

## MINI REVIEW NANOPARTICLES AND THEIR APPLICATIONS IN BIOMEDICAL SCIENCE

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### ABSTRACT

Nanotechnology is associated with nano-meter sized objects. Nanotechnology deals with matter at the scale of 1 billionth of a meter and is also the study of manipulating matter at the atomic and molecular scale. Recently particulate systems like nanoparticles have been used as a physical approach to alter and improve the quality of human life. The potential use of polymeric nanoparticles as carriers for a wide range of drugs for therapeutic applications has been increased due to their versatility and wide range of properties. Nanotechnology is expected to bring revolutionary changes in the field of life sciences including drug delivery, diagnostics and production of bio-materials. Different types of nanoparticulate materials used in electronics, magnetic pharmaceuticals, cosmetics, energy, catalytic and materials industries. For the past few decades, there has been a considerable research interest in particulate delivery systems. So, particulate systems like nanoparticles have been utilized as physical approaches to change and improve the pharmacokinetic and pharmacodynamics properties of various types of drug molecules. In this review the type of nanoparticles, synthesis methods of nanoparticles and their applications has been discussed.

**KEYWORDS:** Nanoparticles, Nanotechnology, nanotoxicity, drug delivery systems.

### INTRODUCTION

Nanotechnology employs knowledge from the fields of physics, chemistry, biology, materials science, health sciences, and engineering. It has immense applications in almost all the fields of science and human life. Nanoparticles can be defined as particulate dispersions or solid particles with a size in the range of 10-1000nm.<sup>[1]</sup> A Nanometres is billionth of a meter, which is 250 millionth of an inch, about 1/80,000 of the diameter of a human hair or 10 times of the diameter of hydrogen atom.<sup>[2]</sup> The term Nanotechnology was coined by Prof. Norio Taniguchi, Tokyo Science University in 1974 to describe the precision manufacture of materials with nanometers tolerances and was unknowingly appropriated by Drexler in his 1986 book „Engines of creation: The Coming Era of Nanotechnology.<sup>[3]</sup> Nanotechnology literally means any technology on a nanoscale that has applications in the real world. Nanotechnology encompasses the production and application of physical, chemical, and biological systems at scales ranging from individual atoms or molecules to submicron dimensions, as well as the integration of the resulting nanostructures into larger systems. Science and technology research in nanotechnology promises breakthroughs in areas such as materials and

manufacturing, nanoelectronics, medicine and healthcare, energy, biotechnology, information technology, and national security. It is widely felt that nanotechnology will be the next Industrial Revolution.<sup>[4]</sup> On December 29, 1959 at the California Institute of Technology, Nobel Laureate Richard P. Feynman gave a talk at the Annual Meeting of the American Physical Society that has become one of the 20th century's classic science lectures, entitled There's Plenty of Room at the Bottom. He presented a technological vision of extreme miniaturization in 1959, several years before the word chip became part of the lexicon. The word nanotechnology is a relatively new word, but it is not an entirely new field. Nature has gone through evolution over the 3.8 billion years since life is estimated to have appeared on Earth. Nature has many materials, objects, and processes which function from the macroscale to nanoscale.<sup>[5]</sup> Understanding the functions provided by these objects and processes can guide us to imitate and produce nanomaterials, nanodevices, and processes. Biologically inspired design, adaptation or derivation from nature is referred to as biomimetics, a term coined by the polymath Otto Schmitt in 1957. Biomimetics is derived from the Greek word biomimesis.<sup>[6]</sup> Other terms used include bionics, biomimicry, and biognosis. The term biomimetics is relatively new; however, our

ancestors looked to nature for inspiration and the development of various materials and devices many centuries ago.<sup>[7]</sup> There are a large number of objects, including bacteria, plants, land and aquatic animals, seashells, and spider web, with properties of commercial interest. In general, the size of a nanoparticle spans the range between 1 and 100 nm. Metallic nanoparticles have different physical and chemical properties from bulk metals (e.g., lower melting points, higher specific surface areas, specific optical properties, mechanical strengths, and specific magnetizations), properties that might prove attractive in various industrial applications.

However, how a nanoparticle is viewed and is defined depends very much on the specific application of particular importance, the optical property is one of the fundamental attractions and a characteristic of a nanoparticle. For example, a 20-nm gold nanoparticle has a characteristic wine red color.<sup>[8]</sup> A silver nanoparticle is yellowish gray. Platinum and palladium nanoparticles are black.<sup>[9]</sup> Not surprisingly, the optical characteristics of nanoparticles have been used from time immemorial in sculptures and paintings even before the 4th century AD. The most famous example is the Lycurgus cup (fourth century AD) illustrated in Fig: 1.



**Figure 01: Lycurgus Cup.**

This extraordinary cup is the only complete historic example of a very special type of glass, known as dichroic glass, that changes color when held up to the light. The opaque green cup turns to a glowing translucent red when light is shone through it internally (i.e., light is incident on the cup at 90° to the viewing direction). Analysis of the glass revealed that it contains a very small quantity of tiny (~70 nm) metal crystals of Ag and Au in an approximate molar ratio of 14: 1, which give it these unusual optical properties. It is the presence of these nanocrystals that gives the Lycurgus Cup its special color display. The reader can marvel at the cup now in the British Museum.<sup>[10]</sup> Recent developments in nanotechnology have shown that nanoparticles (structures smaller than 100 nm in at least one dimension) have a great potential as drug carriers. Due to their small sizes, the nanostructures exhibit unique physicochemical and biological properties (e.g., an enhanced reactive area as well as an ability to cross cell and tissue barriers) that make them a favourable material for biomedical applications.<sup>[11]</sup> The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically

optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability.<sup>[12]</sup> On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties. Nanomedicine is a subset of nanotechnology, which uses tiny particles that are more than 10 million times smaller than the human body. In nanomedicine, these particles are much smaller than the living cell. Because of this, nanomedicine presents many revolutionary opportunities in the fight against all types of cancer, neurodegenerative disorders and other diseases.<sup>[13]</sup>

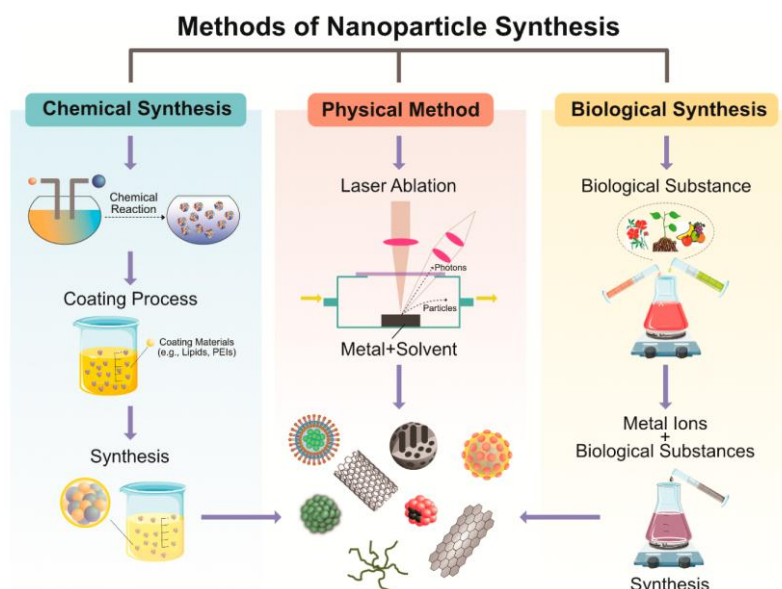
#### **Methods for synthesis of nanoparticles**

Two approaches have been known in the preparation of ultrafine particles from ancient times. The first is the breakdown (top-down) method by which an external force is applied to a solid that leads to its break-up into

smaller particles.<sup>[14]</sup> The second is the build-up (bottom up) method that produces nanoparticles starting from atoms of gas or liquids based on atomic transformations or molecular condensations. The top-down method is the method of breaking up a solid substance; it can be subdivided into dry and wet grinding.<sup>[15]</sup> A characteristic of particles in grain refining processes is that their surface energy increases, which causes the aggregation of particles to increase also. In the dry grinding method the solid substance is ground as a result of a shock, a compression, or by friction, using such popular methods as a jet mill, a hammer mill, a shearing mill, a roller mill, a shock shearing mill, a ball mill, and a tumbling mill.<sup>[16]</sup> Since condensation of small particles also takes place simultaneously with pulverization, it is difficult to obtain particle sizes of less than 3  $\mu\text{m}$  by grain refining. On the other hand, wet grinding of a solid substrate is carried out using a tumbling ball mill, or a vibratory ball mill, a planetary ball mill, a centrifugal fluid mill, an agitating beads mill, a flow conduit beads mill, an annular gap beads mill, or a wet jet mill. Compared with the dry method, the wet process is suitable for preventing the condensation of the nanoparticles so formed, and thus it is possible to obtain highly dispersed nanoparticles. Other than the above, the mechanochemical method and the mechanical alloying method are also known top-down methods.<sup>[17]</sup> The bottom-up approach is roughly divided into gaseous phase methods and liquid phase methods. For the former, the chemical vapor deposition method (CVD) involves a chemical reaction, whereas the physical vapor deposition method (PVD) uses cooling of the evaporated material. Although the gaseous phase

methods minimize the occurrence of organic impurities in the particles compared to the liquid phase methods, they necessitate the use of complicated vacuum equipment whose disadvantages are the high costs involved and low productivity.<sup>[18]</sup> The CVD procedure can produce ultrafine particles of less than 1  $\mu\text{m}$  by the chemical reaction occurring in the gaseous phase. The manufacture of nanoparticles of 10 to 100 nm is possible by careful control of the reaction. Performing the high temperature chemical reaction in the CVD method requires heat sources such as a chemical flame, a plasma process, a laser, or an electric furnace. In the PVD method, the solid material or liquid material is evaporated and the resulting vapor is then cooled rapidly, yielding the desired nanoparticles.<sup>[19]</sup> To achieve evaporation of the materials one can use an arc discharge method. The simple thermal decomposition method has been particularly fruitful in the production of metal oxide or other types of particles and has been used extensively as a preferred synthetic method in the industrial world.<sup>[20]</sup> That is, the synthesis of nanoparticles requires the use of a device or process that fulfils the following conditions

- Control of particle size, size distribution, shape, crystal structure and composition distribution
- Improvement of the purity of nanoparticles (lower impurities)
- Control of aggregation
- Stabilization of physical properties, structures and reactants
- Higher reproducibility
- Higher mass production, scale-up and lower costs.



**Figure 02: Methods of Synthesis of Nanoparticles.**

### Mechanical attrition

Unlike many of the methods mentioned above, mechanical attrition produces its nanostructures not by cluster assembly but by the structural decomposition of coarser grained structures as a result of plastic deformation.<sup>[21]</sup> Elemental powders of Al and  $\beta$ -SiC were

prepared in a high energy ball mill. More recently, ceramic/ceramic nanocomposite WC-14% MgO material has been fabricated. The ball milling and rod milling techniques belong to the mechanical alloying process which has received much attention as a powerful tool for the fabrication of several advanced materials.

Mechanical alloying is a unique process, which can be carried out at room temperature.<sup>[22]</sup> The process can be performed on both high energy mills, centrifugal type mill and vibratory type mill, and low energy tumbling mill.<sup>[23-25]</sup>

#### High energy mills include

- Attrition Ball Mill
- Planetary Ball Mill
- Vibrating Ball Mill
- Low Energy Tumbling Mill
- High Energy Ball Mill

#### Attrition Ball Mill

The milling procedure takes place by a stirring action of a agitator which has a vertical rotator central shaft with horizontal arms (impellers).<sup>[26]</sup> The rotation speed was later increased to 500 rpm. Also, the milling temperature was in greater control.

#### Planetary Ball Mill

Centrifugal forces are caused by rotation of the supporting disc and autonomous turning of the vial. The milling media and charge powder alternatively roll on the inner wall of the vial and are thrown off across the bowl at high speed (360 rpm).

#### Vibrating Ball Mill

It is used mainly for production of amorphous alloys. The changes of powder and milling tools are agitated in the perpendicular direction at very high speed (1200 rpm).

#### Low Energy Tumbling Mill

They have been used for successful preparation of mechanically alloyed powder. They are simple to operate with low operation costs. A laboratory scale rod mill was used to prepare homogenous amorphous Al<sub>30</sub>Ta<sub>70</sub> powder by using S.S. cylinder rods. Single-phase amorphous powder of Al<sub>x</sub>Tm<sub>100-x</sub> with low iron concentration can be formed by this technique.

#### High Energy Ball Mill

High-energy ball milling is an already established technology, however, it has been considered dirty because of contamination problems with iron. However, the use of tungsten carbide component and inert atmosphere and /or high vacuum processes has reduced impurity levels to within acceptable limits. Common drawbacks include low surface, highly poly disperse size distribution, and partially amorphous state of the powder. These powders are highly reactive with oxygen, hydrogen and nitrogen. Mechanical alloying leads to the fabrication of alloys, which cannot be produced by conventional techniques. It would not be possible to produce an alloy of Al-Ta, because of the difference in melting points of Al (933 K) and Ta (3293 K) by any conventional process. However, it can be fabricated by mechanical alloying using ball milling process.

#### Chemical Precipitation

In this strategy the size is control by arrested precipitation technique. The basic trick has been to synthesis and studies the nanomaterial in situ i.e. in the same liquid medium avoiding the physical changes and aggregation of tiny crystallites. Thermal coagulation and Oswald ripening were controlled by double layer repulsion of crystallites using non-aqueous solvents at lower temperatures for synthesis. The synthesis involved reaction between constituent material in suitable solvent. The dopant is added to the parent solution before precipitation reaction. Surfactant is used to maintain separation between the particles formed. Thus formed nanocrystal are separated by centrifugation, washed and vacuum dried. The dried material was further subjected to UV curing for possible polymerization of surfactant capping film on the surface of nano cluster for imparting true quantum confinement.<sup>[27-29]</sup>

#### Sol-Gel Techniques

In addition to techniques mentioned above, the sol-gel processing techniques have also been extensively used. Colloidal particles are much larger than normal molecules or nanoparticles. However, upon mixing with a liquid colloids appear bulky whereas the nanosized molecules always look clear.<sup>[27]</sup> It involves the evolution of networks through the formation of colloidal suspension (sol) and gelatin to form a network in continuous liquid phase (gel). The precursor for synthesizing these colloids consists of ions of metal alkoxides and alkoxy silanes. The most widely used are tetramethoxysilane (TMOS), and tetraethoxysilanes (TEOS) which form silica gels. Alkoxides are immiscible in water. They are organo metallic precursors for silica, aluminum, titanium, zirconium and many others. Mutual solvent alcohol is used. The sol gel process involves initially a homogeneous solution of one or more selected alkoxides. These are organic precursors for silica, alumina, titania, zirconia, among others. A catalyst is used to start reaction and control pH. Sol-gel formation occurs in four stages.<sup>[30-33]</sup>

- Hydrolysis
- Condensation
- Growth of particles
- Agglomeration of particles

#### Hydrolysis

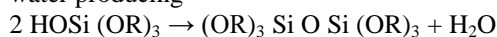
During hydrolysis, addition of water results in the replacement of [OR] group with [OH-]group. Hydrolysis occurs by attack of oxygen on silicon atoms in silica gel. Hydrolysis can be accelerated by adding a catalyst such as HCl and NH<sub>3</sub>. Hydrolysis continues until all alkoxy groups are replaced by hydroxyl groups. Subsequent condensation involving silanol group (Si-OH) produced siloxane bonds (Si-O-Si) and alcohol and water. Hydrolysis occurs by attack of oxygen contained in the water on the silicon atom.

### Condensation

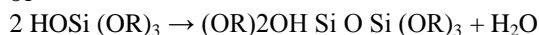
Polymerization to form siloxane bond occurs by either a water producing or alcohol producing condensation reaction. The end result of condensation products is the formation of monomer, dimer, cyclic tetramer, and high order rings. The rate of hydrolysis is affected by pH, reagent concentration and H<sub>2</sub>O/Si molar ratio (in case of silica gels). Also ageing and drying are important. By control of these factors, it is possible to vary the structure and properties of sol-gel derived inorganic networks.

### Growth and Agglomeration

As the number of siloxane bonds increase, the molecules aggregate in the solution, where they form a network, a gel is formed upon drying. The water and alcohol are driven off and the network shrinks. At values of pH of greater than 7, and H<sub>2</sub>O/Si value ranging from 7 to 5. Spherical nano-particles are formed. Polymerization to form siloxane bonds by either an alcohol producing or water producing



or



Above pH of 7, Silica is more soluble and silica particles grow in size. Growth stops when the difference in solubility between the smallest and largest particles becomes indistinguishable. Larger particles are formed at higher temperatures. Zirconium and Yttrium gels can be similarly produced. Despite improvements in both chemical and physical methods of synthesis, there remain some problems and limitations. Laser vaporization technique has offered several advantages over other heating techniques. A high energy pulsed laser with an intensity flux of 106 - 107 W/cm<sup>2</sup> is forced on target material. The plasma causes high vaporization and high temperature (10,000°C). Typical yields are 1014-1015 atoms from the surface area of 0.01 cm in a 10-8 s pulse. Thus a high density of vapor is produced in a very short time (10 s), which is useful for direct deposition of particles.

### Electrodeposition

Nanostructured materials can also be produced by electrodeposition. These films are mechanically strong, uniform and strong. Substantial progress has been made in nanostructured coatings applied either by DVD or CVD. Many other non-conventional processes such as hypersonic plasma particle deposition (HPPD) have been used to synthesize and deposit nanoparticles. The significant potential of nanomaterial synthesis and their applications is virtually unexplored. They offer numerous challenges to overcome. Understanding more of synthesis would help in designing better materials. It has been shown that certain properties of nanostructured deposits such as hardness, wear resistance and electrical resistivity are strongly affected by grain size. A combination of increased hardness and wear resistance results in a superior coating performance.<sup>[34,36]</sup>

### Properties of nanoparticles

The dimension of matter important in nanoscience and nanotechnology is typically on the 0.2- to 100-nm scale (nanoscale). The properties of materials change as their size approaches the nanoscale. Further, the percentage of atoms at the surface of a material becomes more significant.<sup>[37-38]</sup> Bulk materials possess relatively constant physical properties regardless of their size, but at the nanoscale this is often not the case. As the material becomes smaller the percentage of atoms at the surface increases relative to the total number of atoms of the material bulk. This can lead to unexpected properties of nanoparticles which are partly due to the surface of the material dominating over the bulk properties. At this scale, the surface-to-volume ratios of materials become large and their electronic energy states become discrete, leading to unique electronic, optical, magnetic, and mechanical properties of the nanomaterials. In general, as the size of inorganic and organic materials decreases towards the nanoscale, their optical and electronic properties largely varies from the bulk material at the atomic/molecular levels and is size and shape dependent. The various size dependent properties that can be observed are quantum confinement in semi-conductor particles, surface plasmon resonance in noble metal particles and super paramagnetism in magnetic materials. Thus, the crystallographic surface structure and the large surface to volume ratio make the nanoparticles exhibit remarkable properties. Moreover, the increased catalytic activity due to morphologies with highly active facets and the tailoring of its synthesis as per the requirement makes the nanoparticles an attractive tool to solve various technological problems.<sup>[39-42]</sup>

### Applications of nanoparticles

Nanoparticles are used, or being evaluated for use, in many fields. The list below introduces few of the uses under development.

#### Nanoparticle Applications in Medicine

The use of polymeric micelle nanoparticles to deliver drugs to tumors. The use of polymer coated iron oxide nanoparticles to break up clusters of bacteria, possibly allowing more effective treatment of chronic bacterial infections. The surface change of protein filled nanoparticles has been shown to affect the ability of the nanoparticle to stimulate immune responses. These nanoparticles may be used in inhalable vaccines. The cerium oxide nanoparticles act as an antioxidant to remove oxygen free radicals that are present in a patient's bloodstream following a traumatic injury. The nanoparticles absorb the oxygen free radicals and then release the oxygen in a less dangerous state, freeing up the nanoparticle to absorb more free radicals. Researchers are developing ways to use carbon nanoparticles called nanodiamonds in medical applications. For example, Nanodiamonds with protein molecules attached can be used to increase bone growth around dental or joint implants. Researchers are testing the use of chemotherapy drugs attached to

nanodiamonds to treat brain tumors. Other researchers are testing the use of chemotherapy drugs attached to nanodiamonds to treat leukemia.<sup>[43-45]</sup>

#### ***Nanoparticle Applications in Manufacturing and Materials***

Ceramic silicon carbide nanoparticles dispersed in magnesium produce a strong, lightweight material. A synthetic skin that may be used in prosthetics has been demonstrated with both self-healing capability and the ability to sense pressure. The material is a composite of nickel nanoparticles and a polymer. If the material is held together after a cut it seals together in about 30 minutes giving it a self-healing ability. Also the electrical resistance of the material changes with pressure, giving it a sense ability like touch. Silicate nanoparticles can be used to provide a barrier to gasses (for example oxygen), or moisture in a plastic film used for packaging. This could slow down the process of spoiling or drying out in food. Zinc oxide nanoparticles can be dispersed in industrial coatings to protect wood, plastic, and textiles from exposure to UV rays. Silicon dioxide crystalline nanoparticles can be used to fill gaps between carbon fibers, thereby strengthening tennis racquets. Silver nanoparticles in fabric are used to kill bacteria, making clothing odor-resistant.<sup>[46-48]</sup>

#### ***Nanoparticle Applications and the Environment***

Researchers are using photocatalytic copper tungsten oxide nanoparticles to break down oil into biodegradable compounds. The nanoparticles are in a grid that provides high surface area for the reaction, is activated by sunlight and can work in water, making them useful for cleaning up oil spills. Researchers are using gold nanoparticles embedded in a porous manganese oxide as a room temperature catalyst to breakdown volatile organic pollutants in air. Iron nanoparticles are being used to clean up carbon tetrachloride pollution in ground water. Iron oxide nanoparticles are being used to clean arsenic from water wells.<sup>[49-50]</sup>

#### ***Nanoparticle Applications in Energy and Electronics***

Researchers have used nanoparticles called nanotetrapods studded with nanoparticles of carbon to develop low cost electrodes for fuel cells. This electrode may be able to replace the expensive platinum needed for fuel cell catalysts. Researchers at Georgia Tech, the University of Tokyo and Microsoft Research have developed a method to print prototype circuit boards using standard inkjet printers. Silver nanoparticle ink was used to form the conductive lines needed in circuit boards. Combining gold nanoparticles with organic molecules creates a transistor known as a NOMFET (Nanoparticle Organic Memory Field-Effect Transistor). This transistor is unusual in that it can function in a way similar to synapses in the nervous system. A catalyst using platinum-cobalt nanoparticles is being developed for fuel cells that produces twelve times more catalytic activity than pure platinum. In order to achieve this performance, researchers anneal nanoparticles to form

them into a crystalline lattice, reducing the spacing between platinum atoms on the surface and increasing their reactivity. Researchers have demonstrated that sunlight, concentrated on nanoparticles, can produce steam with high energy efficiency. The "solar steam device" is intended to be used in areas of developing countries without electricity for applications such as purifying water or disinfecting dental instruments. A lead free solder reliable enough for space missions and other high stress environments using copper nanoparticles. Silicon nanoparticles coating anodes of lithium-ion batteries can increase battery power and reduce recharge time. Semiconductor nanoparticles are being applied in a low temperature printing process that enables the manufacture of low cost solar cells.<sup>51</sup> A layer of closely spaced palladium nanoparticles is being used in a hydrogen sensor. When hydrogen is absorbed, the palladium nanoparticles swell, causing shorts between nanoparticles. These shorts lower the resistance of the palladium layer.<sup>[52]</sup>

#### **CONCLUSION**

Nanoparticles are the most attractive for commercialization applications. They have been widely used for antimicrobial, electronic and biomedical products. The large surface area provided by nanoparticles, together with their ability to self-assemble on a support surface, could be of use in all of these applications. Nanoparticles have unique properties as compared to micro and macro particles. In this review, we provide a comprehensive understanding of the nanoparticles synthesis methods like mechanical attrition, chemical precipitation, sol-gel techniques, electrodeposition has been briefly explained. The properties of the nanoparticles also described. The list of few of the uses nanoparticles like medicine, manufacturing, environment, energy, antimicrobial effects and electronics, which are under development has been discussed in this study.

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