EAS Journal of Pharmacy and Pharmacology
Abbreviated Key Title: EAS J Pharm Pharmacol
ISSN: 2663-0990 (Print) & ISSN: 2663-6719 (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-8 | Issue-6 | Nov-Dec- 2026 | DOI: https://doi.org/10.36349/easjpp.2026.v08i06.001

Review Article

Nanoparticles - A Review

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Article History
Received: 22.08.2026
Accepted: 28.10.2026
Published: 02.11.2026

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: Nanoparticles are nanoscale structures characterized by a high surface area-to-volume ratio, which imparts distinctive physicochemical properties. Their small size (typically below 100 nm) and the ability to modify their surface enable their application across diverse fields. The properties and functional performance of nanoparticles are influenced by several factors, including synthesis techniques as well as physical characteristics such as size, shape, and morphology. Furthermore, the choice of material used in nanoparticle fabrication plays a crucial role in determining their suitability for specific applications. Based on their composition, nanoparticles are broadly categorized into organic, inorganic, and carbon-based types. These groups encompass a wide range of materials, including polymers, proteins, lipids, metal ions, and magnetic substances. Each material type exhibits distinct features that govern the behaviour, efficiency, and potential toxicity of the nanoparticles. As a result, specific nanoparticles are preferentially utilized in particular applications where their performance and safety profiles are optimized. Therefore, both the classification and material selection are critical considerations in nanoparticle research and practical use. This paper presents a comprehensive overview of nanoparticle classifications, highlights key materials within each category, and discusses their respective application domains. Additionally, it examines the associated toxicity aspects, providing an integrated perspective on nanoparticle materials and their relevance in various fields.

Keywords: Nanoparticles.

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INTRODUCTION

Nanoparticles are the basic building blocks of nanotechnology. They typically range in size from 1 to 100 nm and can be composed of metals, metal oxides, organic substances, or carbon-based materials [12-15].

These particles vary in dimensions, shape, and size, as well as in their composition. Their surface characteristics may be either irregular, showing heterogeneity, or uniform. Nanoparticles may exist in crystalline or amorphous forms and can occur as single-crystal or polycrystalline solids. They may also be found in aggregated (agglomerated) or dispersed (loose) states [12-17].

During the development of new pharmaceutical agents, a significant proportion of drug candidates exhibit poor or negligible aqueous solubility, posing a major challenge to the pharmaceutical industry. One of the primary causes of poor solubility is the complex and high molecular weight structure of these compounds. It has been reported that more than 65% of newly developed active pharmaceutical ingredients (APIs) are either poorly water-soluble or practically insoluble [12-19].

Due to their low aqueous solubility and relatively high permeability, such compounds are classified under Class II of the Biopharmaceutics Classification System (BCS), where dissolution is the

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rate-limiting step governing drug absorption. Consequently, improving the dissolution behaviour of poorly soluble drugs has become a critical objective for enhancing their bioavailability.

Nanoparticles have emerged as a promising approach to address this issue, as they can enhance the stability of drugs and proteins and enable controlled drug release.

This review primarily focuses on the synthesis of various types of nanoparticles using chemical, physical, and biological approaches. While chemical and physical methods are often associated with high cost and potential toxicity, biological methods offer advantages such as simplicity, rapidity, non-toxicity, and environmental compatibility [12-20].

Advantages of Nanoparticles

1. The surface properties and particle size of nanoparticles can be easily modified. This helps in delivering drugs to the target site through both active and passive targeting after injection.
2. Nano-sized quantum dots based on immunofluorescence are used to identify specific bacteria. This makes it easier to detect and eliminate them.
3. Nanotechnology is a rapidly growing field in many industries, especially in aquaculture. It is used in nutrition, reproduction, water purification, fishing, disease control, and in reducing toxicity and harmful effects.
4. When nanoparticles are prepared using biodegradable materials, they can release drugs slowly at the target site for days or even weeks [12-14].

Disadvantages of Nanoparticles

1. Due to their small size and large surface area, nanoparticles are highly reactive in the cellular environment.
2. When used for drug delivery, non-biodegradable particles may accumulate at the site where the drug is delivered. This may cause a chronic inflammatory response.
3. Since the targeting ability of nanoparticles is limited, it is difficult to control or stop the treatment.
4. Nanotechnology is very expensive, and the cost of its development can be even higher [21].

Classification

Nanoparticles are generally classified into Organic, Inorganic, and Carbon-based nanoparticles.

1. Organic Nanoparticles

Micelles, dendrimers, ferritin, and liposomes are commonly known as polymeric or organic nanoparticles. They are non-toxic and biodegradable in nature.

Some particles such as liposomes and micelles have a hollow core, and these are also called nanocapsules. They are highly sensitive to heat and electromagnetic radiation [1].

Biological nanoparticles are widely used in the biomedical field, especially in drug delivery systems. They help deliver drugs to specific parts of the body. This is known as targeted drug delivery.

Examples: Liposomes, dendrimers, micelles.

2. Inorganic Nanoparticles

These are made of non-carbon materials such as metals, metal oxides, and metal salts. Depending on their atomic structure, they occur in various shapes such as spheres, cylinders, cubes, stars, and ellipsoids.

A. Metal-Based Nanoparticles

The synthesis of nanometer-sized metal nanoparticles may be beneficial or harmful.

B. Gold Nanoparticles

Gold nanoparticles are nanometer-sized particles. Due to their special physical and chemical properties, they can absorb and scatter visible light and near-infrared light. They are stable, non-toxic, and easy to synthesize [1].

C. Silver Nanoparticles

Silver nanoparticles possess unique physicochemical properties such as electrical and thermal scattering, catalytic activity, and non-linear optical properties. These features have led to the development of many new products and scientific applications.

D. Metal Oxide Nanoparticles

Because of their small size, they have a larger surface area. Therefore, they are used in biosensors, bio-nanotechnology, and nanomedicine.

Examples: Copper oxide, titanium dioxide, zinc oxide.

E. Ceramic Nanoparticles

These are inorganic materials made of carbides, carbonates, oxides, and phosphates. They are produced at high temperatures and then cooled gradually.

They exist in polycrystalline, dense, amorphous, porous, or hollow forms. They are used in catalysis, photocatalysis, and photodegradation of dyes. They are also used in drug delivery systems for targeting tumors, glaucoma, and certain bacterial infections [1].

F. Polymeric Nanoparticles

These are generally organic-based nanoparticles. In literature, they are called polymer nanoparticles (PNPs).

They exist in the form of nanospheres or nanocapsules. Since they can be easily functionalized, they have many applications.

G. Lipid-Based Nanoparticles

These are usually spherical in shape. Their diameter ranges from 10–100 nanometres. They contain a solid lipid core and a matrix of lipophilic molecules.

Their outer surface is stabilized using surfactants and emulsifiers. They are used in the biomedical field as drug carriers, for drug delivery, and for RNA release in cancer treatment [1].

3. Carbon-Based Nanoparticles

These are made of carbon atoms and contain sp^2 bonds.

They include nanodiamonds, nanohorns, nano-onions, graphene, fullerenes, single-walled and multi-walled carbon nanotubes, carbon nanofibers, and nanographite [11].

Three techniques are used for their production:

1. Chemical Vapor Deposition
2. Laser Ablation
3. Arc Discharge

A. Graphene

Graphene is a single layer of carbon atoms arranged in a hexagonal structure. It has high strength, thermal conductivity, biocompatibility, and low toxicity. Its major use is in biosensing [8].

B. Carbon Nanotubes

They have high surface area and oil-attracting (oleophilic) properties, making them useful in the manufacture of oil-removal membranes [10].

Single-walled carbon nanotubes have a diameter of 0.4–2 nm, while multi-walled carbon nanotubes have a diameter of 2–100 nm. They are made of rolled graphite sheets [9].

C. Fullerenes

Fullerenes are carbon-based nanoparticles made of carbon atoms bonded through sp^2 hybridization.

Single-layer fullerenes have diameters up to 8.3 nm, while multilayer fullerenes have diameters of 4–36 nm. They are formed by combining 28 to 1500 carbon atoms [7].

Methods of Preparation

A. Amphiphilic Macromolecules Cross-Linking Methods

1. Cross-linking in W/O emulsion
2. Emulsion chemical dehydration
3. Phase separation in aqueous medium (Desolvation)
4. pH-induced aggregation

B. Polymerization Methods

1. Emulsion polymerization
2. Dispersion polymerization
3. Interfacial condensation polymerization
4. Interfacial complexation

C. Polymer Precipitation Methods

1. Solvent evaporation / extraction
2. Solvent displacement (Nanoprecipitation)
3. Salting out

A. Amphiphilic Macromolecules Cross-Linking Methods

- Nanoparticles can be prepared from amphiphilic macromolecules, proteins, and polysaccharides that have affinity for aqueous and lipid solvents.
- In this method, aggregation of amphiphilic molecules is carried out first, followed by stabilization through heat denaturation or chemical cross-linking.
- These processes may occur in biphasic O/W or W/O type dispersed systems, which divide the amphiphilic molecules before aggregation.
- This process may also take place in an aqueous amphiphilic solution, where removal of solvent, extraction, or diffusion causes the amphiphilic molecules to aggregate as tiny particles, which are later hardened through chemical cross-linking [2, 3]

1. Cross-Linking in W/O Emulsion

- The cross-linking method is used for nano-encapsulation of drugs.
- In this method, bovine serum albumin (BSA), human serum albumin (HSA), or an aqueous protein solution is emulsified in oil using high-pressure homogenization or high-frequency sonication.
- The formed W/O emulsion is then added to preheated oil (above 100°C). It is stirred for a specific period, causing the protein content in the aqueous phase to completely denature and aggregate, while the water evaporates.
- As a result, protein sub-nanoscopic particles are formed, where the size of the internal phase globules mainly determines the final particle size.
- The particles are then washed with an organic solvent to remove any adhering or adsorbed traces of oil, and later collected by centrifugation.
- The important factors controlling the size and shape of nanoparticles are mainly emulsification energy and temperature (used for denaturation and aggregation) [2, 3].

B. Polymerization Based Methods

The polymers used for nanosphere preparation are as follows:

- Poly (methylmethacrylate)
- Poly(butylcyano-acrylate)
  Poly(acrylamide)
  N-N' methylene-bis-acrylamide

2) Emulsion Chemical Dehydration

- Stabilization can also be achieved by emulsion chemical dehydration.
- A solution of hydroxy propyl cellulose in chloroform is used as the continuous phase.
- A chemical dehydrating agent, **2,2-dimethyl propane**, is dispersed into the internal aqueous phase to form an emulsion [2, 3].

Advantages (ADV):

- This method prevents coalescence of droplets.
- It can produce nanoparticles of smaller size (about 300 nm).

3) Phase Separation in Aqueous Medium (Desolvation)

- Protein or polysaccharide can be desolvated from the aqueous phase by the following methods:
- Change in pH
- Change in temperature
- Addition of suitable counter ions, for example alginate [2, 3].

1. Emulsion Polymerization

- Emulsion polymerization is a method in which the monomer used for polymerization is emulsified in a non-solvent phase.
- Depending on the nature of the continuous phase in the emulsion, this process may be conventional or inverse.

Conventional: The continuous phase is aqueous (O/W)

Inverse: The continuous phase is organic (W/O)

- Two different mechanisms have been proposed for the emulsion polymerization process:

a) Micellar nucleation & polymerization
b) Homogeneous nucleation & polymerization

a) Micellar Nucleation & Polymerization

- In this method, the monomer is emulsified in a non-solvent phase with the help of surfactant molecules.
- This leads to the formation of monomer-swollen micelles and stabilized monomer droplets.
- Monomer-swollen micelles are in the nanometric size range and have a much larger surface area compared to monomer droplets.
- The polymerization reaction proceeds through nucleation and growth stages in the presence of a chemical or physical initiator.
- The energy provided by the initiator creates free monomers in the continuous phase. These collide with other inactive monomers and start the polymer chain.
- Monomer molecules diffuse from the monomer droplets through the continuous phase into the micelles, allowing polymerization to continue within the micelles.
- Here, monomer droplets act as reservoirs of monomers [2, 3].

b) Homogeneous Nucleation & Polymerization

- In this method, the monomer is sufficiently soluble in the outer continuous phase.
- Nucleation and polymerization occur directly in this phase, producing primary chains known as oligomers.
- Here, both micelles and droplets act as monomer reservoirs throughout the polymer chain formation process.
- When oligomers reach a certain length, they precipitate and form primary particles. These are stabilized by surfactants.
- Drugs can be entrapped in these particles to form nanoparticles.
- The rate of polymerization depends on the pH of the medium.
- Anionic polymerization takes place after diffusion of monomer into the micelle through the aqueous phase and is initiated by a negatively charged compound.
- At neutral pH, the rate of polymerization is very fast [2, 3].

2) Dispersion Polymerization

- In emulsion polymerization, the monomer is emulsified in an immiscible phase using a surfactant.
- In dispersion polymerization, the monomer is dissolved in an aqueous medium, which acts as a precipitating agent for the polymer.
- The monomer is introduced into the dispersion medium.
- Polymerization is initiated by adding a catalyst. It proceeds through a nucleation stage followed by a growth stage.
- Nucleation occurs directly in the aqueous monomer solution. A surfactant or stabilizer is not necessary for forming stable nanospheres [2, 3].

3) Interfacial Polymerization

- The preformed polymer phase is finally transformed into an embryonic sheath.
- The polymer and drug are dissolved in a volatile solvent. This solution is poured into a non-solvent unsuitable for both polymer and core material.

- The polymer phase separates as a coacervate phase at the O/W interface.
- The mixture turns milky due to the formation of nanocapsules.
- This method is used for proteins, enzymes, antibodies, and cells.
- The size of nanocapsules ranges from 30–300 nm [2, 3].

4) Interfacial Complexation

- This method is based on the microencapsulation process introduced by Lin & Sun in 1969.
- In nanoparticle preparation, an aqueous polyelectrolyte solution is carefully dissolved in reverse micelles in an apolar bulk phase with the help of a suitable surfactant.
- Subsequently, a competing polyelectrolyte is added to the bulk phase, allowing a layer of insoluble polyelectrolyte complex to form at the interface [2, 3].

C. Polymer Precipitation Methods

Polymer precipitation is carried out through the following methods:

- Increasing the solubility of the organic solvent by adding alcohol (isopropanol) to the external medium.
- Extracting the solvent by adding water to an ultra-emulsion.
- Evaporating the solvent using a vacuum at room temperature.
- Using an organic solvent (such as acetone) that is completely soluble in a continuous aqueous phase —

Nanoprecipitation [2, 3]

1) Solvent Evaporation Method

Preparation of nanoparticles via the emulsion solvent evaporation method:

- In this method, a conventional **O/W (Oil-in-Water)** emulsion is formed using a solvent that is partially soluble in water and contains a stabilizer [2, 3].

Example: PLGA nanospheres.

- The polymer is dissolved in a solvent (chloroform) and dispersed into a gelatin solution through **sonication** to create an O/W emulsion.
- Subsequently, the solvent is removed through evaporation.
- A **homogenizer** is used during the process. It breaks down the initial coarse emulsion into nano-droplets, leading to the formation of nanospheres [2, 3].

2) Solvent Displacement Method (Nanoprecipitation)

- This method involves the deposition of a polymer at the interface following the displacement of a semi-polar, water-miscible solvent from a lipophilic solution.
- The organic solvent immediately diffuses into the external aqueous phase. Since the two phases are completely miscible, polymer precipitation occurs instantly.
- If the drug is highly hydrophilic, it will diffuse into the external aqueous phase.
- If the drug is hydrophobic, it will precipitate as nano-crystals within the aqueous medium [2, 3].

3) Salting Out Technique

- Salting out is a method used to separate a water-miscible solvent from an aqueous solution through the 'salting-out effect.
- First, the polymer and the drug are dissolved in a solvent. This is then emulsified into an aqueous gel containing a salting-out agent.
- Salting-out agents can be electrolytes (magnesium chloride, calcium chloride) or non-electrolytes (sucrose).
- Additionally, colloidal stabilizers such as polyvinylpyrrolidone (PVP) or hydroxyethyl cellulose are used.
- This O/W emulsion is diluted by adding sufficient water or an aqueous solution, causing the solvent to diffuse into the aqueous phase and form nanospheres.
- This differs from the nanoprecipitation method; in nanoprecipitation, the polymeric solution mixes completely with the external phase.
- However, in this technique, the external aqueous phase is saturated by adding PVA and magnesium chloride, which prevents the premature mixing of the two phases [2, 3].

Mechanisms of Drug Release

Drugs can be released from nanoparticles through various pathways:

a) Adsorption or deposition of the drug on the particle surface
b) Diffusion through the internal matrix of nanoparticles
c) Diffusion through the polymeric shell of nanocapsules
d) Degradation or erosion of the matrix
e) A combined process involving both diffusion and erosion

The kinetics of drug release are commonly described using a biexponential (biexponential) model:

C = Ae^(-Bt)

- Where:
  C = Amount of drug remaining in nanoparticles at time t
- **A** = Diffusion-related constant
- **B** = Erosion-related constant

Characterization Parameters of Nanoparticles

Nanoparticles are mainly evaluated based on their particle size, shape, and surface charge.

- Scanning Electron Microscopy (SEM)
- Transmission Electron Microscopy (TEM)
- Atomic Force Microscopy (AFM)
- Size distribution and surface charge influence nanoparticle stability and their biological distribution within the body (in vivo distribution).

1. Nuclear Magnetic Resonance (NMR)

- Used to determine particle size and structural characteristics.
- Provides information based on molecular motion and chemical shift patterns.
- Helps in understanding the physicochemical environment inside nanoparticles [22].

2. Differential Scanning Calorimetry (DSC)

- Used to analyse the physical state of the drug in the nanoparticle system.
- Samples containing about 2 mg of drug, polymer, and nanoparticles are prepared.
- Heated from 25°C to 300°C at a rate of 10°C/min.
- Conducted under an inert nitrogen atmosphere.
- An empty aluminium pan is used as the reference [23].

3. Particle Size Analysis

- Commonly determined using SEM.
- Usually observed in the range of 350–600 nm.
- Particle size and shape are important determinants of performance.
- Smaller particles generally provide faster drug release.
- However, they may tend to aggregate during storage, reducing stability.
- Larger particles may show higher degradation rates, especially in polymers like PLGA. [24]

4. Zeta Potential

The surface charge present on nanoparticles (NPs) is commonly described using zeta potential. It depends on the composition of the particles and the medium in which they are dispersed, and it also indicates the electrical potential of the particles.

NPs with a zeta potential above +30 mV remain stable in suspension because the surface charge prevents the particles from coming together and causing aggregation [25].

5. UV-Visible Absorption Spectroscopy

- This technique is used to determine the optical properties of a solution.
- Light is passed through the sample solution, and the amount of absorbed light is measured.
- Absorbance is measured at different wavelengths.
- The Beer-Lambert law is used to determine the concentration of the solution.
- The UV-visible spectrophotometer shows various absorption peaks, such as 410 nm [26].

6. Scanning Electron Microscopy (SEM)

- This technique is used to study the morphology, size, shape, chemical composition, and orientation of NPs.
- In SEM, the NP solution is first dried into powder and placed on a sample holder.
- Surface information is obtained using secondary electrons and backscattered electrons.
- Morphology is determined by analysing surface features such as depressions and elevations, because electron emission varies according to the surface. [27]

7. Dynamic Light Scattering (DLS)

- This technique is used to determine particle size and size distribution.
- Analysis is carried out at 25°C and a fixed angle of 173° using photon correlation spectroscopy.
- It provides the average particle size (volume diameter) and polydispersity index (PDI).
- The sample is usually analyzed three times. [28]

Applications of Nanoparticles

1. General Applications of Organic Nanoparticles

Micelles

Micelles are extensively utilized in the management of malignant tumors (cancer). They minimize enzymatic degradation and drug inactivation, thereby enhancing drug stability and reducing the critical micellar concentration (CMC).

Liposomes:

Liposomes are widely employed in dairy formulations to fortify products with vitamins, improving their nutritional value and facilitating digestion.

Archaeosomes:

Archaeosomes are vesicular systems derived from polar ether lipids of archaebacteria. In comparison to conventional liposomes (composed of ester phospholipids), they exhibit superior thermostability and enhanced resistance to oxidation, chemical degradation, and enzymatic hydrolysis. Additionally, they maintain stability under acidic conditions and in the presence of bile salts within the gastrointestinal tract.

Dendrimers:

Dendrimers have broad applications in areas such as gene delivery, conjugate-based systems, boron neutron capture therapy, molecular recognition, and drug

delivery. They also function as contrast agents (e.g., in MRI) and play a crucial role as drug carriers in cancer therapy. Furthermore, they improve drug stability by preventing enzymatic degradation and inactivation.

2. General Applications of Inorganic Nanoparticles:
Anti-infective Agents:

Metallic nanoparticles have emerged as promising therapeutic candidates for HIV prevention. metallic nanoparticles have demonstrated potent antiviral activity against a range of viruses, including herpes simplex virus, influenza virus, and respiratory syncytial virus.

Anti-angiogenic Agents:

Angiogenesis, the formation of new blood vessels, is a critical process in both physiological development and pathological conditions. It plays a pivotal role in diseases such as cancer and rheumatoid arthritis. Under normal physiological conditions, angiogenesis is tightly controlled by a balance between pro-angiogenic growth factors and anti-angiogenic factors. In pathological states, this balance is disrupted, leading to excessive angiogenesis. Conventional anti-angiogenic therapies Metallic nanoparticles offer a potential alternative due to their ability to function as effective anti-angiogenic agents with possibly reduced toxicity.

Tumor Therapy:

Experimental studies have demonstrated that unmodified (naked) gold nanoparticles (AuNPs) inhibit the activity of heparin-binding growth factors such as VEGF165 and bFGF in vitro, as well as suppress VEGF-induced angiogenesis in vivo. Further investigations suggest that these proteins adsorb onto the surface of AuNPs and undergo structural denaturation [31].

Multiple Myeloma:

Recent advances have led to the development of nanoparticle-based therapeutic strategies that demonstrate efficacy in the treatment of multiple myeloma in murine models. Multiple myeloma is a malignancy characterized by the uncontrolled proliferation of plasma cells [31].

3. Common Applications of Nanoparticles
Nanoparticles for Gene Delivery

Polynucleotide-based vaccines operate by delivering genes encoding target antigens into host cells, where they are expressed to produce antigenic proteins. These proteins are synthesized in proximity to professional antigen-presenting cells, thereby triggering an immune response. Such vaccines are capable of eliciting both humoral and cell-mediated immunity, as intracellular antigen production activates multiple arms of the immune system [30].

Nanoparticles for Brain Drug Delivery

The blood–brain barrier (BBB) represents a critical limitation in the development of therapeutics for the central nervous system (CNS). It is characterized by tightly joined endothelial cells, enzymatic barriers, and active efflux transport mechanisms, which collectively restrict permeability. The BBB effectively blocks the entry of hydrophilic molecules from systemic circulation into the CNS and can further limit the accumulation of lipophilic compounds via enzymatic metabolism and efflux pumps [30].

Nanoparticles in Food and Cosmetic Applications

Amorphous silica nanoparticles are extensively utilized as anti-caking agents in powdered food products (e.g., instant soups) to preserve flowability and are also employed as thickening agents in semi-solid formulations. The conventional form of amorphous silica is designated as food additive E551.

In addition, nanoparticles are widely applied in cosmetic formulations, particularly in sunscreens. Titanium dioxide and zinc oxide nanoparticles are commonly incorporated due to their ability to efficiently reflect and scatter ultraviolet (UV) radiation while remaining optically transparent.

Their nanoscale size enhances consumer acceptability and provides improved protection against UV-induced skin damage [29].

CONCLUSION

Nanoparticulate systems demonstrate significant potential in modern drug delivery by transforming poorly soluble, inadequately absorbed, and unstable bioactive compounds into effective therapeutic agents. These systems are capable of encapsulating a wide range of substances, including drugs, enzymes, and genetic materials. Their extended circulation time is largely attributed to the presence of a hydrophilic outer layer, which helps evade detection and clearance by the reticuloendothelial system.

To fully harness the advantages of nanoparticle-based delivery, a deeper understanding of their interactions within biological environments, along with advancements in particle design and engineering, is essential. Continued research and innovation are necessary to translate nanoparticle technology from a conceptual framework into a practical and reliable next-generation drug delivery platform.

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Cite This Article: Roopesh, P. T., Sellamuthu, V., Vismaya Babu, K. K., Azeez, A. A., Sherin, A., Ferin, A. K., & Ahsana, T. K. (2026). Nanoparticles - A Review. *EAS J Pharm Pharmacol, 8*(6), 98-105. https://doi.org/10.36349/easjpp.2026.v08i06.001