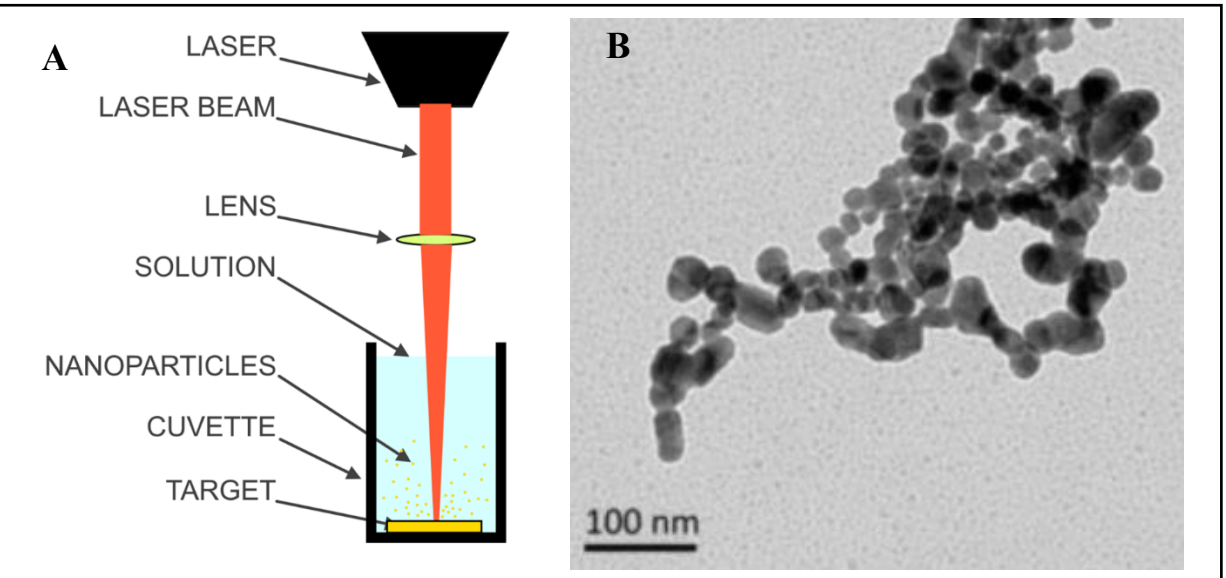

Figure 2. (A): Laser beam propagation and interaction with a target; (B): Transmission Electron Microscopy image of Ag nanoparticles obtained in water by laser ablation with Green-nanosecond laser

Table 1. Summary of methods

Nanoparticle Type	**Properties/image**	**Applications**	**References**
Flame Spray Pyrolysis	Optimal for high-performance industrial production of nanoceramics and catalysts	Catalysts, oxides for optics and energy	1-14
Hydrothermal Flow Synthesis (HFS)	Indispensable for obtaining high-quality crystals, especially in mineralogy and materials science	Manufacture of synthetic quartz, gemstones, and complex oxides	15-33
Spark Discharge Generation	Promising in terms of scalability and environmentally friendly approaches to the production of nanoparticles from a variety of electrically conductive materials	Production of metallic, oxide, and semiconductor nanoparticles for catalysis, environmental, and toxicological research	34-46
Chemical synthesis	The most versatile and widely used in research due to its simplicity and flexibility	Optics, catalysis, coatings, electronics	47-53
Pulsed Laser Ablation in Liquid	Ideal when the highest purity and precise control of nanoparticles is required, especially in the fields of photonics and biomedicine	Biotechnology, medicine, research, quantum dots, nanowires, carbon nanostructures, catalysis, photonics	55-66

1. Teoh, W.Y., Amal, R., and Madler, L. (2010). Flame spray pyrolysis: An enabling technology for nanoparticles design and fabrication. Nanoscale *2*, 1324–1347. 10.1039/c0nr00017e.
2. Rudin, T., Wegner, K., and Pratsinis, S.E. (2011). Uniform nanoparticles by flame-assisted spray pyrolysis (FASP) of low cost precursors. J Nanopart Res *13*, 2715–2725. 10.1007/s11051-010-0206-x.
3. Pokhrel, S., and Madler, L. (2020). Flame-made Particles for Sensors, Catalysis, and Energy Storage Applications. Energy Fuels *34*, 13209–13224. 10.1021/acs.energyfuels.0c02220.
4. Dimitriou, C., Psathas, P., Solakidou, M., and Deligiannakis, Y. (2023). Advanced Flame Spray Pyrolysis (FSP) Technologies for Engineering Multifunctional Nanostructures and Nanodevices. Nanomaterials (Basel) *13*. 10.3390/nano13233006.
5. Simmler, M., Meier, M., and Nirschl, H. (2022). Characterization of Fractal Structures by Spray Flame Synthesis Using X-ray Scattering. Materials (Basel) *15*. 10.3390/ma15062124.
6. Tsikourkitoudi, V., Karlsson, J., Merkl, P., Loh, E., Henriques-Normark, B., and Sotiriou, G.A. (2020). Flame-Made Calcium Phosphate Nanoparticles with High Drug Loading for Delivery of Biologics. Molecules *25*. 10.3390/molecules25071747.
7. Mädler, L., Kammler, H.K., Mueller, R., and Pratsinis, S. (2002). Controlled synthesis of nanostructured particles by flame spray pyrolysis. Journal of Aerosol Science *33*, 369–389. 10.1016/S0021-8502(01)00159-8.
8. Lamm, B.W., and Mitchell, D.J. (2023). Chemical Vapor Deposition of Zirconium Compounds: A Review. Coatings *13*, 266. https://doi.org/10.3390/coatings13020266.
9. Ding, S., Chen, H.-A., Mekasuwandumrong, O., Hülsey, M.J., Fu, X., He, Q., Panpranot, J., Yang, C.-M., and Yan, N. (2021). High-temperature flame spray pyrolysis induced stabilization of Pt single-atom catalysts. Applied Catalysis B: Environmental *281*, 119471. https://doi.org/10.1016/j.apcatb.2020.119471.
10. Estévez, M., Cicuéndez, M., Crespo, J., Serrano Lopez, J., Colilla, M., Fernández-Acevedo, C., Oroz-Mateo, T., Rada-Leza, A., Gonzalez, B., izquierdo-barba, I., and Vallet-Regí, M. (2023). Large-scale Production of Superparamagnetic Iron Oxide Nanoparticles by Flame Spray Pyrolysis: In Vitro Biological Evaluation for Biomedical Applications. Journal of Colloid and Interface Science *650*. 10.1016/j.jcis.2023.07.009.
11. Mueller, R., Mädler, L., and Pratsinis, S. (2003). Nanoparticle Synthesis at High Production Rates by Flame Spray Pyrolysis. Chemical Engineering Science - CHEM ENG SCI *58*, 1969–1976. 10.1016/S0009-2509(03)00022-8.
12. Sahm, T., Mädler, L., Gurlo, A., Barsan, N., Pratsinis, S., and Weimar, U. (2004). Flame Spray Synthesis of tin oxide nanoparticles for gas sensing. Sensors and Actuators B: Chemical *98*, 148–153. 10.1016/j.snb.2003.10.003.
13. Heel, A., Holtappels, P., Hug, P., and Graule, T. (2010). Flame Spray Synthesis of Nanoscale La0.6Sr0.4Co0.2Fe0.8O3–δ and Ba0.5Sr0.5Co0.8Fe0.2O3–δ as Cathode Materials for Intermediate Temperature Solid Oxide Fuel Cells. Fuel Cells *10*, 419–432. 10.1002/fuce.200900093.
14. Lei, S., Zhang, Y., Jin, X., Li, Y., Fang, Z., and Li, S. (2025). Spray flame synthesis of Y2O3-MgO nanoparticles for mid-infrared transparent nanocomposite ceramics 10.48550/arXiv.2507.22443.
15. Rendón-Angeles, J.C., and Seong, G. (2023). Editorial for the Special Issue: “Hydrothermal Synthesis of Nanoparticles”. Nanomaterials *13*. 10.3390/nano13091463.
16. Schäf, O., Ghobarkar, H., and Knauth, P. (2004). Hydrothermal Synthesis of Nanomaterials. In pp. 23–41. 10.1007/0-306-47722-X_2.
17. Dunne, P.W., Munn, A.S., Starkey, C.L., Huddle, T.A., and Lester, E.H. (2015). Continuous-flow hydrothermal synthesis for the production of inorganic nanomaterials. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences *373*, 20150015. 10.1098/rsta.2015.0015.
18. Weng, X., Cockcroft, J., Hyett, G., Vickers, M., Boldrin, P., Tang, C., Thompson, S., Parker, J., Knowles, J., Rehman, I., et al. (2009). High-Throughput Continuous Hydrothermal Synthesis of an Entire Nanoceramic Phase Diagram. Journal of combinatorial chemistry *11*, 829–834. 10.1021/cc900041a.
19. Walker, A. (2006). Hydrothermal Synthesis of Quartz Crystals. Journal of the American Ceramic Society *36*, 250–256. 10.1111/j.1151-2916.1953.tb12877.x.

20. Pukkella, A.K., Nadimpalli, N.R.V., Runkana, V., and Subramanian, S. (2022). A novel spiral infinity reactor for continuous hydrothermal synthesis of nanoparticles. Scientific Reports *12*, 8616. 10.1038/s41598-022-11141-8.
21. Feigelson, R. (2015). Crystal Growth through the Ages. In pp. 1–83. 10.1016/B978-0-444-56369-9.00001-0.
22. Dunne, P., Munn, A., Starkey, C., Huddle, T., and Lester, E. (2015). Continuous-flow hydrothermal synthesis for the production of inorganic nanomaterials. Philosophical transactions. Series A, Mathematical, physical, and engineering sciences *373*. 10.1098/rsta.2015.0015.
23. Li, Q., Liu, L., Wang, Z., and Wang, X. (2022). Continuous Hydrothermal Flow Synthesis and Characterization of ZrO2 Nanoparticles Doped with CeO2 in Supercritical Water. Nanomaterials *12*. 10.3390/nano12040668.
24. Gruar, R., Tighe, C., and Darr, J. (2013). Scaling-up a Confined Jet Reactor for the Continuous Hydrothermal Manufacture of Nanomaterials. Industrial & Engineering Chemistry Research *52*, 5270–5281. 10.1021/ie302567d.
25. Howard, D.P., Marchand, P., Johnson, I.D., Carmalt, C.J., Parkin, I.P., and Darr, J.A. (2016). Conducting Al and Ga-doped zinc oxides; rapid optimisation and scale-up. Journal of Materials Chemistry A *4*, 12774–12780. 10.1039/C6TA03364D.
26. Li, Q., Wang, Z., and Wang, X. (2023). CFD–PBM Simulation for Continuous Hydrothermal Flow Synthesis of Zirconia Nanoparticles in a Confined Impinging Jet Reactor. Materials *16*. 10.3390/ma16093421.
27. Darr, J.A., Zhang, J., Makwana, N.M., and Weng, X. (2017). Continuous Hydrothermal Synthesis of Inorganic Nanoparticles: Applications and Future Directions. Chemical Reviews *117*, 11125–11238. 10.1021/acs.chemrev.6b00417.
28. Yoko, A., Seong, G., Tomai, T., and Adschiri, T. (2020). Continuous Flow Synthesis of Nanoparticles Using Supercritical Water: Process Design, Surface Control, and Nanohybrid Materials. KONA Powder and Particle Journal *37*, 28–41. 10.14356/kona.2020002.
29. Saba, A., McGaughy, K., and Reza, M.T. (2019). Techno-Economic Assessment of Co-Hydrothermal Carbonization of a Coal-Miscanthus Blend. Energies *12*. 10.3390/en12040630.
30. Huston, M., DeBella, M., DiBella, M., and Gupta, A. (2021). Green Synthesis of Nanomaterials. Nanomaterials *11*. 10.3390/nano11082130.
31. Buitrago, M., González, J., and Orozco, C. (2016). Evaluation of methods for centrifugation and hydrothermal treatment for obtaining of calcium phosphate nanoparticles. Revista Ingeniería y Competitividad *19*.
32. Xue, C., Chen, Y., Huang, Y., and Zhu, P. (2015). Hydrothermal Synthesis and Biocompatibility Study of Highly Crystalline Carbonated Hydroxyapatite Nanorods. Nanoscale Research Letters *10*, 316. 10.1186/s11671-015-1018-9.
33. Ramis, J.M., Coelho, C.C., Córdoba, A., Quadros, P.A., and Monjo, M. (2018). Safety Assessment of Nano-Hydroxyapatite as an Oral Care Ingredient according to the EU Cosmetics Regulation. Cosmetics *5*. 10.3390/cosmetics5030053.
34. Salman Tabrizi, N., Ullmann, M., Vons, V.A., Lafont, U., and Schmidt-Ott, A. (2009). Generation of nanoparticles by spark discharge. Journal of Nanoparticle Research, 11 (2) *11*. 10.1007/s11051-008-9407-y.
35. Schlag, L., Isaac, N.A., Nahrstedt, H., Reiprich, J., Ispas, A., Stauden, T., Pezoldt, J., Bund, A., and Jacobs, H.O. (2021). Nanoparticle gas phase electrodeposition: Fundamentals, fluid dynamics, and deposition kinetics. Journal of Aerosol Science *151*, 105652. https://doi.org/10.1016/j.jaerosci.2020.105652.
36. Fang, B., Lu, A., Sun, J., Li, X., and Shen, T. (2023). The Simulation of Extremely Low Cycle Fatigue Fracture Behavior for Pipeline Steel (X70) Based on Continuum Damage Model. Metals *13*, 1238. 10.3390/met13071238.
37. Kuhn, J., Vallabani, N.V.S., Montes, A.M., Juárez-Facio, A.T., Introna, M., Steimer, S.S., Patel, A., Manem, D.B., Tsyupa, B., Mancini, A., et al. (2025). Unraveling toxicity of nanoparticles from different subway materials in lung epithelial cells and macrophages. Environmental Research *271*, 121027. https://doi.org/10.1016/j.envres.2025.121027.
38. Dolai, J., Mandal, K., and Jana, N.R. (2021). Nanoparticle Size Effects in Biomedical Applications. ACS Applied Nano Materials *4*, 6471–6496. 10.1021/acsanm.1c00987.
39. Jasinski, D.L., Li, H., and Guo, P. (2018). The Effect of Size and Shape of RNA Nanoparticles on Biodistribution. Molecular Therapy *26*, 784–792. 10.1016/j.ymthe.2017.12.018.

40. Efimov, A.A., Arsenov, P.V., Borisov, V.I., Buchnev, A.I., Lizunova, A.A., Kornyushin, D.V., Tikhonov, S.S., Musaev, A.G., Urazov, M.N., Shcherbakov, M.I., et al. (2021). Synthesis of Nanoparticles by Spark Discharge as a Facile and Versatile Technique of Preparing Highly Conductive Pt Nano-Ink for Printed Electronics. Nanomaterials (Basel) *11*. 10.3390/nano11010234.
41. Hallberg, R.T., Ludvigsson, L., Preger, C., Meuller, B.O., Dick, K.A., and Messing, M.E. (2018). Hydrogen-assisted spark discharge generated metal nanoparticles to prevent oxide formation. Aerosol Science and Technology *52*, 347–358. 10.1080/02786826.2017.1411580.
42. Sakudo, A., Yagyu, Y., and Onodera, T. (2019). Disinfection and Sterilization Using Plasma Technology: Fundamentals and Future Perspectives for Biological Applications. Int J Mol Sci *20*. 10.3390/ijms20205216.
43. Messing, M.E. (2016). The Advantages of Spark Discharge Generation for Manufacturing of Nanoparticles with Tailored Properties. Journal of Green Engineering *5*, 83–96. 10.13052/jge1904-4720.5346.
44. Gröhn, A., Pratsinis, S., Sanchez-Ferrer, A., Mezzenga, R., and Wegner, K. (2014). Scale-up of Nanoparticle Synthesis by Flame Spray Pyrolysis: The High-Temperature Particle Residence Time. Industrial & Engineering Chemistry Research *53*. 10.1021/ie501709s.
45. Kohut, A., Villy, L.P., Keri, A., Belteki, A., Megyeri, D., Hopp, B., Galbacs, G., and Geretovszky, Z. (2021). Full range tuning of the composition of Au/Ag binary nanoparticles by spark discharge generation. Sci Rep *11*, 5117. 10.1038/s41598-021-84392-6.
46. Meuller, B.O., Messing, M.E., Engberg, D.L.J., Jansson, A.M., Johansson, L.I.M., Norlén, S.M., Tureson, N., and Deppert, K. (2012). Review of Spark Discharge Generators for Production of Nanoparticle Aerosols. Aerosol Science and Technology *46*, 1256–1270. 10.1080/02786826.2012.705448.
47. Schaming, D., and Remita, H. (2015). Nanotechnology: from the ancient time to nowadays. Foundations of Chemistry *17*, 187–205. 10.1007/s10698-015-9235-y.
48. Walter, P., Welcomme, E., Hallégot, P., Zaluzec, N.J., Deeb, C., Castaing, J., Veyssière, P., Bréniaux, R., Lévêque, J.-L., and Tsoucaris, G. (2006). Early Use of PbS Nanotechnology for an Ancient Hair Dyeing Formula. Nano Letters *6*, 2215–2219. 10.1021/nl061493u.
49. Topuz, B., Şimşek, D., and Çiftçioğlu, M. (2015). Preparation of monodisperse silica spheres and determination of their densification behaviour. Ceramics International *41*, 43–52. https://doi.org/10.1016/j.ceramint.2014.07.112.
50. Della Gaspera, E. (2021). Special Issue "Wet Chemical Synthesis of Functional Nanomaterials". Nanomaterials *11*. 10.3390/nano11041044.
51. Kanelidis, I., and Kraus, T. (2017). The role of ligands in coinage-metal nanoparticles for electronics. Beilstein Journal of Nanotechnology *8*, 2625–2639. 10.3762/bjnano.8.263.
52. Li, Y., Lin, H., Zhou, W., Sun, L., Samanta, D., and Mirkin, C.A. Corner-, edge-, and facet-controlled growth of nanocrystals. Science Advances *7*, eabf1410. 10.1126/sciadv.abf1410.
53. Kumari, S., Raturi, S., Kulshrestha, S., Chauhan, K., Dhingra, S., András, K., Thu, K., Khargotra, R., and Singh, T. (2023). A comprehensive review on various techniques used for synthesizing nanoparticles. Journal of Materials Research and Technology *27*, 1739–1763. https://doi.org/10.1016/j.jmrt.2023.09.291.
54. Bernal-Chávez, S., Prado-Audelo, M., Caballero, H., Giraldo, D., Figueroa-González, G., Reyes-Hernández, O., del Carmen, M., González Torres, M., Cortés C, H., and Leyva-Gómez, G. (2021). Insights into Terminal Sterilization Processes of Nanoparticles for Biomedical Applications. Molecules *26*, 2068. 10.3390/molecules26072068.
55. Theerthagiri, J., Karuppasamy, K., Lee, S.J., Shwetharani, R., Kim, H.-S., Pasha, S.K.K., Ashokkumar, M., and Choi, M.Y. (2022). Fundamentals and comprehensive insights on pulsed laser synthesis of advanced materials for diverse photo- and electrocatalytic applications. Light: Science & Applications *11*, 250. 10.1038/s41377-022-00904-7.
56. Fazio, E., Gökce, B., De Giacomo, A., Meneghetti, M., Compagnini, G., Tommasini, M., Waag, F., Lucotti, A., Zanchi, C.G., Ossi, P.M., et al. (2020). Nanoparticles Engineering by Pulsed Laser Ablation in Liquids: Concepts and Applications. Nanomaterials *10*. 10.3390/nano10112317.
57. Arepalli, S. (2003). Review of Laser Ablation Process for Single Wall Carbon Nanotube Production. Johnson Space Center.
58. Khairani, I.Y., Mínguez-Vega, G., Doñate-Buendía, C., and Gökce, B. (2023). Green nanoparticle synthesis at scale: a perspective on overcoming the limits of pulsed laser ablation in liquids for

high-throughput production. Physical Chemistry Chemical Physics *25*, 19380–19408. 10.1039/D3CP01214J.

59. Forsythe, R.C., Cox, C.P., Wilsey, M.K., and Müller, A.M. (2021). Pulsed Laser in Liquids Made Nanomaterials for Catalysis. Chemical Reviews *121*, 7568–7637. 10.1021/acs.chemrev.0c01069.
60. Felix, E., Mánuel, J.M., Litrán, R., Rodríguez, M.A., Román-Sánchez, S., Lahoz, R., Natividad, E., Fernández-Ponce, C., Garcia-Cozar, F., Llaguno-Munive, M., et al. (2023). Scanning pulsed laser ablation in liquids: An alternative route to obtaining biocompatible YbFe nanoparticles as multiplatform contrast agents for combined MRI and CT imaging. Ceramics International *49*, 9324–9337. https://doi.org/10.1016/j.ceramint.2022.11.099.
61. Yu, J., Nan, J., and Zeng, H. (2017). Size control of nanoparticles by multiple-pulse laser ablation. Applied Surface Science *402*, 330–335. https://doi.org/10.1016/j.apsusc.2017.01.094.
62. Gatsa, O., Tahir, S., Flimelová, M., Riahi, F., Doñate-Buendia, C., Gökce, B., and Bulgakov, A.V. (2024). Unveiling Fundamentals of Multi-Beam Pulsed Laser Ablation in Liquids toward Scaling up Nanoparticle Production. Nanomaterials *14*. 10.3390/nano14040365.
63. Nagy, E., Kopniczky, J., Smausz, T., Náfrádi, M., Alapi, T., Bohus, J., Pajer, V., Szabó-Révész, P., Ambrus, R., and Hopp, B. (2023). A comparative study of femtosecond pulsed laser ablation of meloxicam in distilled water and in air. Scientific Reports *13*, 10242. 10.1038/s41598-023-36922-7.
64. Imran, H.J., Hubeatir, K.A., and Aadim, K.A. (2023). A novel method for ZnO@NiO core–shell nanoparticle synthesis using pulse laser ablation in liquid and plasma jet techniques. Scientific Reports *13*, 5441. 10.1038/s41598-023-32330-z.
65. Fernández-Arias, M., Vilas, A.M., Boutinguiza, M., Rodríguez, D., Arias-González, F., Pou-Álvarez, P., Riveiro, A., Gil, J., and Pou, J. (2022). Palladium Nanoparticles Synthesized by Laser Ablation in Liquids for Antimicrobial Applications. Nanomaterials *12*. 10.3390/nano12152621.
66. Tareq, M.S., Hameed, A.K., Saleem, A.H., and Rasheed, B.G. (2025). In vitro antimicrobial activity of silver nanoparticles synthesis by lasers against teeth caries bacteria (S-mutans). Lasers Med Sci *40*, 271. 10.1007/s10103-025-04530-8.