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REVIEW

Fabrication of aerosol-based nanoparticles and their applications in biomedical fields

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Abstract

Background Traditionally, nanoparticles for biomedical applications have been produced via the classical wet chemistry method, with size control remaining a major problem in drug delivery. In recent years, advances in aerosol-based technologies have led to the development of methods that enable the production of nanosized particles and have opened up new opportunities in the field of nano-drug delivery and biomedicine. Aerosol-based technologies have been constantly used to synthesize multifunctional nanoparticles with different properties, which extends their possible biological and medicinal applications. Moreover, aerosol technologies are often more beneficial than other existing approaches because of the major disadvantages of these other techniques.

Area covered This review provides a brief discussion of the existing aerosol-based nanotechnologies and applications of nanoparticles in a variety of diseases. Various types of nanoparticles, such as graphene oxide, Prussian blue, black phosphorous, gold, copper, silver, tellurium, iron oxide, titania, magnesium oxide, and zinc oxide nanoparticles, prepared using aerosol technologies are discussed in this review. The different tactics used for surface modifications are also outlined. The biomedical applications of nanoparticles in chemotherapy, bacterial/fungal/viral treatment, disease diagnosis, and biological assays are also presented in this review.

Expert opinion Aerosol-based technologies can be used to design nanoparticles with the desired functionality. This significantly benefits the nanomedicine field, particularly as product parameters are becoming more encompassing and exacting. One of the biggest issues with conventional methods is their scale-up/scale-down and clinical translation. Aerosol-based nanoparticle synthesis helps enhance control over the product properties and facilitate their use for clinical applications.

Keywords Aerosol · Spark discharge · Biomedical · Atomization · Pyrolysis · Theragnostic

Introduction

Organic and inorganic nanoparticles are the most widely investigated nanomaterials and are particularly important in nanotechnologies. Different synthetic routes have been developed to fabricate the desired metallic nanomaterials, such as wet chemical methods or physical processing, mechanical milling, or high-vacuum temperature techniques (Byeon and Kim 2012). Chemical processing methods require expensive chemical precursors and solvents in liquid or gaseous forms to prepare nanocomposites. Although various physical and chemical methods have been adopted to synthesize different nanocomposites, these methods are still limited as they involve sophisticated setups, a significant amount of chemical waste, the production of partly contaminated particles, and difficulty in handling toxic chemicals (Messing 2015; Khan et al. 2019). Mechanical milling techniques are cost-effective, reliable, easy to operate, and applicable in both dry and wet conditions. However, possible contamination due to the use of surfactants, the formation of irregular shapes, and long cleaning times limit their application (Piras et al. 2019). The direct mixing and dispersion of materials depend on the physicochemical properties of the materials employed, which can hinder the fabrication of the desired nanoparticles in the case of unfavorable combinations. A significant drawback of these techniques is the introduction of impurities that are often more abundant in liquids than in gases. Due to these shortcomings, researchers have focused on developing more convenient

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fabrication techniques for selective drug delivery and biomedical applications.

Recently, the aerosol-based (gas phase) preparation technique has gained popularity due to its simplicity, good control over particle shape and size, low cost, versatility, and ability to generate pure particles with a nominal effect on the environment. This aerosol-based technique offers high-purity nanoparticles and can be used to synthesize nanoparticles in a continuous process. In contrast to traditional wet chemical methods, aerosol-based methods involve a limited number of fabrication steps (Shields et al. 2010). This system has been widely adopted on a commercial scale because it allows the direct collection of nanoparticles in one step and produces low waste when compared to wet chemical processes (Filho et al. 2020).

The aerosol-based technique involves different mechanisms which are used to generate specific nanostructures via vapor deposition, measurement of particle size in the aerosol state, or by use of other chemical properties (Wang et al. 2020). Aerosol-based nanoparticles can be prepared using a variety of methods, depending on the desired composition, shape, and size (An et al. 2010). Moreover, preparation techniques can be easily manipulated to prepare specific gas-suspended vapor structures, making this method broadly applicable in the field of nanotechnology. Aerosol-based techniques have been widely used for the preparation of optoelectronic and nanoelectronic devices, which have been shown to have enhanced catalytic and gas-sensing properties (Shandilya et al. 2014). In addition, aerosol-based materials are extensively employed in the biomedical field for cancer treatment, as well as for their antibacterial activity (Athanassiou et al. 2010). Due to the properties of organic or inorganic nanoparticles, they have also been utilized for the treatment of various disease models. In this paper, we outline the different methods used for the preparation of aerosol-based nanoparticles and also describe the use of these nanoparticles for biomedical applications.

Fabrication of aerosol-based nanocomposites

The preparation of nanoparticles via aerosol-based technologies provides a powerful method for the fabrication of nanoconstructs with precise morphology and chemical composition. Aerosol-based nanoparticles can be synthesized by either atomizing a solution with a defined composition to form fine droplets that crystallize to solid nano-constructs upon the subsequent evaporation of the solvent or by aero-to-particle conversion through nucleation and growth via condensation and coagulation, respectively (Graves et al. 2020a, b; Mohammadi 2020). Atomization of different types of solutions can be achieved either by nebulization or electrohydrodynamic atomization, while aero-to-particle preparation can be accomplished via spark discharge, flame, furnace or plug-in-play plasma techniques. Of the various methods presented, some aerosol-based techniques are outlined and discussed in detail below.

Atomization of liquid solvents

Different techniques, such as electrospray, ultrasound, and pneumatic atomization, can be used to generate aerosol particles by atomizing solvents with a specific chemical composition (Wang et al. 2008; Kim et al. 2017). In this technique, the main principle behind nanoparticle formation is that upon the evaporation of the solvent in the atomized droplets (1–10 μm in diameter), the droplets crystallize to form a solid nanocomposite. In liquid atomization, a liquid feed is broken into fine droplets using a nozzle. Different atomizers, such as hydraulic pressure, pneumatic, ultrasonic nozzle, or rotary disk atomizers, can be employed to produce fine droplets of different sizes (Yu Vasilyev et al. 2019). Pneumatic atomizers are typically used for pharmaceutical applications due to their suitability (twin-fluid nozzles). These atomizers are commonly used because they can be effectively exploited in small-scale plants to generate smaller droplets (Kemp et al. 2013). In a previous report, silica nanoparticles were synthesized via flame pyrolysis using a two-fluid nozzle spray (Chang et al. 2008), as shown in Fig. 1. Tetraethyl orthosilicate was dissolved in ethanol and used as a silica precursor. Then, the liquid phase precursor solution

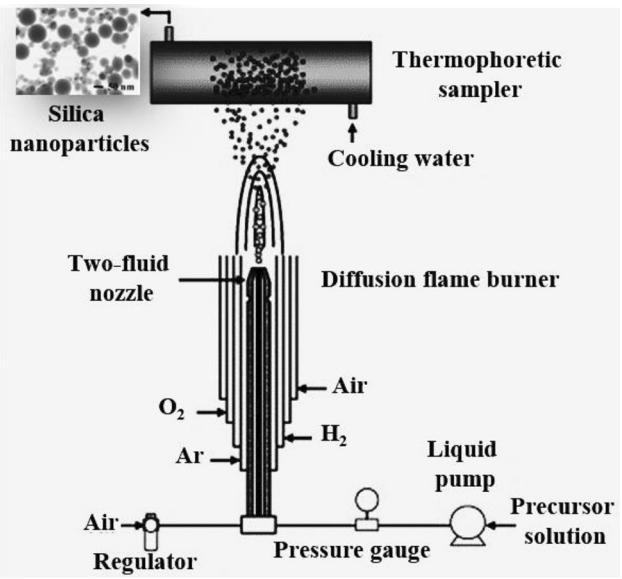

Fig. 1 A schematic diagram of the experimental apparatus for the synthesis of silica nanoparticles via flame spray pyrolysis using a two-fluid nozzle spray. The given figure was adopted from Chang et al. (2008)

was sprayed through a two-fluid nozzle, with the flame being generated by the combustion of the precursor, argon, hydrogen, oxygen, and air, which were separately passed through four concentric stainless tubes. Finally, the silica nanoparticles were collected by solvent evaporation, precipitation, decomposition, and oxidation of the solute particles.

Spark-discharge generator

This method involves the generation of aerosol vapors from different materials via spark discharge. Plasma techniques have been adopted to prepare organic or inorganic nanoparticles containing biological materials. In this method, two different conducting electrodes are heated up to 20,000 K and nanoparticles are obtained via vapor displacement through thermophoretic deposition (Gautam et al. 2019a, b). The vapor can be generated by placing a different pair of electrodes with a continuous power supply, following which the vapor is passed through a thermal reactor for vapor deposition. The ambient heterogeneous spark discharge technique has been used to synthesize gold (Au) and Au-titanium dioxide (Au–TiO_2) nanoparticles used for photothermal therapy against cancer cells, as shown in Fig. 2 (Byeon and Kim 2014). The electrical current on the two different titanium (Ti) and Au rods was used to vaporize the Ti and Au under a continuous airflow to produce ultrafine Au nanoparticles (lateral dimension of approximately 2 nm). Furthermore, these ultrafine nanoparticles were then patched up with TiO_2 nanoparticles to form Au–TiO_2 heterodimers (lateral dimension of approximately 38 nm), which were then used to induce apoptosis under visible light in HeLa cells.

In addition, the significant toxicity of silver (Ag) and copper (Cu) nanoparticles in humans has been reduced by designing metal-doped tellurium (Te) nanoparticles, which were used as antibacterial agents in one study (Park et al. 2019). The safe-by-design plug-and-play technique was employed under a continuous nitrogen flow to produce Ag (or Cu)-doped Te (Ag- or Cu–Te) nanoparticles with antibacterial activity and better safety (Fig. 3). Moreover, the ratio between individual Ag or Cu can be modulated (5–8% atomic Ag and Cu) to prepare biocompatible metal-doped nanoparticles with enhanced antibacterial activity. The prepared nanoparticles were shown to exhibit an optimal safety index and significantly decreased the minimum inhibitory concentration of the individual Te nanoparticles.

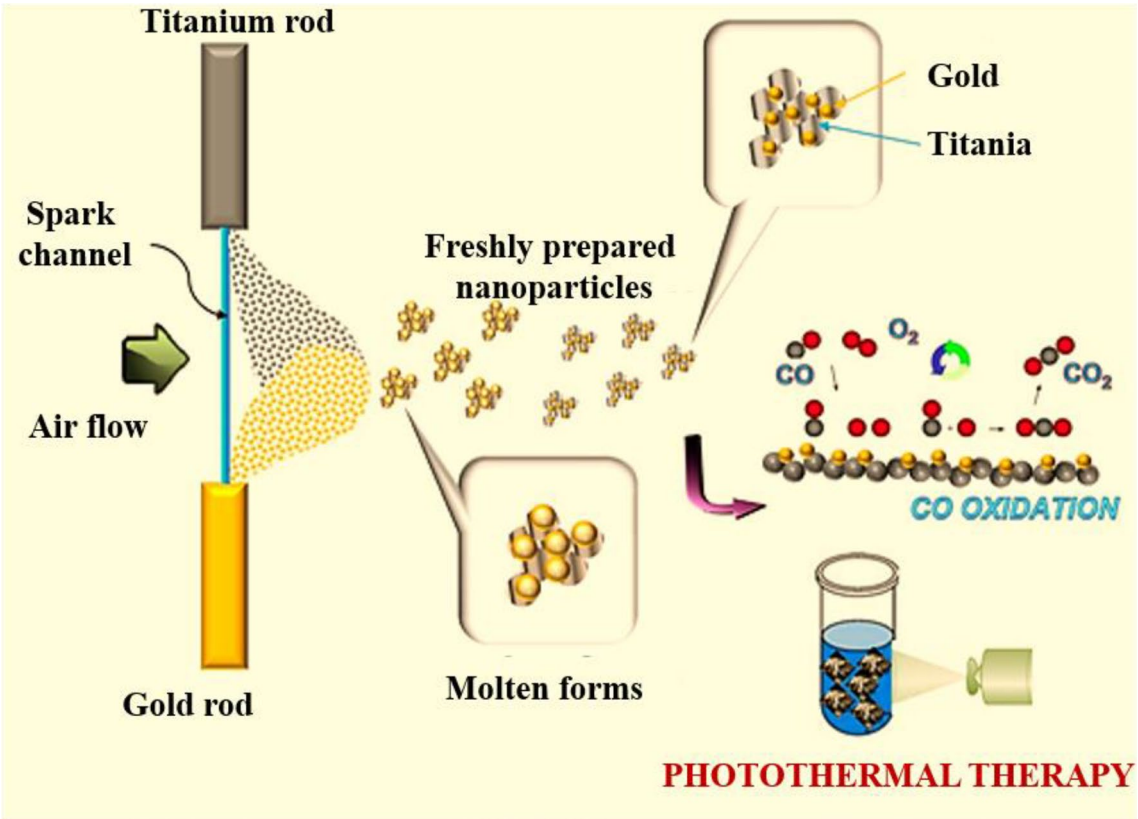

Fig. 2 Ambient heterogeneous spark discharge to synthesize Au–TiO_2 heterodimers in a gaseous phase for photocatalytic and photothermal applications. The given figure was adopted from Byeon and Kim (2014)

Fig. 3 Schematic of spark ablation used to prepare Ag or Cu-doped Te nanoparticles from three Ag or Cu anodes (green) and a Te cathode (red) inside a chamber under a nitrogen gas flow. The given figure was adopted from Park et al. (2019)

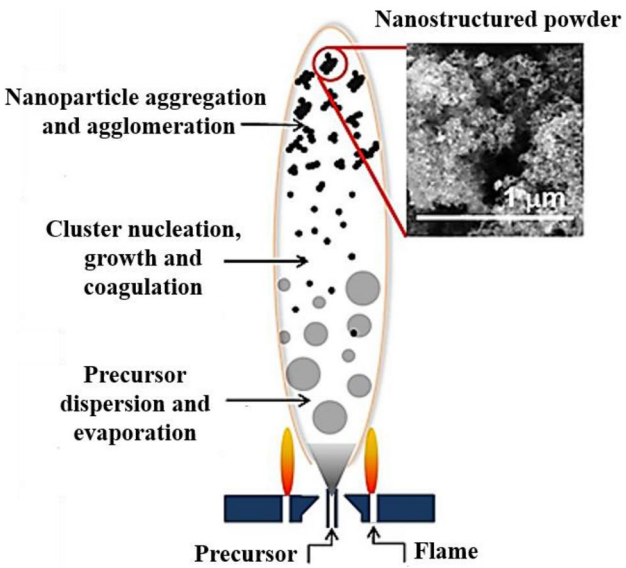

Fig. 4 Schematic of the preparation of nanoparticles via flame spray pyrolysis. The given figure was adopted from Bettini et al. (2015)

Flame spray pyrolysis

Flame spray pyrolysis generates nanoparticles in the gaseous phase at high temperatures using a flame. This technique involves the deposition of thin oxide films onto a substrate via the evaporation and decomposition of sprayed liquid precursors. This process is based on the exothermic combustion of the liquid phase, followed by evaporation, oxidation, and nucleation under a high flame to form subsequent solid nanoparticles via coagulation, sintering/coalescence, and agglomeration (Teoh et al. 2010; Meierhofer et al. 2020), as shown in Fig. 4. The diameter and structure of the produced nanoparticles are dependent on the feed rates of the liquid precursor and oxygen, as well as the atomizer nozzle configuration.

Based on this mechanism, on-demand nanoplatforms have been synthesized for combination cancer therapy (Gautam et al. 2018). Near-infrared (NIR) responsive chemo-photothermally active nanoparticles were designed using an aero–hydro–aero single-pass production system. In this system, the inorganic core of titanium peroxide ($yTiO_2$) was prepared via flame pyrolysis of vaporized $TiCl_4$, subsequently followed by ultrasonic H_2O_2 treatment. Then, the nanocomposite was synthesized by patching it up with graphene oxide (GO), which is a photoactivable agent, doxorubicin (D), which is a chemotherapeutic agent, and a stealth agent, namely polyethylene glycol (P), as shown in Fig. 5. The prepared nanoparticles were shown to exhibit a greater photothermal effect and selective tumor distribution, with enhanced tumor cell killing activity in SCC-7 carcinoma cells.

Magnetic nanoparticles encapsulated in a silica matrix (C/SiO_2@Fe composites) can also be prepared via carbon laser (1500 W CW)-induced pyrolysis of aerosols and can be used as contrast agents for magnetic resonance imaging (MRI) or magnetic hyperthermia (Veintemillas-Verdaguer et al. 2007). To prepare the contrast agent, ferrocene, an organometallic compound, is nebulized with a toluene solution in the presence of tetraethoxysilane to form the aerosol. The aerosol is then passed into the reaction chamber via gas influx and the nanosized particles are then obtained through pyrolysis using a carbon laser beam.

Plasma synthesis

Plasma science is another emerging field in nanoparticle synthesis. The multifunctional synthetic approach is one of the most used systems in biomedicine, polymer science, industrial sterilization, and food safety. Two types of plasma

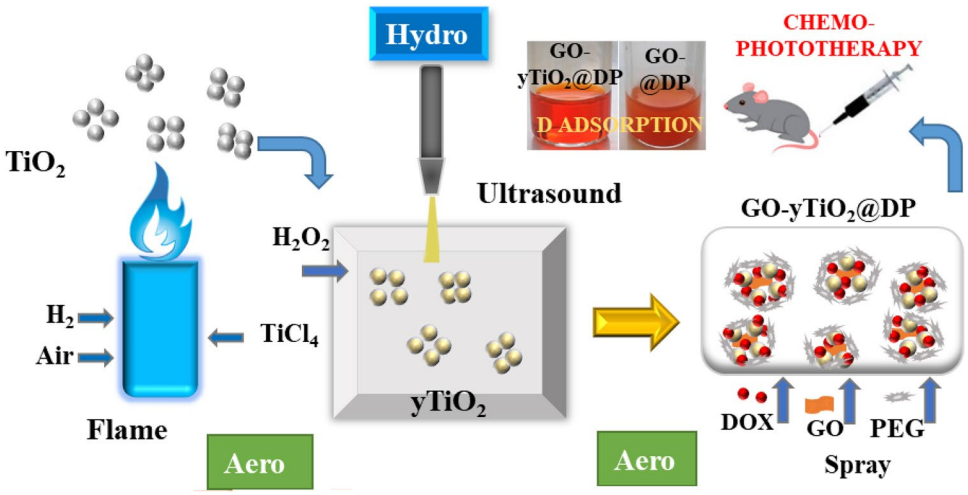

Fig. 5 Schematic of the aero–hydro–aero route to produce graphene oxide-patched titania nanoparticles for chemo-phototherapeutic applications. The given figure was adopted from Gautam et al. (2018)

(thermal and non-thermal) can be used to prepare different types of nanocomposites. In thermal plasma, the temperatures of gas molecules and free electrons are approximately identical, whereas in non-thermal plasma, free electrons have a temperature of several electron volts, while the overall gas temperature is close to or slightly above room temperature. Moreover, non-thermal plasma can be generated at both low and atmospheric pressure (Palma et al. 2020; Stryczewska 2020).

In non-thermal plasma, volatile precursors (hydrocarbons, volatile silicon compounds, Ti or metal halides) are passed into the plasma chamber as vapor, along with the carrier gas (Blanquart and Roest 2019). In the plasma chamber, the introduced precursor vapor is dissociated by the energetic species to form silicon atoms or metal aerosols. Because of the overall low gas temperature, these atoms quickly nucleate to form a cluster and then grow into nanoparticles due to the continuous condensation of vapors. In the case of hydrocarbons, they tend to polymerize to form nanocomposites under the influence of active species (Kakiuchi et al. 2013; Naz et al. 2020). Titanium has a broad range of applications, being used in solar cells, electronics, biomedicine, and photocatalysis. Hence, thin Ti films have been synthesized using non-thermal atmospheric pressure plasma deposition methods, which are generally used in various fields (Banerjee et al. 2020). Photoluminescent silicon nanoparticles have been prepared by using the non-thermal plasma technique and tested for their use as potential sensors and optoelectronics, as well as for their potential applications in medicine and natural sciences (Müller et al. 2020). In this system, silica nanoparticles are prepared using low-pressure radio frequency plasma in a flow-through glass tube reactor, followed by surface modifications in both air and vacuum chambers. Au nanoparticles have also been fabricated using the pulse-modulated radio-frequency atmospheric pressure glow discharge technique. The fabricated Au nanoparticles were then further passed into an aqueous gelatin solution and turmeric oil to prepare an oil-in-water nanoemulsion. Interestingly, the prepared nanoemulsion showed enhanced cytotoxic activity against two breast cancer cell lines, namely MDA-MB-231 and MCF-7 (Dzimitrowicz et al. 2020). Moreover, other non-thermal plasma techniques have been used to produce carbon, iron, and palladium nanoparticles (Chawdhury et al. 2020; Li et al. 2020).

Various types of materials can be processed through the thermal plasma technique, which has been considered as a more efficient, attractive, and active technique in the industrial and biomedical fields. Thermal plasma synthesis involves the dissociation of precursors (gas, liquid, or solid phase) under highly reactive and extremely high-temperature conditions. Due to the extremely high temperatures, solid-phase compounds evaporate into micron-sized solid particles in their aerosol state and then recondense under controlled conditions to form nanoparticles. This process is performed mainly in inductively coupled radiofrequency plasma torches (Kim et al. 2020) and thermal microwave plasmas (Graves et al. 2020a, b). Titanium boride nanoparticles (10–30 nm in diameter) have been prepared using radiofrequency induction thermal plasma techniques, by introducing and rapidly evaporating titanium and boron powder in a plasma reactor to form nanoparticles by using a quenching process (Cheng et al. 2012). Moreover, their applications in various fields have been investigated. Zinc oxide nanosheets (approximately 25 nm) were also prepared using the thermal plasma technique and their fluorescence quenching mechanism was studied using α-amylase (Khade et al. 2017). Carbon-based nanoparticles have been extensively used in various biomedical fields, such as cancer therapy, drug delivery, theragnostic applications, and biosensors (Gautam et al. 2019a, b; Maiti et al. 2019). Therefore, the radiofrequency thermal plasma technique can be used to prepare extremely thermally stable (up to 500 K) carbon-coated magnetic

nanocomposites, which can have various biomedical applications (Bystrzejewski et al. 2007).

Laser ablation

Laser-based nanoparticle synthesis is a commonly used technique in the fields of imaging, sensors, catalysis, and biomedicine. It is also frequently used to generate nanoparticles in a gaseous phase. The excimer laser beam is delivered into the ablation chamber through a quartz window to vaporize the solid target material. Due to the effect of the laser beam, the surface of the target material melts and forms vapors when the temperature rises beyond its boiling point. After the application of the carrier gas, the vapors are then transported from the ablation chamber, cooled down to form clusters, and then converted into nanoparticles by the further condensation of the vapors (Ullmann et al. 2002). This method is versatile and the composition of the prepared nanoparticles can be easily modified by changing the target material and varying the pulse energy and frequency of the applied laser (Fazio et al. 2020). Titanium, silicon, aluminum, iron, and tungsten oxide aerosols have been synthesized by reactive laser ablation, using oxygen as the carrier gas. Nanometer-sized aerosols of carbon and Au were also prepared by non-reactive laser ablation under a continuous flow of nitrogen gas (Ullmann et al. 2002). Recently, the pulsed laser deposition method has been widely utilized to generate thin films for multipurpose applications. This technique has been used to modulate the thickness of inorganic oxide films and its effect on the luminescent properties of these films has also been investigated (Ogugua et al. 2020). Polymer-metal nanoparticles have also been fabricated using UV-pulsed laser deposition, in which metal clusters (Au, Cu, Ag, or Pd) were deposited onto a polymer [polycarbonate, poly-(methyl methacrylate), or bisphenol A dimethacrylate] surface using a pulsed laser to prepare polymer/metal multilayer nanoparticles (Darwish et al. 2013). However, the concentration of nanoparticles produced using the laser ablation method is often low, thus, making this technique difficult to implement on an industrial scale, as it requires high investment costs due to the high price of a laser system, as well as a considerable amount of energy. Therefore, to be economically convenient, colloids should be prepared in large quantities and fairly frequently (Sportelli et al. 2018).

Application of aerosol-based nanotechnologies

Aerosol-based nanoparticles have been widely used for therapeutic or theragnostic applications in nanomedicine. Nanocomposites loaded with a therapeutic agent can be delivered efficiently to different organs, either by targeting or non-targeting strategies. The applications of aerosol-based nanoparticles are as follows:

Biomedical applications

Different organic and inorganic nanoparticles have been synthesized using the aerosol technology and tested for their potential biomedical applications in terms of their biocompatibility, pharmacokinetics, immunogenicity, bioavailability, and toxicity. Their potential applications in various biomedical fields include cancer treatment, antimicrobial applications, clinical diagnosis, protein detection, and different biological assays, as illustrated in Fig. 6.

Cancer treatment

Various therapeutic nanoparticles have been engineered via aerosol techniques to overcome the shortcomings of cancer monotherapy, and are employed through combination therapies of chemo-phototherapy, photodynamic therapy (PDT), or photo-immunotherapy. These combination therapies help to enhance the therapeutic efficacy of the nanoparticles by reducing off-target effects and tumor-induced immunosuppression. Compared to conventional chemotherapy, PDT is considered a promising noninvasive technique due to its selective and localized therapeutic applications in cancer treatment. In this method, a light-activable photosensitizer agent is delivered into the tumor area, where it induces tumor cell death via elevated temperatures and reactive oxygen species (ROS) production (Poudel et al. 2020). Accordingly, GO was prepared using the spark discharge technique and patched up with imatinib-loaded mesoporous Ti to form photoactivable nanocomposites. The prepared nanoparticles were then used for the treatment of colorectal cancer, with the chemo-photothermal activity of the nanoparticles being further enhanced after polyethylene glycol (PEG) coating (Gautam et al. 2020a, b).

Although considerable achievements have been made in the development of photodynamic agents in the past decade, a substantial barrier to their clinical translation is their toxicity and efficacy. Hence, clinically translatable nanoparticles were prepared by coating the surface of Prussian blue nanocages, an FDA-approved agent, with GO nanoflakes, which were then used for the treatment of pancreatic cancer. As expected, the temperature of the prepared nanoparticles was significantly enhanced after GO coating and exhibited excellent chemo-photodynamic therapy outcomes in the presence of the chemotherapeutic agent doxorubicin (Gautam et al. 2020a, b). Low tumor penetration of NIR light and thermotolerance after initial therapy has limited the application of PDT in cancer treatment (Vankayala et al. 2014). Various physiological barriers associated with the

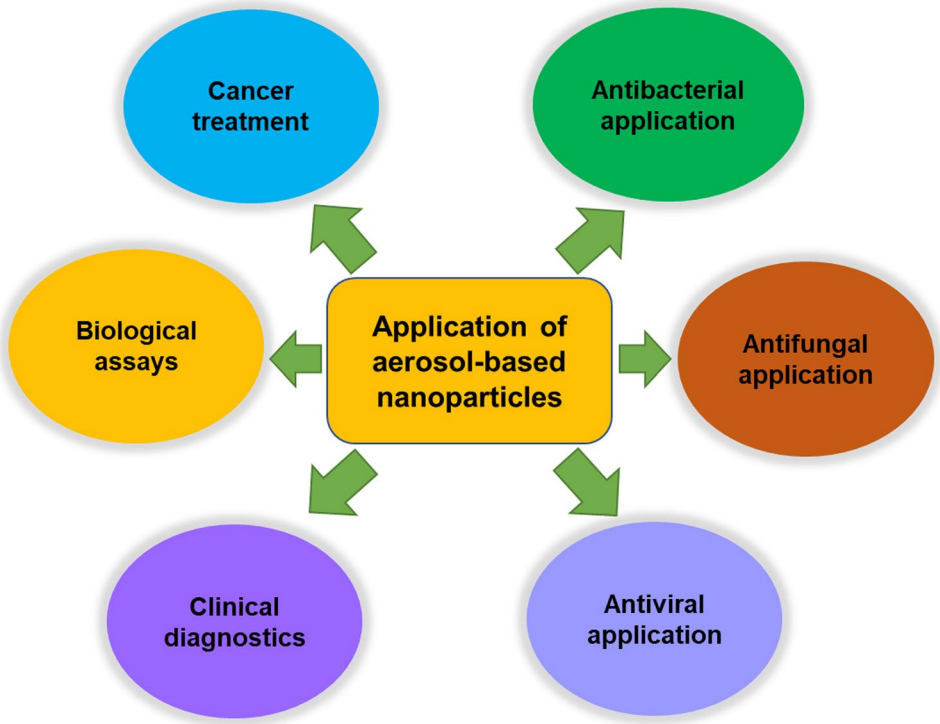

Fig. 6 Biological applications of aerosol-based nanocomposites

tumor microenvironment can also noticeably hinder the effective delivery of nanoparticles into tumor cells (Zhang et al. 2019). To enhance tumor targetability, various targeting agents have been developed and coated onto the surface of nanocomposites. The attachment of polymeric or biological targeting agents significantly promotes tumor accumulation and reduces their toxic effects in healthy cells. Thus, to adequately deliver GO nanoflakes into the tumor area, the nanoflakes were coated with both PEG and chitosan in the liquid phase and were then administered to treat various cancer types. A biodistribution study demonstrated that the delivery and delivery speed of chitosan-coated nanoparticles into the tumor area were significantly increased compared with the non-coated nanoparticles, therefore leading to an enhanced targeted antitumor effect (Thapa et al. 2017). The use of biodegradable and disintegrable inorganic nanosystems for cancer treatment has become dramatically more frequent due to the nanopaticles' less toxic effects on vital organs.

The use of immune checkpoint blockers (ICBs) and cancer-targeted antibodies has further helped to overcome tumor-induced immunosuppression and non-targeting issues. As such, ICB (PD-L1) and a cancer-targeting antibody (CXCR4) were loaded onto black phosphorous (BP) using plug-and-play devices to prepare photoimmunotherapeutic core–shell nanoparticles containing dabrafenib, which is a B-Raf inhibitor (Nguyen et al. 2019). Upon NIR laser irradiation, the prepared nanoparticles were shown to induce a strong immune response against human skin cancer cells. A core–shell nanocomposite with a base core of poly-L-histidine (H)-grafted BP and a shell consisting of an erythrocyte membrane (BP-H-ILsi-X@EM-YSA) were also prepared for combined chemo-photo-immunotherapeutic applications (Ou et al. 2019). The prepared nanoparticles were then used to treat MC-38 tumors (colon adenocarcinoma). Interestingly, they were shown to have enhanced tumor targetability and endosomal escape, thereby inducing efficient antitumor immune responses. Although many multifunctional nanoparticles have been synthesized for cancer treatment, a key burden is their effective delivery to the tumor sites. Moreover, safety issues remain a major concern for their translation into clinical practice.

Antibacterial applications

Recent advances in nanotechnology have led to the development of biodegradable antibacterial agents and synthetic approaches to effectively address bacterial resistance issues. Many obstacles, such as cost-effectiveness, antibacterial mechanisms, metabolic effects, toxicity, and the unwanted environmental impacts of nanomaterials, have hindered their applications as antibacterial agents. Effective antibacterial agents have been developed using Cu, Te, Ag, Au, Ti, MgO, and Zn-based nanocomposites, which have strong and broad-spectrum antibacterial activity (Vimbela et al. 2017). Due to their unique physical and chemical properties, these inorganic nanoparticles are considered as an alternative to several antibiotics. The effectiveness of these materials depends

on the surface/volume ratio, as well as their dimensions and compositional variations. Studies regarding compositional/crystalline modifications and surface coatings based on complex chemistry may lead to the generation of effective and sustainable antibacterial agents (Wang et al. 2017).

The exact antimicrobial mechanisms of nanoparticles remain unclear. However, thus far, three different possible mechanisms have been investigated. The first involves free metal ion toxicity, which occurs during the production of free metal ions from the surface of inorganic nanoparticles. The second involves the direct physical interaction between a metal surface and the bacterial cell wall, which can damage the outer membrane. Finally, the thrid involves oxidative stress, which is induced via ROS production. Other mechanisms which may be involved in the antibacterial activity of nanoparticles are shown in Fig. 7. Notably, aerosol-based nanoparticles have been synthesized in response to the issue of antimicrobial resistance and they have attracted great interest for their antibacterial applications. Ag nanoparticles were synthesized using a green aerosol technique, which involves an electrical discharge between two electrodes under a continuous supply of inert gas under ambient conditions (Hontanon et al. 2014). The antibacterial activity of Ag nanoparticles was then tested against both gram-positive (*Staphylococcus aureus*) and gram-negative (*Klebsiella pneumoniae*) bacteria and were shown to be significantly effective as bactericidal agents. Ag nanoparticles release toxic Ag^+ ions, which can cause the inactivation of bacterial proteins and enzymes by interacting with their thiol groups, thereby leading to metabolic disturbances which result in the production of ROS. In addition, after penetrating the cell surface, Ag^+ ions interact with DNA and induce DNA damage by preventing its replication process (Le Ouay and Stellacci 2015).

Cu and Cu-based alloys are widely used to control the growth and spread of harmful bacteria. Cu is a crucial micronutrient for humans but it is very toxic to bacterial cells due to Cu^{2+} ion-induced ROS production and DNA damage (Graves et al. 2020a, b). Thermal-sprayed Cu coatings on hospital equipment with different composites have been shown to significantly inhibit the growth of pathogenic microorganisms. Moreover, the antibacterial efficacy of Cu has been reported to increase when the Cu content in the nanoparticles is increased (Michels et al. 2005). To reduce the free metal-associated toxicity and enhance their stability, chitosan-coated Cu–Ag

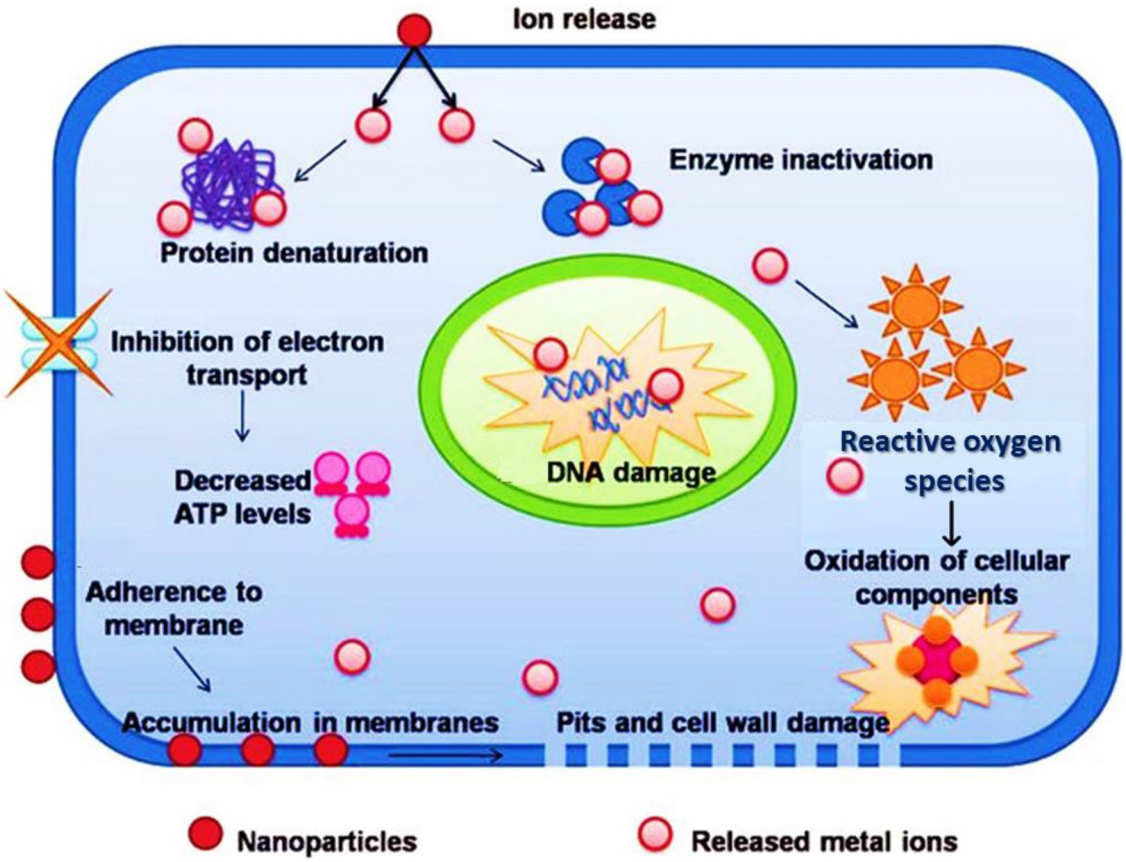

Fig. 7 Different mechanisms of the antimicrobial action of nanoparticles. The given figure was adopted from Jamdagni et al. (2018)

nanobunches were prepared via a gas–liquid hybrid chemical route under ultrasound irradiation. Chitosan is nonantigenic, biocompatible, nontoxic to human cells, and can easily conjugate with metallic ions. Chitosan-based nanoparticles constructed using various versatile, simple, and green techniques showed the highest antibacterial activity against Escherichia coli and S. aureus, among the different antibacterial nanoparticles. Greater antimicrobial activity was associated with enhanced cellular uptake mediated by the strong electrostatic interaction between chitosan and the bacterial surface (Byeon 2016). Thermoresponsive polymers, such as poly-N-isopropyl acrylamide and poly-N-vinyl caprolactam, have been used to develop thermoresponsive antibacterial coatings. Below the transition temperature, these polymers undergo conformational changes to enhance the exposure of bacteria to antibacterial agents. Hence, thermo-responsive antibacterial nanoparticles containing thermo-responsive polymer-incorporated Ag nano-constructs with silica nanoparticles or carbon nanotubes were fabricated via a single-pass gas-to-liquid process (Poudel et al. 2017). The antibacterial activity of the prepared nanoparticles was evaluated against *E. coli* and *Staphylococcus epidermidis* and they were shown to be highly effective at higher temperatures. Notably, particle diameter, shape, and surface properties directly influence their effects of the nanoparticles on bacterial cells and surface-modified nanoparticles have been shown to have superior antibacterial activity against resistant strains (Dong et al. 2019). A spark plasma reactor and a flow heater (maintained at room temperature, 400 °C, and 800 °C) were employed to synthesize Cu-doped Te nanocomposites with different shapes (Gautam et al. 2019a, b). Using temperature modulation, Cu–Te nanoparticles with a dendritic, spiky, or cubic shape were obtained and tested against *E. coli,* extended spectrum β-lactamase (ESBL)-producing *E. coli, S. epidermidis,* and methicillin-resistant *S. aureus* (*MRSA*). The prepared Cu–Te nanoparticles showed synergistic antibacterial activity due to the release of Cu^{2+} and TeO_3^{2-} or TeO_4^{2-} ions, when compared to individual Cu and Te nanoparticles (Gautam et al. 2019a, b) (Table 1).

Although a vast number of nanoparticles have been developed and used for antibacterial purposes, it is necessary to understand their toxicity and outcomes. For a long time, pharmaceutical fields have employed different nanoparticles to minimize the toxicity of the metal components. Nevertheless, there are some safety concerns regarding the use of nanocomposites in biomedical or pharmaceutical fields. Frequently reported toxic effects include respiratory and neurological damage, as well as hematological and nephrological problems, which limit the use of the antibacterial nanocomposites. Indeed, newly developed engineering techniques should be used to prepare antibacterial agents with lower toxicity and better health benefits.

Table 1 List of different formulations used for the treatment of various diseases

Preparation/delivery technique	Formulation	Application/treatment	References
Collison-type atomizer	BP-H-ILsi-X@EM-YSA	Colon adenocarcinoma (MC-38)	(Ou et al. 2019)
Spark discharge and surface modification	S-MTN@IG-P	Colon cancer (HT-29 and HCT-116)	(Gautam et al. 2020a, b)
Spark discharge and surface modification	PB-Dpeg@nGO	Pancreatic cancer (PANC-1)	(Gautam et al. 2020a, b)
Single-pass gas-phase self-assembly	nGO@DOX-cPEG	PC3, DU145, and LNCaP tumor cells	(Thapa et al. 2017)
Spark ablation	BP@DHCA	Human skin cancers (B-16)	(Nguyen et al. 2019)
Green aerosol	Ag-nanoparticles	*S. aureus* and *K. pneumoniae*	(Hontanon et al. 2014)
Gas–liquid green route	Chitosan-capped Cu-Ag nanobunches	*E. coli* and *S. aureus*	(Byeon 2016)
Spark plasma reactor and flow heater	Cu−Te (RT, 400 °C, or 800 °C) NPs	*E. coli, ESBL-producing E. coli, S. epidermidis, and MRSA*	(Gautam et al. 2019a, b)
Single-pass gas-to-liquid process	Ag-SNP@TRP and Ag-CNT@TRP	*E. coli* and *S. epidermidis*	(Poudel et al. 2017)
Spray-congealing with wide pneumatic nozzle	Polymer–lipid mucoadhesive microspheres	*Candida albicans*	(Albertini et al. 2009)
Aerosol	Aerosolized amphotericin B	Antifungal prophylaxis in the early post lung transplantation	(Drew et al. 2004)
Aerosol	Amphotericin B liposome	Prevention of invasive pulmonary aspergillosis in neutropenia	(Rijnders et al. 2008)
Transdermal spray	Voriconazole transdermal spray	*Candida albicans*	(Mori et al. 2017)
Inhalable dry powder	Controlled Release Voriconazole Dry Powder	Invasive pulmonary aspergillosis	(Arora et al. 2015)
Ionic gelation using spray drying technique	Itraconazole encapsulated chitosan-based dry powder	Pulmonary drug delivery for fungal infection	(Jafarinejad et al. 2012)

Antifungal applications

Nanotechnology has led to the development of several antifungal agents which have been used to treat different fungal infections caused by *Candida*, dermatophytes, *Pityrosporum,* and other strains. For decades, numerous antifungal agents, such as griseofulvin, which acts by disturbing spindle and cytoplasmic microtubule function, amphotericin B and ketoconazole, which act by binding or depleting ergosterol, and terbinafine, which induces squalene accumulation, were continuously used to treat fungal infections (Ali Malayeri et al. 2018). The main concern regarding the use of conventional antifungal agents in a clinical setting is the development of antifungal multidrug resistance. The molecular mechanism of multidrug resistance is associated with alterations in drug target abundance, drug affinity, decreased intracellular drug levels caused by efflux pumps, and biofilm formation (Cowen et al. 2014). To counter this problem, aerosol-based methods have been employed to modify the nature of conventional antifungal agents. These techniques are gaining popularity due to the unique physical and chemical properties of these novel nanoparticles. As the particle size of the nanoparticles decreases, their surface-to-volume ratio increases, which leads to improved antifungal activity (Suresh et al. 2016). Polymer lipid-based microspheres were prepared via a spray-congealing process using a pneumatic nozzle (Albertini et al. 2009). Different mucoadhesive polymers, such as sodium carboxymethylcellulose, chitosan, and poloxamers, were added to a lipid-hydrophilic matrix to enhance the antifungal activity of econazole nitrate for vaginal drug delivery. The prepared microspheres were shown to effectively inhibit *Candida albicans* with improved solubility and bioavailability. Adverse effects remain a major problem when delivering a drug via different administration routes. This problem was mitigated by delivering amphotericin B in aerosol form in the early stages after lung transplantation, as an antifungal prophylaxis agent (Drew et al. 2004). In addition, a liposomal form of amphotericin B was delivered in an aerosolized form to prevent invasive pulmonary aspergillosis associated with prolonged neutropenia during chemotherapy (Rijnders et al. 2008). Moreover, chitosan, a biocompatible polymer, was utilized to enhance the inhalable dose of itraconazole. Different chitosan and tripolyphosphate ratios were used to prepare the dry powder via spray drying and the prepared formulation was shown to exhibit enhanced pulmonary deposition after inhalation (Jafarinejad et al. 2012). Dermatological fungal infections (e.g., dermatophytoses and candidiasis) are most common in Asian and African countries, affecting approximately 15% of the total population. The major obstacles to treating these infections include the low efficacy of antifungal agents, poor minimum inhibitory concentrations (MIC), and drug resistance to topical antifungal agents. Therefore, a transdermal spray of voriconazole was prepared using Eudragit RLPO and ethyl cellulose (film-forming polymers) to treat fungal infections (Mori et al. 2017). Due to the wide spectrum of voriconazole, an inhalable, sustained-release dry powder was also formulated and delivered to combat invasive pulmonary aspergillosis (Arora et al. 2015).

Recently, metal-based nanoparticles, such as Cu (Muñoz-Escobar and Reyes-López 2020), Pd (Osonga et al. 2020), and Ag (Suresh et al. 2016) nanoparticles, have been used to treat fungal infections because they can be easily modified and have high stability, low toxicity, low price, and durability. To enhance antifungal activity, an Ag-based ketoconazole gel had been prepared and tested against *Malassezia furfur*, which is responsible for dermal infections (Mussin et al. 2019). The prepared gel was shown to exhibit synergistic fungicidal action with low MIC values than conventional dosage forms. Recently, chitosan-coupled Cu nanoparticles were fabricated via an ion gelation technique using sodium tripolyphosphate (Vanti et al. 2020). The toxicity of individual Cu nanoparticles was found to be significantly decreased after chitosan coating, while their activity against the damping off disease was highly enhanced. Although several types of nanoparticles have been developed to treat fungal infections, the safety of metal-based nanoparticles remains a challenging issue. The development of surface-modified noble metal nanoparticles via aerosol techniques could represent a milestone in the treatment of multidrug-resistant fungal infections.

Antiviral applications

The recurrence of pathogenic resistance, including that of viruses, is a major cause of death and a serious challenge to medical science. Many efforts have been made to develop stable drugs and vaccines against re-emerging viruses but the development of cheap, novel, and broad-spectrum antiviral agents remains difficult. Current developments in nanomedicine offer a novel platform for the synthesis of potentially effective antiviral metal nanoparticles via appropriate surface modifications. Metal nanoparticles act as antiviral agents by inhibiting viral replication. The antiviral properties of metal nanoparticles are ascribed to the release of free metal ions, which leads to the production of ROS, resulting in the oxidation of capsid proteins (Rai et al. 2016).

Ag nanoparticles are one of the best candidates for antiviral agents due to their broad range of action. They have been shown to have effective inhibitory activity against severe acute respiratory syndrome-coronavirus (SARS-CoV), influenza A/H1N1, influenza A/H5N1, hepatitis B virus, and human immunodeficiency virus (Haider and Kang 2015; Verma and Maheshwari 2019). The interaction between the Ag nanoparticle and the virus particle also plays a vital role and it has been shown that the smaller nanoparticles

have more effective antiviral activity. Moreover, it has been reported that conjugation of Ag nanoparticles with different polymers has a beneficial role in antiviral treatment (Salleh et al. 2020). Polyvinylpyrrolidone (PVP)-coated Ag nanoparticles have been shown to effectively inhibit the respiratory syncytial virus. The proposed underlying mechanism of action involves the interaction between PVP-coated Ag nanoparticles and G proteins on the viral surface, which suppresses the attachment of the virus to the host cells (Haider and Kang 2015). Chitin/chitosan-based Ag nanoparticles have also been shown to exert enhanced antiviral activity (Nakamura et al. 2019). Furthermore, Ag-coated nanoparticles have been widely used in industrial applications. The spark discharge technique was used to produce Ag nanoparticles for air-filter coatings. The antiviral activity of the Ag-coated filter was tested against aerosolized bacteriophage MS2 virus particles and it was shown to significantly reduce viral loads (Joe et al. 2016). The same strain of virus was also killed using a carbon nanotube-coated glass fiber prepared via an electro-aerodynamic deposition technique under ambient conditions (Park and Hwang 2014). Recently, specific viral antigens immobilized on reduced GO biosensors via the aerosol jet nano-printing technique were used to detect COVID-19 antibodies within seconds (Ali et al. 2020). It was also shown that Cu can inhibit the replication of SARS-CoV-2, MERS, or influenza and Cu oxide can be used in face masks, protective clothing, and filters to prevent bacterial and viral transmission (Cortes and Zuñiga 2020). Cu-coating (approximately 0.05 mm thick) of aluminum substrates via the cold-spray surface coating method has also been used to inactivate the influenza A virus through a contact-killing mechanism (Sundberg et al. 2015). In addition, Au and other metal particles are extensively used as antiviral agents, which suggests that this field has great potential for the development of novel antiviral treatments.

Clinical diagnostics

Several metal nanoparticles are readily implemented in a clinical setting as theragnostic agents due to their small size and unique physicochemical properties. The combination of diagnosis and therapy has a crucial role in cancer diagnosis and treatment. Several nanoparticles (Au, iron, quantum dots, inorganic phosphor, copper, and other metals) have been used to detect cancer markers, such as circulating tumor cells, vesicles, nucleic acids, and proteins (Huang et al. 2017). Recently, different features have been added to single particles to improve their diagnostic and imaging capabilities. Thus, the multiple properties of plasmonic magnetic nanoparticles are attracting considerable attention in bioimaging, diagnosis, and targeted drug delivery. Previously, silica-coated dumbbell-like Ag–Fe_2O_3 bio-probes were synthesized using the flame aerosol technique for bioimaging and drug delivery (Sotiriou et al. 2011). The purpose of the silica coating was to reduce the release of toxic Ag^+ from the surface of the nanocomposite. Here, the thin nano-silica coating did not hamper the magnetic and plasmonic properties of the nanoparticles. Size-controlled plasmonic Ag nanoparticles were prepared using the aerosol method. By using the evaporation–condensation system, monodispersed and spherical Ag nanoparticles were prepared and their sizes were measured using a differential mobility analyzer. The dipole peak of the plasmon resonance changed between the wavelengths of 398 and 448 nm (Harra et al. 2012). Among the various metal nanoparticles, Au nanoparticles possess unique optical and surface plasmon resonance properties. Consequently, they have been considered for applications in the biomedical and diagnostic fields. Moreover, due to their optical properties, Au nanoparticles are utilized in imaging-based diagnostic methods and for ultrasensitive detection in the treatment of cancer and other lethal diseases. Studies have been conducted to prepare ultrapure Au nanoparticles via a pulsed spark-discharge (PSD) technique in the absence of stabilizers and chemical surfactants. Au electrodes were used to generate and condense the vapor within the spark chamber in the presence of a dielectric ethanol medium (Tseng and Huang 2011). Thus, it was shown that PSD can be an alternative green technique for the synthesis of highly stable Au nanoparticles.

Theragnostic approaches have a significant role in personalized therapy due to controlled drug delivery and imaging techniques. MRI is used to detect the presence or progression of various diseases and to maximize therapeutic outcomes, enabling personalized treatment (Ho et al. 2020; Avugadda et al. 2021). Inhalable metal–organic framework nanoparticles were synthesized by spray drying to enhance the localized delivery of antibiotics for tuberculosis treatment. Moreover, the local delivery of a drug into the lungs can be greatly enhanced through MRI contrast agent-guided pulmonary drug delivery systems (Wyszogrodzka-Gaweł et al. 2019). Superparamagnetic reduced Fe_3O_4 nanoparticles were synthesized using a gas-phase flame method. Interestingly, this technique produced size-controlled magnetic iron nanoparticles under reduced conditions, which have been widely tested in clinical diagnostics (Kumfer et al. 2010). In another study, iron oxide nanoparticles were obtained via flame pyrolysis of a $Fe(NO_3)_3 \cdot 9H_2O$ and $FeC_6H_5O_7 \cdot 4H_2O$ solution. The synthetic reaction conditions, such as the key precursor solution, solution amount, and reaction environment, were maintained to obtain nanoparticles with a precise particle size, structural phase, and texture (Shen et al. 2020). Recently, the flame spray pyrolysis technique was modified using the SpraySyn nozzle. Iron oxide nanoparticles were prepared using a phase-selective laser-induced breakdown spectroscopy method by varying the composition of spray solution (Stodt et al. 2020). Different types of

iron oxide nanoparticles, such as ferumoxide, ferucarbotran, and ferumoxytol, have been approved for clinical diagnostic applications (Liu et al. 2020). Hopefully, the continuous development of aerosol-based technologies can pave the way for the production of useful diagnostic agents for clinical application.

Biological assays

Bioassays determine the relative strength of a substance, either qualitatively or quantitatively, in the test organisms, by comparing with a standard. Biological assays are used to determine the concentration, biological activity, or purity of different compounds in cells, tissues, organisms, or receptors (Dafale 2016; Serrano et al. 2020). Organic and inorganic nanoparticles have been used for analytical detection assays and bioassays. The unique optoelectronic (metal nanoparticles), catalytic (metal, quantum dots, and oxide nanoparticles), magnetic (cobalt and iron oxide nanoparticles), and other physicochemical properties make metal nanoparticles particularly useful for chemical and biological detection when combined with other specific probes (Castro et al. 2014). Due to the surface plasmon resonance properties of Au and Ag nanoparticles, they have high extinction coefficients and exhibit different colors in the visible light region of the spectrum. A well-designed aptamer-conjugated Au nanoparticle was prepared for the direct detection of cancer cells using a colorimetric assay. The assay showed excellent sensitivity and selectivity and was able to distinguish between cancerous and non-cancerous samples. Similarly, dopamine-stabilized Ag nanoparticles have also been proposed to detect melamine in milk samples (Gasparyan 2009; Vilela et al. 2012). Ag-nanoparticle-based nanosensors have also been developed to detect serum p53 levels, which are associated with head and neck squamous cell carcinoma (Zhou et al. 2011). Moreover, photoluminescent Ag nanoparticles were synthesized to detect hydrogen peroxide via fluorescence. Then, the method was coupled with glucose oxidase to determine serum glucose levels (Zhou et al. 2021). The levels of organophosphate pesticides have also been detected using Au and Ag nanoparticles via colorimetric analysis (Che Sulaiman et al. 2020). Core–shell structured luminescent and magnetic nanoparticles were also synthesized using the flame spray pyrolysis technique for immunological assays. The prepared nanoparticles have magnetic cores of iron oxide doped with cobalt and neodymium and luminescent shells of europium-doped gadolinium oxide (Eu:Gd_2O_3). Interestingly, magnetic/luminescent core/shell particles have several potential biological applications, including the easy detection of bacteria, viruses, and cells (Dosev et al. 2007). Finally, detection assays are directly dependent on the properties of the nanoparticles and for correct interpretation of the results, both quantitative and qualitative changes should be thoroughly monitored.

Conclusion

This review encompasses various synthesis approaches and biomedical applications of aerosol-based nanoparticles in different fields. Various organic and inorganic nanoparticles can be synthesized using different methods, among which the aerosol-based technique is one of the most promising approaches for large-scale manufacturing of highly pure nanoparticles. The ability of the aerosol-based technique to operate in continuous rather than batch-to-batch manufacturing makes it favorable for industrial and technological applications. In this regard, the utilization of aerosol-based nanoparticles can be highly beneficial to the biomedical field. Aerosol technology presents an innovative and modern approach to develop and test different nanoparticle formulations with anticancer, antibacterial, antiviral, and antifungal properties. The prepared nanoparticles have also been shown to have significant potential as diagnostic agents and in biological assays. Moreover, the theragnostic properties of nanoparticles have facilitated the timely detection of lethal diseases and have proven to be helpful for the early treatment of these diseases.

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Declarations

Conflict of interest The authors (M. Gautam, J.O. Kim, and C.S. Yong) declare that they have no conflict of interest.

Research involving human and/or animal participants This article does not contain any studies with human participants or animals performed by any of the authors.

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