International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

"Pharmaceutical Nanoparticles: Detailed Review of Types, Preparation Methods, and Applications"

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Date of Submission: 20-04-2025 Date of Acceptance: 30-04-2025

ABSTRACT:
Nanoparticles are emerging as pivotal components in the development of novel drug delivery systems (NDDS), significantly enhancing the efficacy, bioavailability, and targeted delivery of therapeutics across various medical fields, including cancer therapy, cardiovascular treatment, and vaccine development. This review explores the synthesis methods, structural characteristics, and functionalization of nanoparticles that enable their role as advanced pharmaceutical carriers. The unique properties of nanoparticles, such as their nanoscale size and high surface area-to-volume ratio, facilitate improved drug solubility and permeability, while also allowing for stimuli-responsive release mechanisms. By integrating personalized medicine approaches, these systems aim to address the limitations of conventional drug delivery methods, including adverse effects and poor bioavailability. Additionally, safety and toxicity concerns associated with the use of nanoparticles in medical applications are discussed, emphasizing the need for comprehensive evaluation in the context of nanomedicine. This work underscores the transformative potential of nanotechnology in revolutionizing pharmaceutical practices and improving therapeutic outcomes.Recent developments in nanomedicine have broadened the utility of nanoparticles in cancer therapy, cardiovascular treatments, respiratory disorders, and vaccine innovation, while their integration with imaging, diagnostics, and biosensing technologies has significantly enhanced disease detection and monitoring capabilities. Nonetheless, the field faces challenges, including toxicity concerns, large-scale production issues, and regulatory hurdles that hinder the progression of nanoparticle-based drug development. Ongoing research efforts are focused on addressing these challenges, refining nanoparticle technologies to ensure safer and more effective pharmaceutical applications. As advancements continue, nanoparticles are poised to redefine medicine, facilitating more precise, efficient, and personalized treatment options.

Key Words: Nanoparticles, Drug Delivery Systems, Bioavailability, Therapeutic Applications, Synthesis Methods, Advanced Pharmaceuticals, Nanotechnology.

I. INTRODUCTION

Novel drug delivery System:

A suitable medicine delivery system aims to give an effective remedial cure at the targeted point at the right time and at suitable intervals until the asked cure is achieved. Before the new medicine delivery systems (Novel Drug Delivery System), conventional systems were utilized, followed by immediate- release formulations, sustained- release systems (frequently given through oral administration), and long- acting injectables. Given the enervating goods of several conditions similar as cancer, diabetes and hypertension, and the problems associated with traditional delivery systems like metabolism, medicine insolubility, commerce with food and digestive enzymes, adverse goods of the medicine on other cells and organs, discoursing on Novel Durg Delivery Systems (NDDSs) which would propel themselves to the targeted point and release the loaded medicine at the right time is pivotal. [1]These systems frequently use carriers and their internal or external terrain. Carriers that have been utilized in these NDDSs include artificial medicine carriers (nanoparticles, nanotubes, dendrimers, liposomes, ethosomes, aquasomes, polymersomes, niosomes, lathers, hydrogels, cubosomes and quantum dots), natural medicine carriers (nanoerythrosomes, exosomes) and macrophages.[2] The nano size of nanoparticles and their high face area to volume rate make for high permeability and high capacity of medicines to be loaded. These nanoparticles can also cross physiological walls due to their nano sizes. Another advantage of

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nanoparticles is their eventuality to deliver multiple functions, including medicine delivery, imaging and monitoring. Frequently, they're functionalized to respond to changes in stimulants, which could be endogenous or exogenous. Endogenous stimulants include redox responses, enzymatic responses, and changes in hydrogen ion attention. Exogenous stimulants include changes in temperature, light, ultrasound, glamorous field, and electric field. This review expatiates on new medicine delivery systems, nanocarriers and the recent operations of smart bias. It further describes personalized drugs and the problems associated with their operation. [3]

Nanoparticles are revolutionizing pharmacy by enhancing drug delivery, targeting, and efficacy, offering advantages like improved solubility, bioavailability, and controlled release, while also enabling new diagnostic and therapeutic approaches.

Colloidal conformations made of synthetic or semi synthetic polymers are known as polymeric nanoparticles. The medicine is either absorbed, paralyzed, reprised, or clicked using a nanoparticle matrix. Depending on the medication system, nanoparticles, nanospheres, or nano capsules can be produced. In discrepancy to nano capsules, which retain the drug in a depression and are sealed off by a specific polymer membrane, nanospheres are matrix systems in which the medicine is physically and unevenly distributed. Nano Particles can have a variety of forms, confines, and structures. They might be irregular.10 or globular, spherical, conical, tubular, concave core, helical, etc. Nano Particles can range in size from 1 to 100 nm. Atom clusters is generally recommended if the size of Nano Particles is lower than 1 nm. Nano Particles can be amorphous or crystalline, having single or numerous crystal-clear solids. Nano Particles can be Agglomerated or loose. [4]

Nano Particles:

Drug delivery systems now dominate nanomedicine, with earnings counting for over 75 of total deals. he size of nanoparticles falls within the range of 10 to 1000 nm in diameter. Entrapped, encapsulated, dissolved, or linked to the nanoparticle matrix is the active pharmaceutical component (API). Nanoparticles can be made by altering the system of fabrication. Nanoparticles have been proven to be useful as medicine delivery vehicles. Numerous uses for nanoparticulate medicine delivery systems live, including gene remedy, cancer remedy, AIDS remedy, and radiation. It can facilitate the transport of proteins, antibiotics, and vaccines while also serving as vesicles to cross the blood-brain barrier. The major points of nanoparticle design as a delivery system are to control particle size, surface properties, and medicine delivery and API release so as to insure point- targeted medicine exertion at an applicable remedial rate and dosing regimen.[5]

Structure of nanoparticle

The design of a nanoparticle (NP)-based drug delivery platform is influenced by key factors such as the size, shape, stiffness (composition), and surface properties of the NPs.

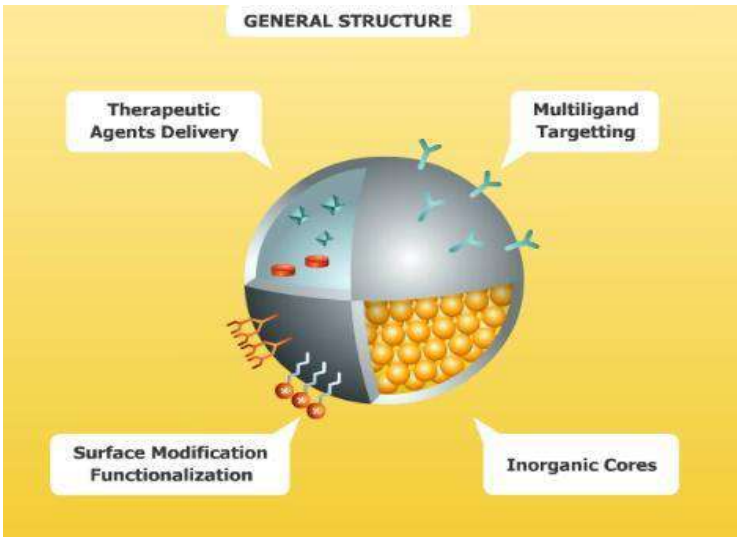

Figure 1. Structure of Nanoparticles [6]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

Aids of Nano Medicine

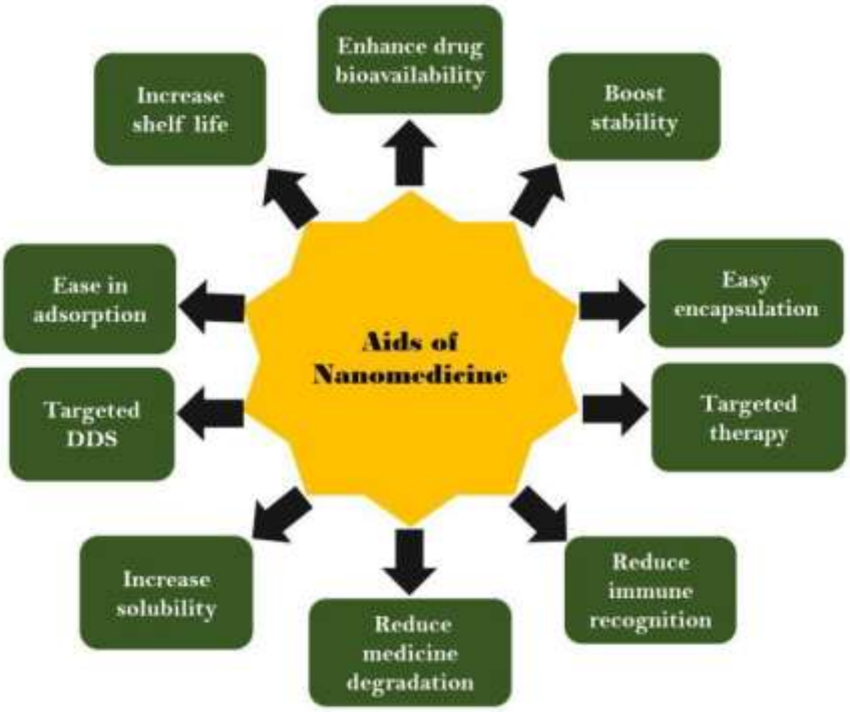

Figure 2. Aids of Nano Medicine [7]

Benefits of utilizing nanoparticles as a drug delivery

The benefits of employing nanoparticles as medicine vehicles are because of two crucial characteristics their small size and the use of biodegradable materials in the majority of cases. The effectiveness of utmost drug delivery styles is set up to be largely reliant on particle size. Medicinal nanoparticles have increased solubility and superior bioavailability which is a result of their small particle size and large surface area. Also, their capability to cross the blood brain hedge, entering pulmonary system, endothelium of tumors and immersion through tight junctions of skin endothelial cells, give them added value. The nano- range size of these particles, in general, allows for effective immersion by variety of cell types as well as selective medicine accumulation in the target locales. Nanoparticles also have the benefit of being more acceptable for intravenous administration than conventional microparticles. The lowest body capillaries have a periphery of 5 – 6 m. To make sure that particles don't cause embolism, the size of particles dispersed in the rotation should be mainly lower than 5 m. Using both natural and synthetic biodegradable polymers for nanoparticle medication give them the advantages of targeted medicine delivery, improve bioavailability and achieve sustained release behavior of specifics from a single cure at the target point over a prolonged period of time; by adaption of the system, endogenous enzymes can be averted from destroying the medicine. Likewise, typical oral or injectable drugs now accessible for use are now inescapably handed in the most suitable expression. [5]

Types of nano particles:

Depending on their morphology, size, and chemical properties, nanoparticles (NPs) are divided into various types. Based on physical and chemical characteristics, some of the well-known classes of NPs are given as below.[8]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

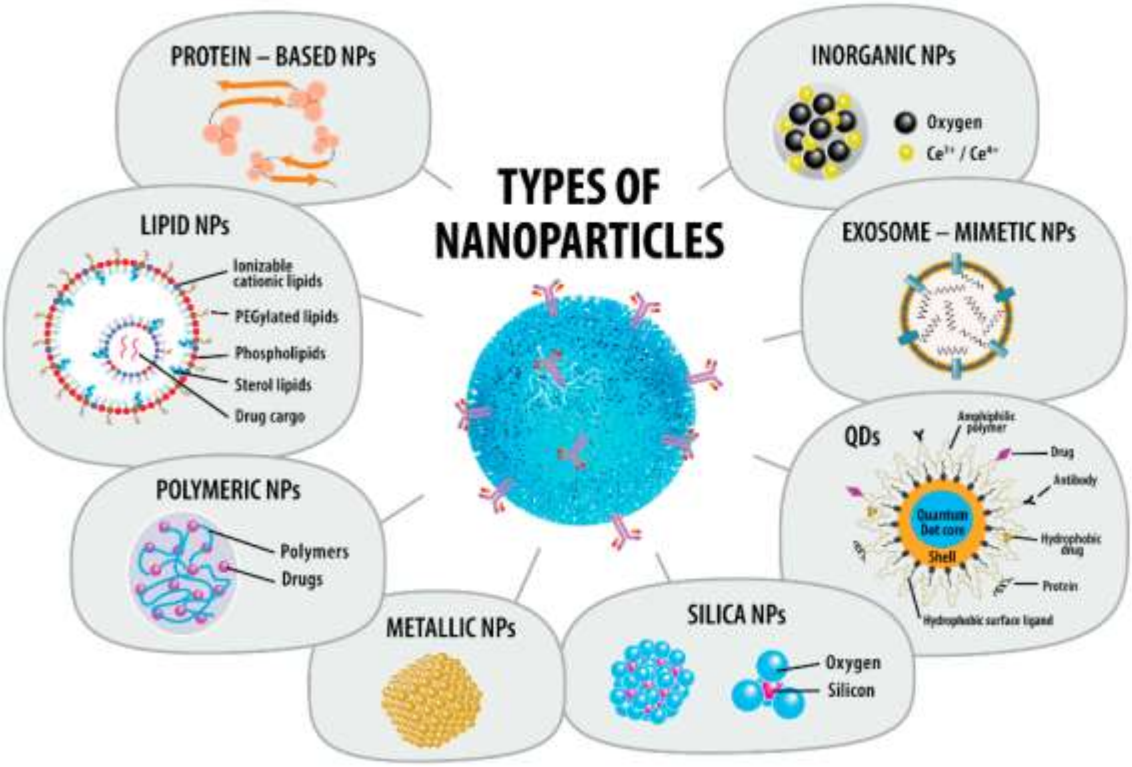

Figure 3. Types of Nanoparticles [8]

1. Protein Based Nanoparticles:

Protein-based nanoparticles (PNPs) are nanostructures composed of proteins, offering unique properties for various applications, including drug delivery, diagnostics, and therapeutics, due to their biocompatibility and ability to be manufactured for specific functionalities.[9] Various proteins are utilized in PNP synthesis. The types of PNPs have similar physical properties such as high biocompatibility, non-immunogenicity, high drug efficiency, high biodegradability, and high cell uptake. Due to the abundance of proteins necessary for proper bodily function, the body has developed processes to modernize proteins into tissues and cells. [10, 11] PNPs take advantage of these natural processes to enhance their cellular uptake. This availability and the natural sourcing subsequent purification of the proteins also reduce the immunogenic responses and produce low toxin levels situation in the body. As the PNPs are degraded, the tissues assimilate the amino acids into energy or protein product. Due to PNPs' breadth of favorable pharmacokinetic properties similar as high biocompatibility, high biodegradability, high modifiability, low toxicity, high cell uptake, and a fast excretion rate, PNPs are demanded for anti-cancer remedy.[12] In addition to active tumor targeting, PNPs can also be manufactured to respond to changing external environments such as pH, temperature, or enzyme concentration. The tumor environment is slightly acidic, so PNPs can be manufactured to only release their drug cargo under specificphysiological conditions. Another application is photothermal or photodynamic remedy.[13]

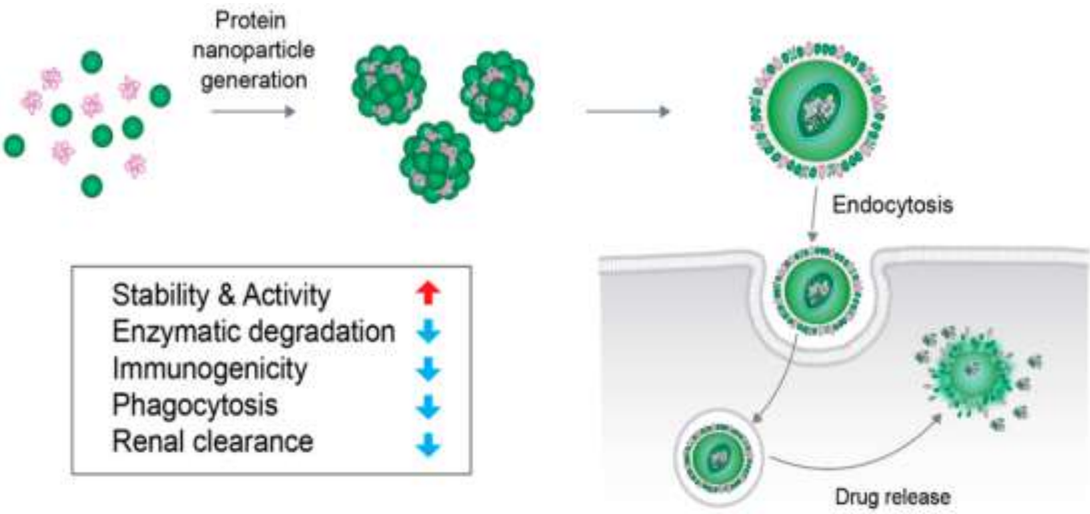

Figure 4.Protein Nanoparticles [14]

PNPs widely accumulate into the tumor microenvironment where they are subsequently irradiated using a 1064 nm wavelength laser. The light energy is transferred into heat energy, increasing the temperature of the tumorenvironment to reduce tumor growth. Ferritin is an ideal protein for this application because of its exceptional thermal stability.In-vivo imaging is another application of PNPs. PNPs can carry fluorescent dyes that selectively accumulate in the tumor microenvironment.[15]

2. Lipid Nanoparticles:

Lipid-based nanoparticles (LNPs) are a largely adaptable class of nanocarriers that have gained widespread use in medical research and pharmacology. Lipid-based nanoparticles (LBNPs) such asliposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have got great attention in drug discovery and cancer treatment. These nanoparticles can transport hydrophobic and hydrophilic entities, display veritably low or no toxicity, and increase the time ofaction by means of a prolonged half-life and a controlled release of the medication. In addition, they can be prepared in formulations sensitive to the pH in order to increase drug release in an acid terrain, and can also be associated with antibodies that recognize tumor cells or their receptors. LNPs generally consist of four main lipid components: phospholipids and cholesterol, which are necessary for particle conformation and stability; cationic or ionizable lipids, which enable binding with negatively charged nucleic acids, thereby adding drug loading; and PEGylated lipids, which contribute to enhanced particle stability and circulation time within thesystem. LNPs can be subdivided into five subgroups: liposomes, lipid nanoemulsions, solid lipid nanoparticles,nanostructured lipid carriers, and lipid–polymer hybrid nanoparticles.

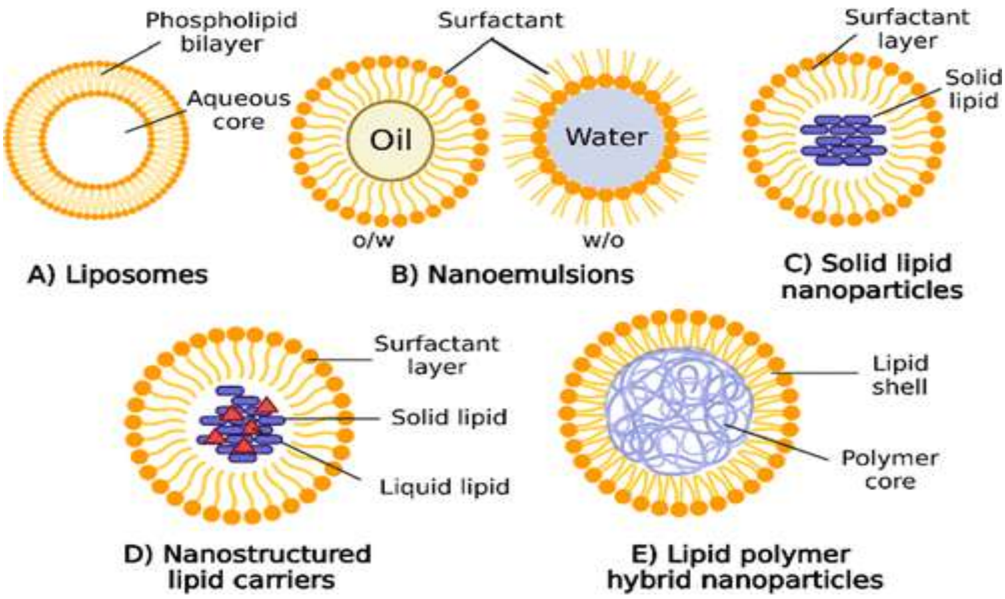

Figure 5. Subtypes of Lipid Nanoparticles[16]

LNs have been considerably studied for drug delivery of active anticancer medication, andits applications are mostly in Bowel cancer, Stomach cancer, Breast Tumor, GlandularCarcinoma, etc.[16,17,18]

3. Polymeric Nano Particles:

Polymeric nanoparticles (PNPs) are solid, colloidal particles, typically ranging from 1 to 1000 nanometers in size, composed of biodegradable and biocompatible polymers or copolymers, used as drug carriers or for other biomedical applications. Basically, polymeric nanoparticles are simply made up of polymer(s), surface active agent(s), and aqueous phase. Polymers are the main excipient of polymeric nanoparticles. Generally, they are made up of large repeating units known as monomers. Polymers are basically distributed into two classes according toorigin source; natural polymers and synthetic polymers.

Types of polymeric nanoparticles according to structural organization.

The structures ofpolymeric nanoparticles: (A) micelles, (B) dendrimers, (C) polymersomes, (D) hydrogel, (E) metal–organic framework (MOF).[19]

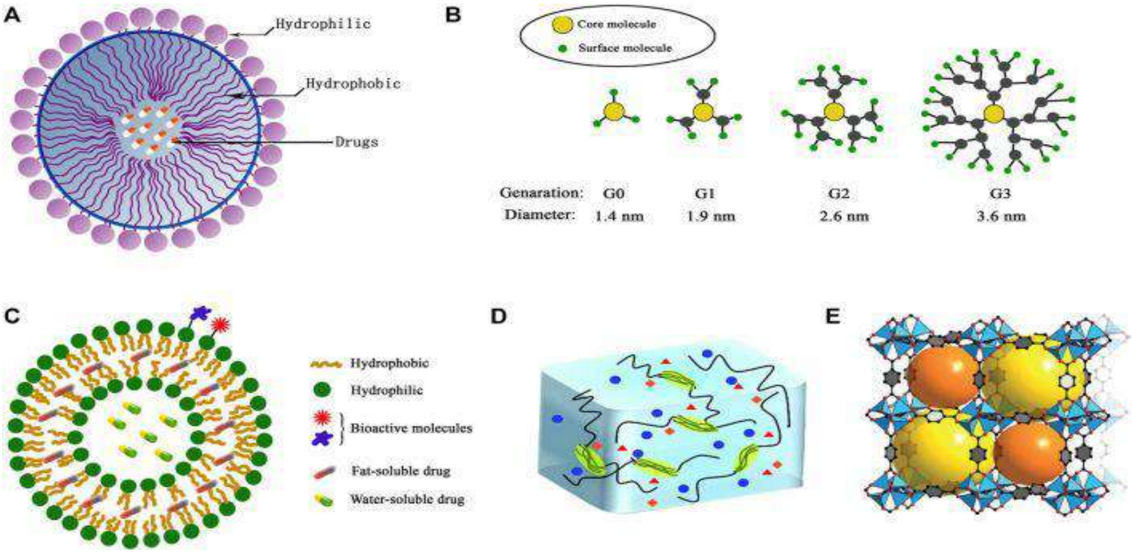

Figure 6. Structures of polymeric nanoparticles [19]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

4. Metallic Nano Particles:

Metallic nanoparticles (MNPs) are metal particulate of nanodimensions (as gold NPs, silver NPs, and iron oxide NPs) that have been attracting the scientist over a century in variety of fields and now widely exploited for medicine delivery and diagnostic applications. These nanostructured particles can be synthesized, and their surface is functionalized with different functional groups allow them to conjugate with moieties like therapeutics, diagnostics, and ligands. [22] Metallic nanoparticles have fascinated scientist for over a century and are now heavily employed in biomedical sciences and engineering. They are a focus of interest because of their huge eventuality in nanotechnology. At present these materials can be synthesized and modified with number of chemical functional groups which allow them to be conjugated with antibodies, ligands, and drugs of choice and therefore opening a wide range of applications in biotechnology, magnetic separation, and preconcentration of target analytes, targeted drug delivery, and vehicles for gene and drug delivery and more importantly diagnostic imaging. MNPs have variety of reaction response mechanisms and can penetrate the target organs and cross biological membrane barriers without any difficulty. MNPs can alter cellular function by getting attached with cellular proteins and nucleic acids and expressing enhanced biological exertion due to their smaller particle size and simultaneously high surface area. Gold and silver are extensively used more than other MNPsand its nanoparticles are used in different drug delivery and diagnostic cases.[24]

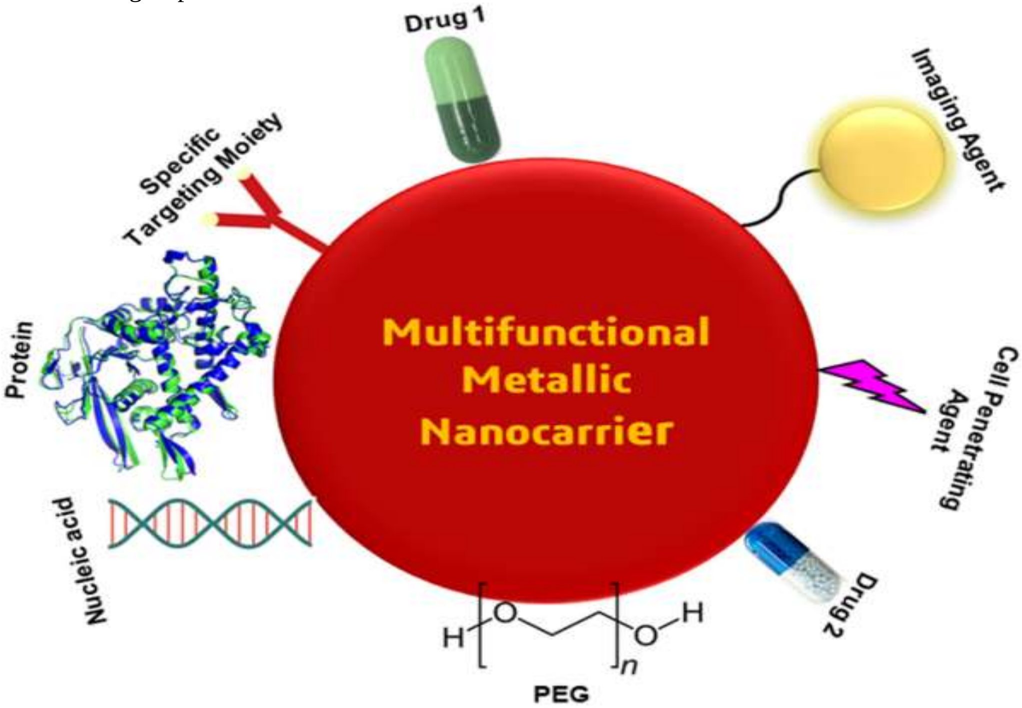

Figure 7. Classification of polymeric nanoparticles according to structural organization[21]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

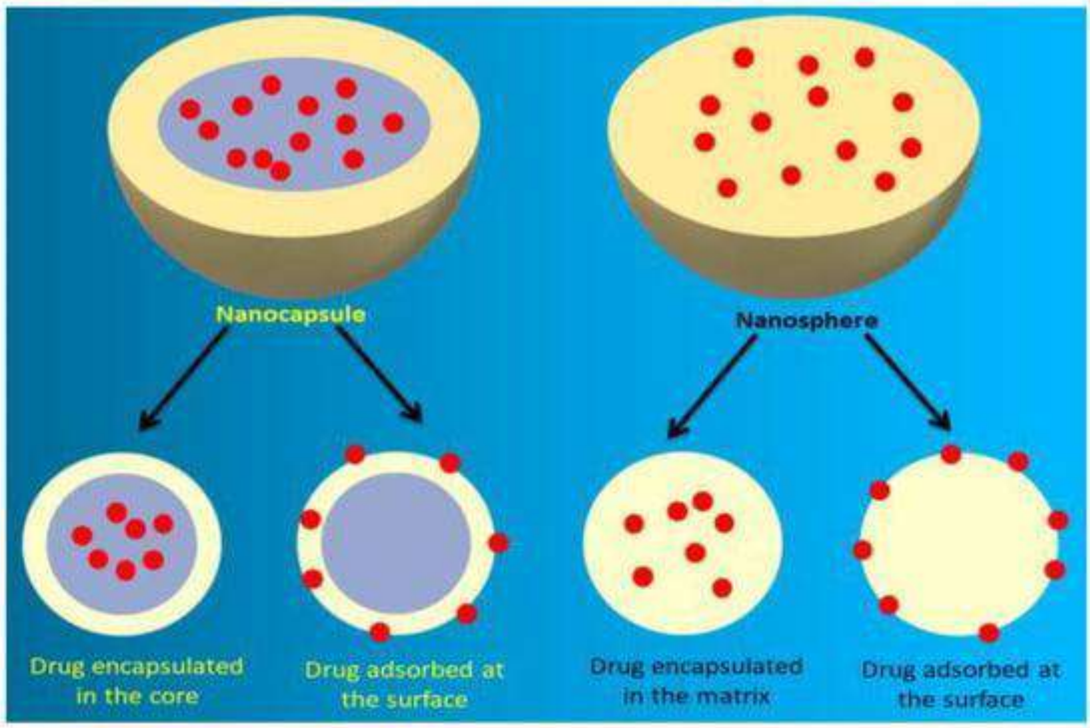

Figure 8. Multifunctional MNP-based delivery systems for targeting, delivery, and imaging [23]

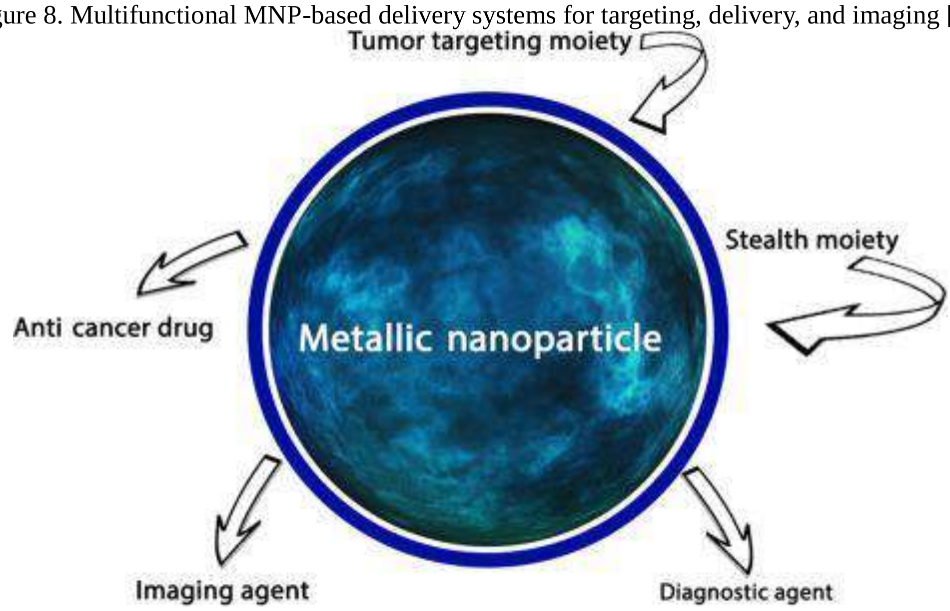

Figure 9. Applications of Metallic Nanoparticles [22]

MNPs may be produced using a straightforward laboratory process in a variety of size ranges. They are also biocompatible, non-toxic, and inert. Because of their straightforward structure and ease of synthesis, MNPs offer flexible surface functionalization. Because of these characteristics, MNPs offer a promising use for the binding of targeting ligands on the surface at low core sizes, making them ideal for use in drug delivery systems.[25]

5. Silica Nanoparticles:

Silica-based nanoparticles, SNP, are very attractive due to their ease of synthesis, colloidal stability, variable particle size, ease of surface functionalization, biocompatibility, and potentially scalable synthesis. Silica nanoparticles (SNPs),

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

particularly mesoporous silica nanoparticles (MSNs), are promising drug delivery vehicles due to their biocompatibility, variable properties, andcapability to protect and deliver medication to specific target sites. MSNs have unique characteristics that make them ideal nanocarriers to host, protect and transport drugs. It is easy to incorporate targeting agents in the external surface of MSNs to send them to the unhealthy tissues aimed at increasing specificity and therefore reducing undesired side effects. Another vital challenge is to avoid the release of drug before reaching the target. To avoid this, the pore entrances of MSNs can be capped by using stimuli-responsive doorkeepers. Therefore, the exposure to internal or external stimuli would cause pore opening and allow drug departure. Most of the research effort on MSNs for drug delivery has been committed to cancer remedy. Medical uses of SNP for delivery of anti-cancer, diagnostic and theranostic purposes are now becoming more useful and demanding.[27, 28]

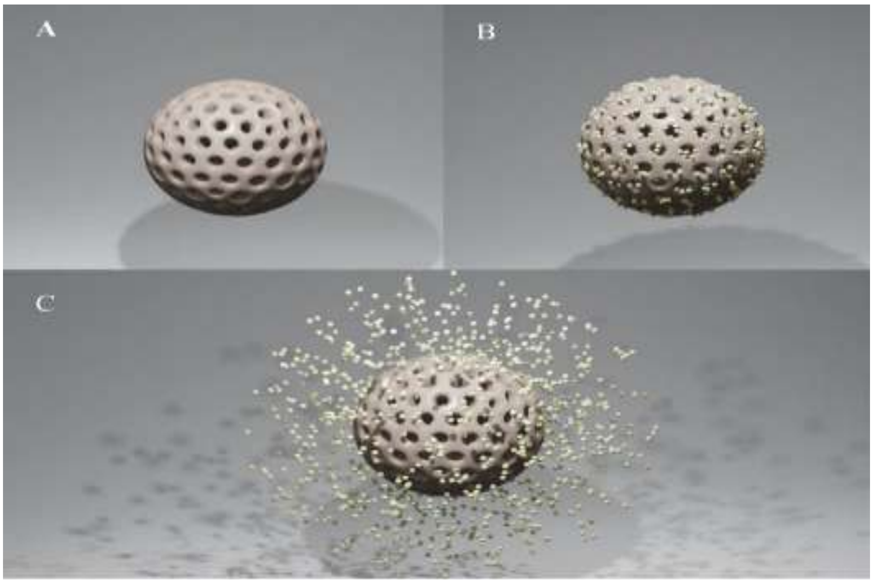

Figure 10. (A) Mesoporous silica nanoparticle (MSN). (B) MSN as a vehicle for drugs. (C) The agent's release of drug-loaded MSNs. [26]

6. Quantum Dot Cores:

Quantum dots (QDs) are luminescent nanocrystals with rich surface chemistry and unique optic properties that make them useful as carriers for traceable targeted delivery and therapy operations.

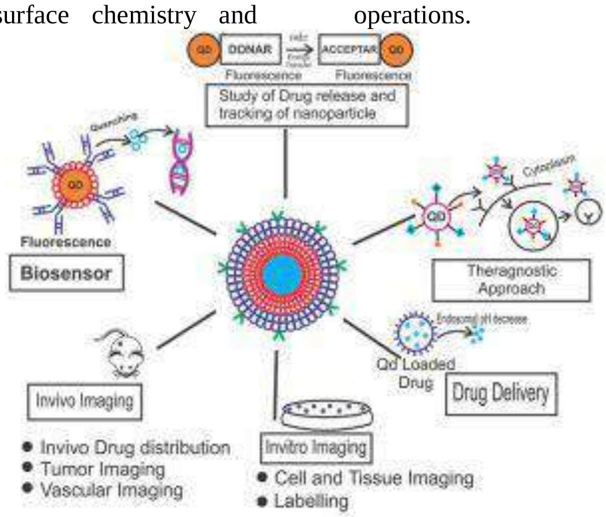

Figure 11. Various Appliations of Quantum Dots. [29]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

QDs can be used to target specific cells or tissues by conjugating them with targeting site/ligands. QDots feature small size and versatile surface chemistry, allowing their incorporation within virtually any NDD vehicle with minimal effect on overall characteristics, and offer superb optical properties for real-time monitoring of NDD vehicle transport and drug release at both cellular and systemic levels.

Though the direct use of Q Dots for drug delivery remains questionable due to their potential long-term toxicity, the Q Dot core can be easily replaced with other organic drug carriers or more biocompatible inorganic contrast agents (such as gold and magnetic nanoparticles) by their analogous size and surface properties, helping easy translation of well characterized NDD vehicles to the clinic, maintaining NDD imaging capabilities, and potentially providing additional therapeutic functionalities such as photothermal therapy and magneto-transfection. In this review we outline unique features that make Q Dots an ideal platform for nanocarrier design and discuss how this model has been applied to study NDD vehicle behavior for diverse drug delivery applications. Bio conjugated quantum dots (QDs) show promise in applications spanning both diagnostics and therapeutics. QDs have been used for further than a decade as optical discrepancyagent for bioimaging. For targeted delivery uses, QDs must be conjugated with biorecognition ligands similar to antibodies, DNA, biotin, streptavidin, or peptides.[30]

7. Exosome Mimetic Nano Particles:

Exosomes are tiny-sized extracellular vesicles (EVs) ranged from 40 to 100 nm that are secreted by many types of cells. Exosomes have been an ideal molecule to deliver various drugs in treating various cancers. However, their further operationsarelessened by the low production yield and lack of targeting properties. Therefore, artificially produced nanovesicles, which act same as the structure of exosomes, have received good attention in drug delivery. Exosome-mimics, prepared by extruding whole cells or cell membranes through certain-sized filters, have analogous structures and characteristics to exosomes.

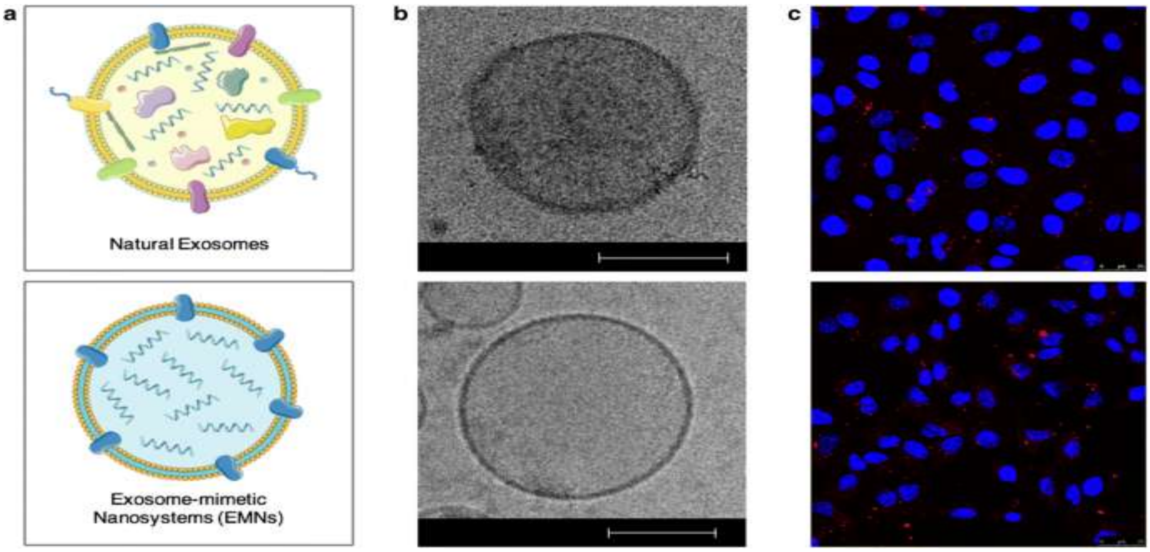

Figure 12. Comparison of natural exosomes and EMNs morphology.[31]

Synthetic exosome-mimics, having the natural properties of cells, can be applied to developing new remedial strategies. Various studies have shown that exosome-mimics can result in a 100-fold increase in production yield in comparison with natural exosomes. Exosome-mimetic nanovesicles have similar capabilities as drug delivery systems compared with exosomes. Cancer immunotherapy, which aims to damage cancer cells by the host immune system, has grabbed significant attention during the once decade.[32]

Until now, exosome-mimics prepared from variety of cell membranes or platelet membranes could be used in developing cancer vaccination and drug delivery systems. Exosome-mimicking PLGA nanoparticles exhibited greater stability and efficacy compared to bare nanoparticles. Those derived from T cell membranes retained T cell receptors on their

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

surface, enabling them to bind to the HIV surface glycoprotein gp120 and prevent gp120-induced CD4+ T cell damage, positioning them as a promising therapeutic candidate for HIV infection. Likewise, exosome-mimics sourced from gastric epithelial cell membranes, macrophage membranes, platelet membranes, and neutrophil membranes have demonstrated enhanced effectiveness in treating gastric diseases.[32]

8. Inorganic Nano Particles:

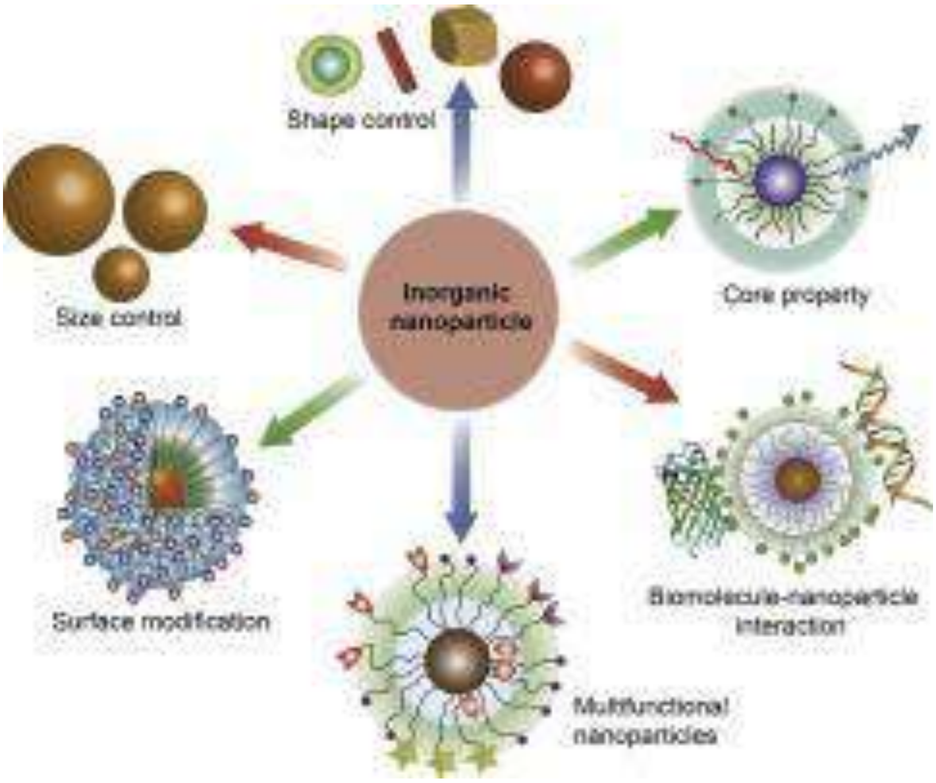

Figure 13. Inorganic Nanoparticles [33]

Inorganic nanoparticles are highly stable, non-toxic, hydrophilic, and biocompatible. It poses unique physicochemical properties such as high surface area per unit volume and unique optical and magnetic properties and can be utilized with various specific ligands to enhance their affinity toward target cells or molecules. Apart from their ability of controlled drug release profile, inorganic nanoparticles safeguard the drug from deterioration and can reduce the frequency of administration and dose of the drug, thereby a significant reduction in the toxicity of drugs.Compared to organic nanoparticles, inorganic nanoparticles exhibit stability, possess diverse physicochemical, mechanical, magnetic, and optical properties, and can be modified with specific ligands to enhance their affinity for target-site molecules, making them highly suitable for bio-imaging and drug delivery applications. A key advantage of the inorganic nanoparticle-drug combination is its ability to deliver drugs directly to the affected cells, minimizing side effects such as cytotoxicity and enhancing the therapeutic efficacy.[34,35]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

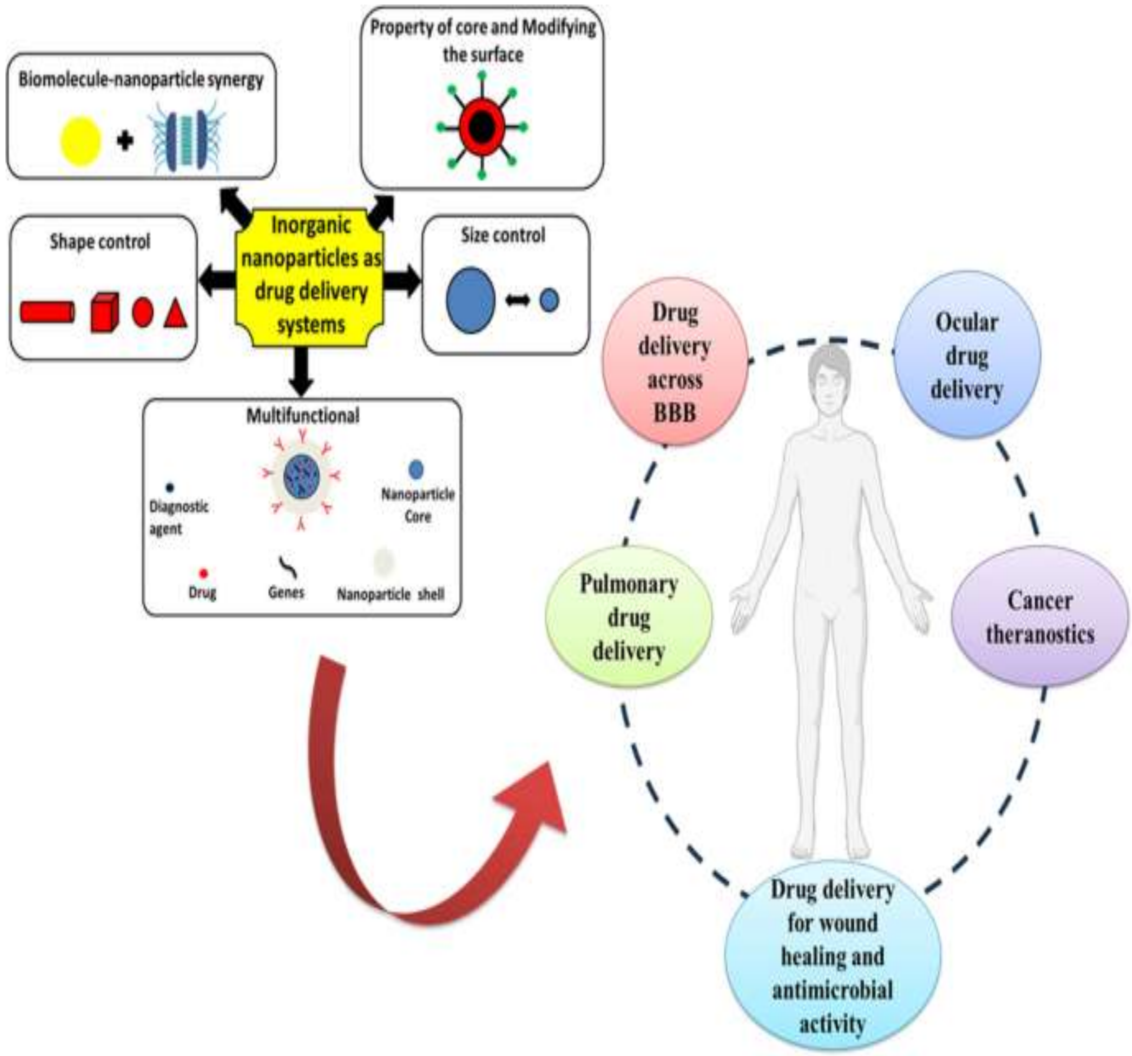

Figure 14. Inorganic Nanoparticles as DDS [34]

Preparation/Synthesis Methods of Nano Particles

Nanoparicles can be produced using two primary methods:

- **Top-down approach** – This technique involves reducing bulk materials into nanoscale structures by breaking them down into smaller components.
- **Bottom-up approach** – This method focuses on assembling individual atoms and molecules to create larger nanostructures.[36]

Top-down approach: This method involves breaking down larger materials into nanoscale structures. Common techniques include mechanical milling, nanolithography, laser ablation, sputtering, thermal decomposition, and pulsed electrochemical etching. The focus of this approach is to refine bulk materials into smaller, functional nanostructures.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

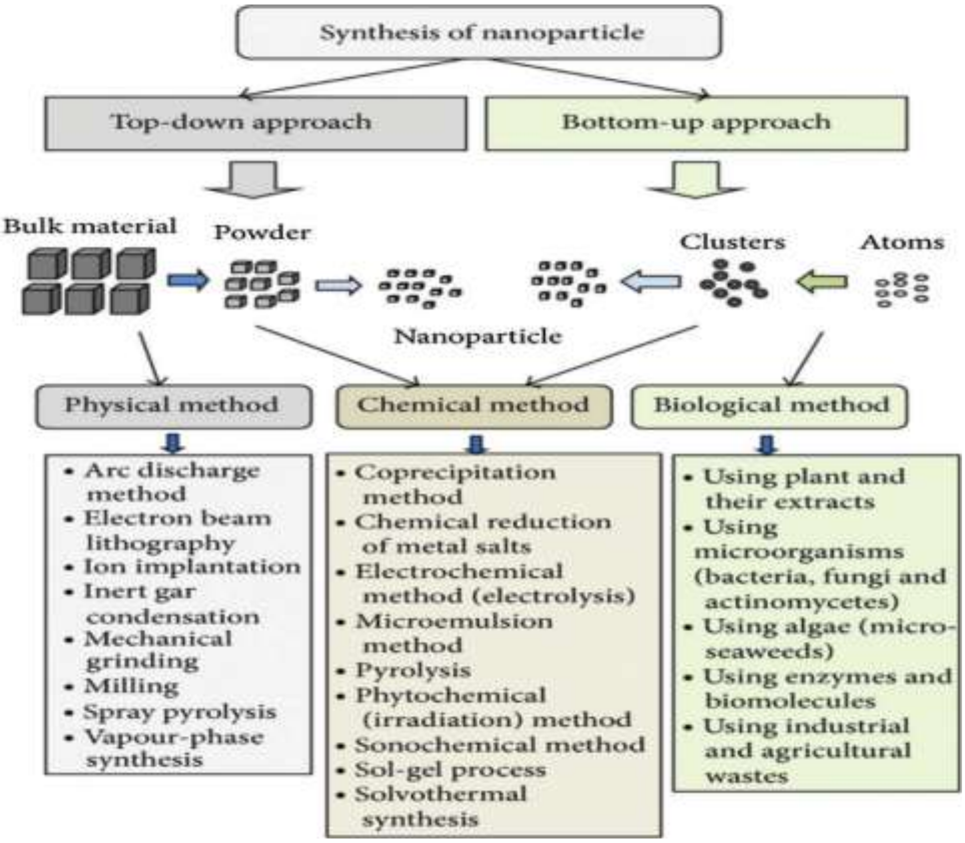

Figure 15. Synthesis of Nanoparticles [37]

Bottom-up approach: In contrast, the bottom-up method constructs nanostructures by assembling individual atoms and molecules. Techniques such as sol-gel processing, electrospinning, chemical vapor deposition (CVD), laser pyrolysis, template-assisted synthesis, plasma or flame spray synthesis, and atomic or molecular condensation are commonly employed. Additionally, biosynthesis using biological agents such as bacteria, plant extracts, fungi, yeasts, and algae is also utilized in this approach. [38]

Physical Methods:

1. Arc Discharge Method:

The arc discharge method involves creating an electric arc between two electrodes, typically in an inert gas environment, to vaporize and condense the material, resulting in the formation of nanoparticles.

An electric arc is formed between two electrodes (anode and cathode) within a controlled environment (e.g., inert gas like helium or argon).

The high temperature generated by the arc vaporizes the electrode material (e.g., carbon, metals).

The resulting vapor condenses and agglomerates, forming nanoparticles.

The nanoparticles are then collected from the reaction chamber. [39]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

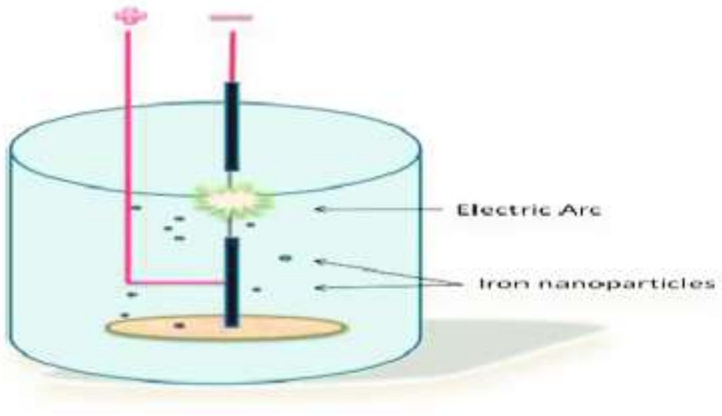

Figure 16. Experimental setup of electric arc discharge method for the synthesis of nanoparticles [39]

2. Electron Beam Lithography Method:

Electron Beam Lithography (EBL) is a crucial nanofabrication technique used to design devices, systems, and functional materials at the nanoscale. This miniaturization process transforms large-scale structures into precisely patterned, small-scale components.An Electron Beam Lithography (EBL) system comprises a vacuum chamber, an electron source, and a computer-controlled interface for managing the beam and generating patterns. This advanced technique is used to fabricate ultra-fine patterns, typically around 50 nm in size.Originating from early scanning electron microscopes, Electron Beam Lithography (EBL) involves directing a focused electron beam across a surface coated with an electron-sensitive resist film. This process selectively deposits energy onto the resist, creating the intended pattern. It is a high-resolution patterning technique in which high energy electrons (10-100 keV) are focused into a narrow beam & are used to expose electron sensitive resists. [40]

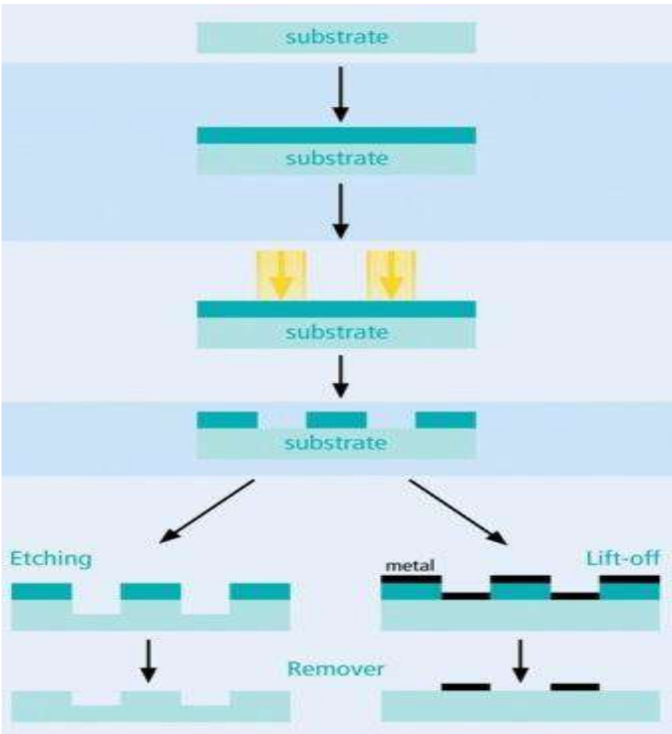

Figure 17. Electron beam lithography process [40]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

3. Ion Implantation Method:

This method involves accelerating ions (charged atoms) and bombarding them into a solid target, altering its properties (like composition, structure, or electrical conductivity). While it can introduce nanoparticles, it's not the primary method for their preparation in pharmacy.

Why Ion Implantation isn't the Primary Method:

- **Targeted Modification:** Ion implantation is primarily used to modify the properties of a solid material, rather than creating nanoparticles from scratch.
- **Pharmaceutical Applications:** The focus in pharmaceutical applications is on creating nanoparticles with specific properties for drug delivery, and ion implantation doesn't directly address these needs.

4. Inert Gas Condensation Method:

As a class of bottom-up viewpoint in nanoparticle synthesis, inert gas condensation is a perfectly developed and popular **nanoparticle synthesis technique** owing to its capability and flexibility to control the synthesis process. Briefly, the material is evaporated under the pure helium atmosphere with the helium atoms serving as a cooling agent condensing the atoms to finalize the formation of nanoscale particles.

This technique is widely employed to synthesize various nanomaterials, including intermetallic compounds, semiconductors, ceramics, composites, and alloys, as well as metallic and metal oxide nanoparticles. It enables the production of nanoparticles in a range of sizes, which can be controlled by factors such as chamber pressure, the type and amount of inert gas introduced, and temperature conditions.

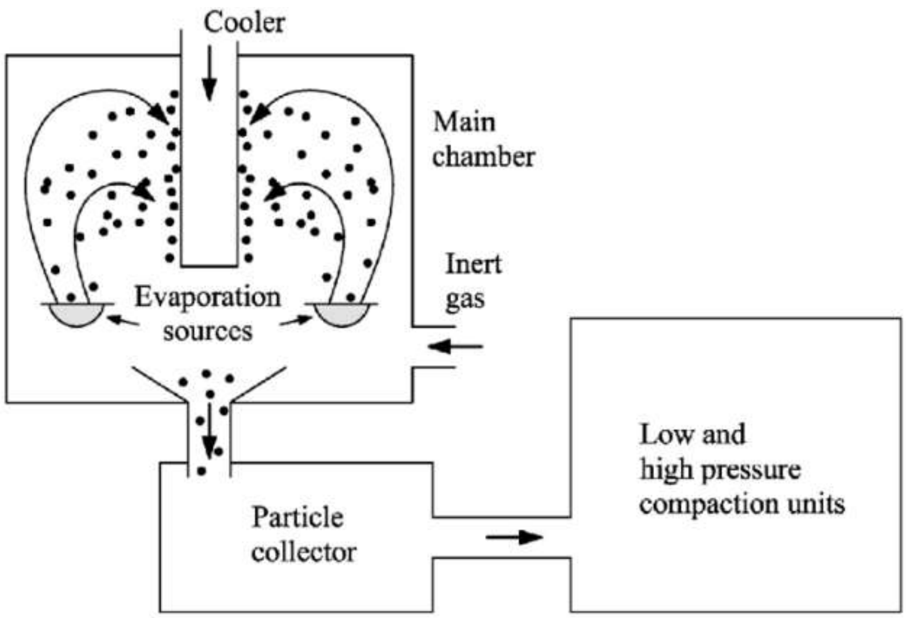

Figure 18. Schematic diagram of an inert gas condensation apparatus [41]

The **Inverse Gas Chromatography (IGC) method** has been utilized to produce size-controlled copper nanoparticles. Similarly, IGC has been applied in the synthesis of silver nanoparticles, where inert gas pressure and evaporation temperature significantly impact their crystallinity, size distribution, and morphology.

Furthermore, **inert gas condensation** has proven to be a highly effective technique for fabricating high-quality silver and platinum nanoparticles. This method has also been employed to develop **metallic-dielectric multi-core-shell nanoparticles**, demonstrating its versatility in producing ultrafine nanostructures.

The metal vapor migrates from the hot source into the cooler inert gas by a combination of convective flow and diffusion and the evaporated atoms collide with the gas atoms within the chamber, thus losing kinetic energy. Ultimately, the particles are collected for subsequent consolidation, usually by deposition on a cold surface.[42]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

5. Mechanical Grinding/ Milling Method:

The synthesis of nanomaterials with high yield, simplicity, and cost-effectiveness has remained a significant challenge since the early days of nanoscience. To address this, various **top-down and bottom-up approaches** have been developed for the large-scale production of nanomaterials.

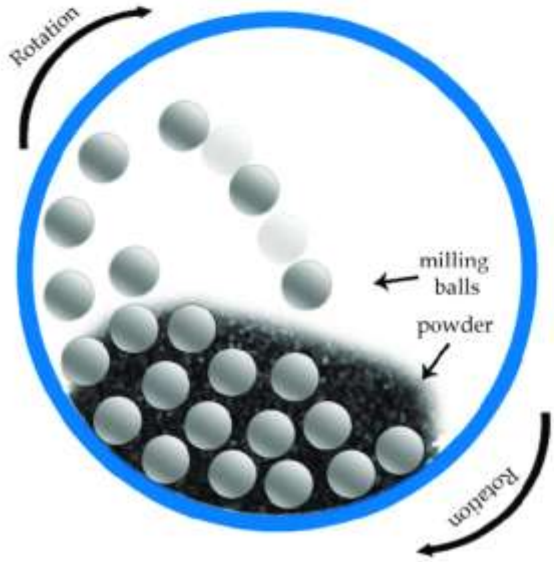

Figure 19. High-energy ball milling process [43]

Among the **top-down techniques**, **high-energy ball milling** is one of the most extensively used methods for fabricating nanomaterials, including nanograins, nanoalloys, nanocomposites, and nano-quasicrystalline materials. Additionally, **mechanical alloying** has been widely applied to produce amorphous and nanocrystalline alloys, as well as metal/non-metal nanocomposites, through milling and subsequent annealing of elemental or compound powders in an inert atmosphere.

Mechanical alloying is a **non-equilibrium processing technique** where different elemental powders are milled in an inert environment, resulting in a uniform mixed powder with the same composition as the initial materials. During **high-energy ball milling**, several key mechanisms come into play: **plastic deformation** alters the particle shape, **cold-welding** increases particle size, and **fracture** reduces particle size. These combined effects lead to the formation of finely dispersed alloying particles within a grain-refined soft matrix.[44]

6. Spray Pyrolysis Method:

Spray Pyrolysis (SP) is a widely used technique for synthesizing nanomaterials, where a precursor solution or suspension is atomized and introduced into a high-temperature furnace or heated environment. Upon exposure to heat, the precursor undergoes thermal decomposition, leading to the formation of nanoparticles.

This method is regarded as **cost-effective and scalable**, making it suitable for transitioning from laboratory research to industrial production. One of its key advantages is the ability to **synthesize a diverse range of nanomaterials**, including metals, semiconductors, and ceramics, in a **single-step process**.[45]

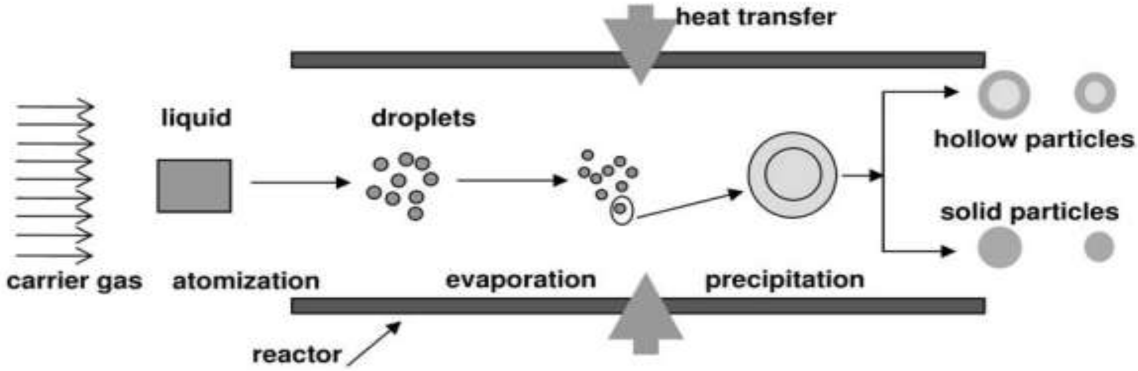

Figure 20. Basic steps of spray pyrolysis/drying method[46]

In this method, a highly diluted solution is atomized into fine droplets, though they are not necessarily nanoscale in size. As the solvent, which constitutes the majority of the droplet's volume, evaporates, the remaining solute condenses to form a single nanoparticle.This approach has been patented for the synthesis of **semiconductor nanoparticles**. It involves dissolving salts of the desired semiconductor, such as **ZnS, CdS, PbS, or GaN**, in a suitable solvent to create a precursor solution. Additionally, **metal oxides like ZnO** can be incorporated into the semiconductor solution to modify the resulting nanoparticles. Upon solvent evaporation, a continuous stream of free-standing semiconductor nanoparticles is generated and subsequently collected on a solid substrate.[46]

7. Vapor Phase Synthesis Method:

Vapor-phase synthesis of nanoparticles involves creating a thermodynamically unstable vapor phase mixture, inducing nucleation and controlled growth of nanoparticles, and then quenching the system to prevent further growth, resulting in high-purity, potentially polycrystalline nanomaterials.

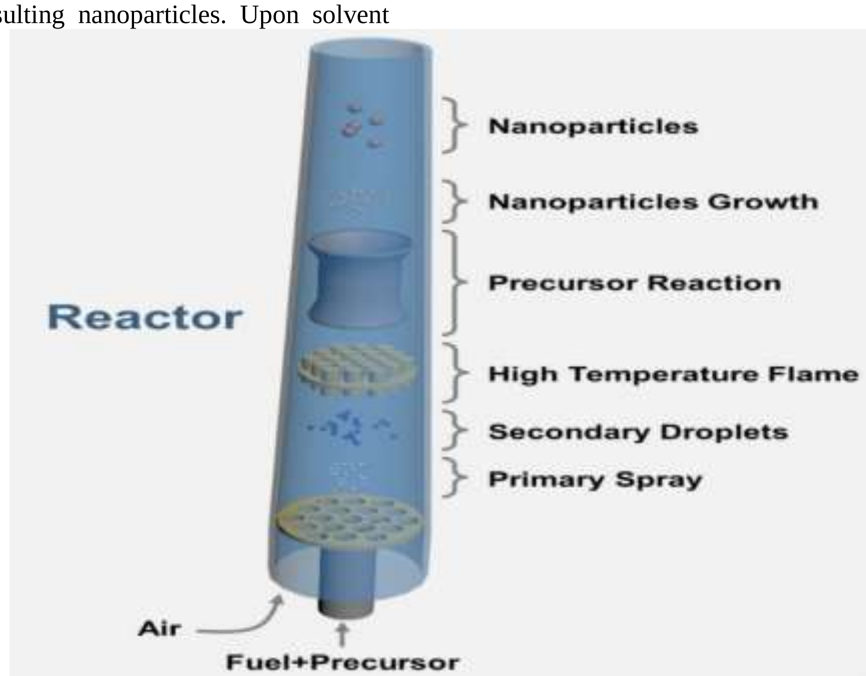

Figure SEQ Figure * ARABIC 21. The different stages during the synthesis process of nanoparticles using the vapor-phase method [47]

Figure 21. The different stages during the synthesis process of nanoparticles using the vapor-phase method [47]

In vapor-phase nanoparticle synthesis, conditions are manipulated to ensure that the vapor-phase mixture is thermodynamically unstable compared to the formation of solid nanoparticles. This typically involves a supersaturated vapor but can also include what may be termed "chemical supersaturation," where vapor-phase molecules preferentially react to form a condensed phase. If supersaturation is sufficiently high and reaction or condensation kinetics allow, homogeneous nucleation occurs. Once nucleation begins, excess supersaturation is alleviated through condensation or reaction on the newly formed particles, promoting growth rather than additional nucleation. To achieve smaller nanoparticles, a high nucleation density is induced by maintaining significant supersaturation, followed by rapid quenching—either by eliminating the supersaturation source or slowing reaction kinetics—to prevent further particle growth.[48]

Chemical Methods:

1. Co-precipitation Method:

In pharmaceutical nanoparticle synthesis, the co-precipitation method involves combining multiple metal salts in a solution, adding a precipitant, and controlling conditions to form a solid precipitate containing the desired nanoparticles. This method is simple, cost-effective, and allows for the synthesis of nanoparticles with controlled size and morphology.

Co-precipitation is a simple method for synthesizing nanoparticles that can be made in a variety of sizes. Several techniques have been developed to produce more uniformly sized nanoparticles. One approach involves combining an iron source with a sodium hydroxide nano emulsion to synthesize magnetite (Fe_3O_4) nanoparticles. After their formation, the nanoparticles are extracted using acetone lysis, and the surfactant is subsequently removed with ethanol. These colloidal nanoparticles exhibit strong magnetic properties, including superparamagnetic.

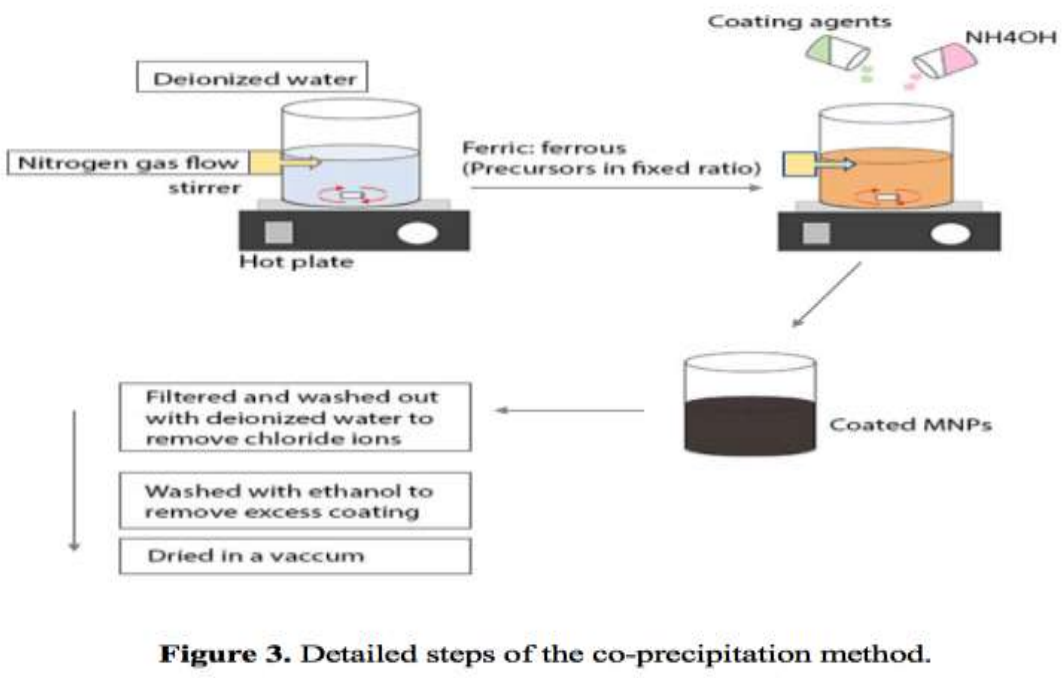

Figure 22. Steps of the Co-precipitation Method [49]

The dissolved compounds are distributed between the oil and water phases, and the physicochemical properties of the system are crucial in selecting an appropriate surfactant material.[50]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

2. Chemical Reduction of Metal Salts Method:

Chemical reduction of metal salts is a common, cost-effective method for synthesizing nanoparticles in pharmacy, involving reducing metal ions (from salts) to their metallic form using reducing agents like sodium borohydride or ascorbic acid, often in the presence of stabilizing agents.

As the name suggests, chemical reduction involves the use of chemical-reducing agents. This method can be categorized based on the energy source utilized or the type of reaction apparatus, offering diverse approaches for nanoparticle production. Among the various chemical synthesis techniques, chemical reduction remains the most widely used and straightforward method for nanoparticle fabrication.

As the name suggests, chemical reduction utilizes chemical-reducing agents to synthesize nanoparticles. This method can be categorized based on the energy source used or the type of reaction apparatus, offering various possibilities for nanoparticle production. Among the numerous chemical synthesis techniques, chemical reduction is the most common and straightforward approach.

In this process, metal nanoparticles are produced by reducing metal salts with a suitable reducing agent in the presence of a stabilizer. The stabilizer plays a crucial role in preventing the nanoparticles from clustering into larger aggregates.

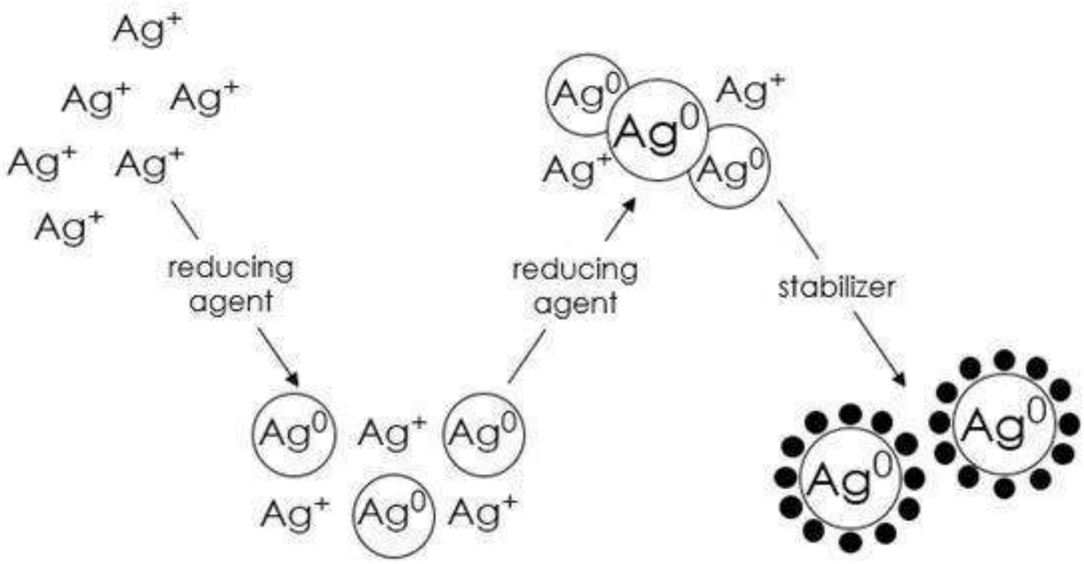

Figure 23. Scheme of nanoparticle formation (using silver as an example) by chemical reduction [51]

The synthesis occurs in three main stages:
Redox Reaction – Electrons from the reducing agent are transferred to metal ions, leading to the formation of free metal atoms.
Nucleation – These free metal atoms collide and coalesce to form stable nuclei.
Stabilization – Stabilizing agents are introduced to inhibit further aggregation, ensuring the nanoparticles remain well-dispersed.
In the last—third stage, stabilizers are added, which prevents the aggregation of nanoparticles.[51]

3. Electrochemical Method (Electrolysis):

Electrochemical synthesis, or electrosynthesis, using electrolysis is a method for nanoparticle synthesis in pharmacy that involves driving a chemical reaction through an electrochemical cell to produce desired nanoparticles, offering precise control over particle size and composition. The electrochemical synthesis of silver nanoparticles has been widely researched in recent years. This method involves the dissolution of a metallic silver anode in an aprotic solvent. The nanoparticles are formed through the electroreduction of silver ions, which are anodically dissolved in acetonitrile containing tetrabutylammonium. The resulting silver nanoparticles typically range in size from 2 to 7 nm. [52]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

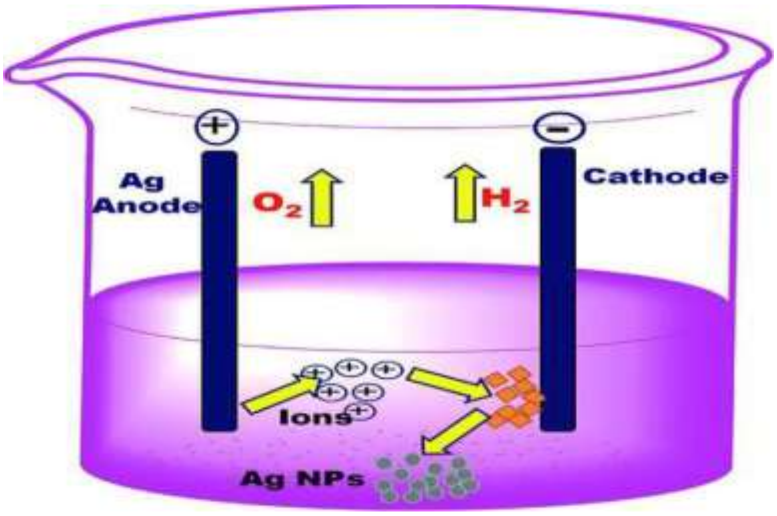

Figure 24. Schematic representation of electrochemical formation of Ag NPs in distilled water [52]

4. Microemulsion Method:

The microemulsion method in pharmacy allows for the synthesis of nanoparticles with controlled size, morphology, and homogeneity, by using microemulsions as nanoreactors to encapsulate and stabilize nanoparticles, leading to improved drug delivery and stability. The water droplets in the microemulsion act as nanoreactors, providing a controlled environment for nanoparticle synthesis.

Microemulsions are self-assembled colloidal systems that offer a controlled environment, making them highly suitable for use as nanoreactors. They serve as confined reaction spaces where nanoparticle properties can be precisely regulated with ease. [53]

The microemulsion technique for preparing chitosan nanoparticles was first developed by Maitra et al. This method relies on the formation of covalent cross-links between chitosan chains and a functional cross-linking agent. It was initially utilized to synthesize chitosan nanoparticles by encapsulating 5-fluorouracil, where glutaraldehyde acted as the cross-linking agent, binding with the amino groups in the chitosan molecular chain.[54]

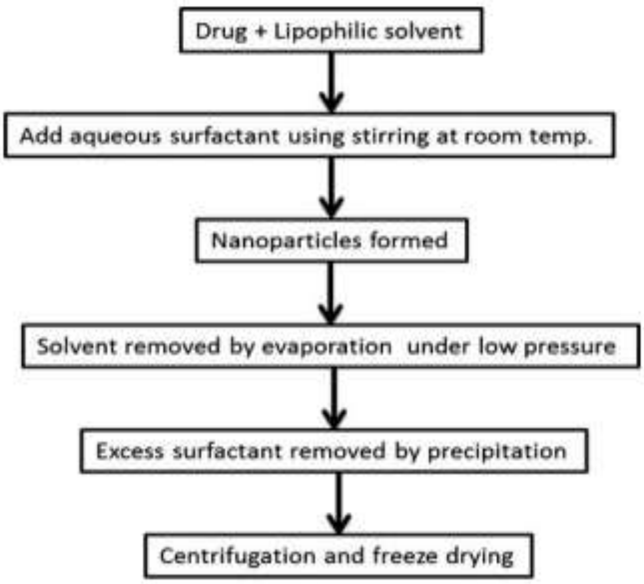

Figure 25.Synthesis of NPs by microemulsion method [54]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

5. Phytochemical (irradiation) Method:

The use of nanoparticles (NPs) in medicine has made it possible to create medication delivery methods that are Nano formulated.Nanotechnology-based natural agent delivery systems offer several advantages. One key benefit is their ability to protect pharmaceuticals encapsulated within nanoparticles from external environmental factors, ensuring prolonged systemic circulation and enhanced stability.[55]Approximately 70% to 80% of the world population prefers herbal therapy as their primary type of treatment, making it one of the most significant forms of traditional medicine. Numerous plants have the ability to produce nanoparticles with applications in medicine, life sciences, and the pharmaceutical industry. Phytochemicals, which are biologically active compounds found in plant-based foods such as fruits, vegetables, grains, and nuts, exhibit various health benefits, including anticancer, antioxidant, anti-inflammatory, and immunomodulatory properties. These compounds are broadly categorized into five groups: phenolics, carotenoids, alkaloids, organosulfur compounds, and nitrogen-containing compounds.[56,57]

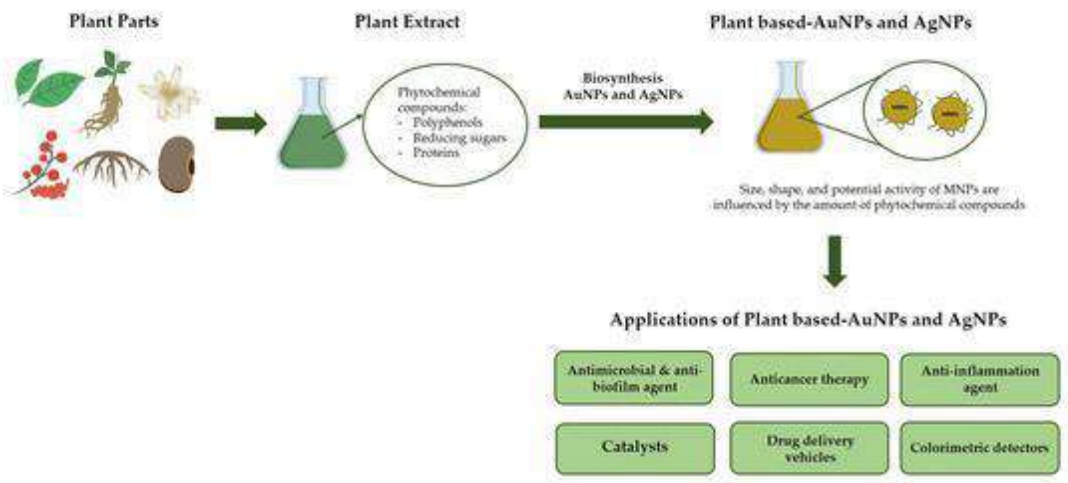

Figure 26. Phytochemical (plant based) Nano particles [60]

The synthesis of nanoparticles using plant extracts offers several advantages over other biological methods. One key benefit is the faster synthesis kinetics, which are comparable to chemical methods and significantly higher than other biosynthetic approaches. Additionally, phytochemicals exhibit a broad apparent volume of distribution, leading to their accumulation in various organs. However, a major challenge in utilizing phytomedicines for cancer treatment is the potential development of resistance through multiple pathways, which can limit their therapeutic effectiveness. Nanotherapeutics are being developed to address the limitations of conventional therapies, offering improved efficacy, targeted drug delivery, reduced side effects, and enhanced bioavailability. Nanotechnology-based delivery of phytochemicals offers several advantages, including passive transport across biological membranes, enhanced permeation and bioavailability, targeted deliveryto specific sites, protection against biological and environmental degradation, and controlled release for sustained therapeutic effects.[58,59].

6. Sono chemical Method:

Sono chemical synthesis, using ultrasound waves to drive chemical reactions and create nanoparticles, offers a promising, greener approach in pharmacy, accelerating reactions, reducing particle size, and minimizing hazardous byproducts compared to traditional methods.

Bioactive compounds found in citrus fruits serve as effective stabilizing agents while also facilitating the reduction of metal ions, enabling the synthesis of nanoparticles with controlled morphology, size, and stability. Additionally, citrus fruit extracts are readily available, cost-effective, and biocompatible, making them ideal for green synthesis approaches. Furthermore, ultrasonic energy has emerged as a powerful technique for nanoparticle synthesis, as it can induce chemical reactions and enhance reaction efficiency. Sono chemical methods offer several advantages, including rapid reaction rates, uniform particle size distribution, and reduced energy consumption.

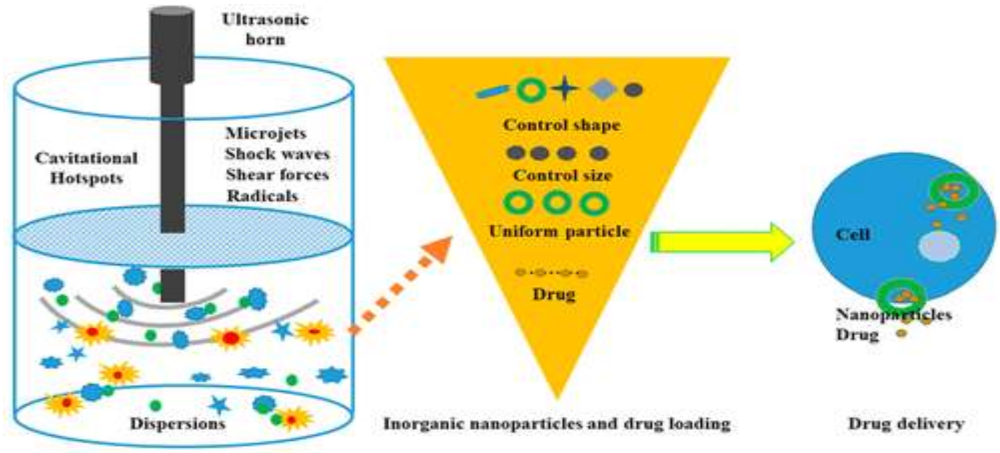

Figure 27. Sono chemical synthesis of NPs. [61]

The Sono chemical technique creates acoustic cavitation during irradiation, promoting the formation of free radicals and enable the metal ions to be reduced to create nanoparticles.The acoustic cavitation phenomenon induced by ultrasonic waves contributes to generate reactive species such as $HO_2\cdot$, $H\cdot$, and $OH\cdot$ which promotes the nucleation and Sono-crystallization processes of NPs.[62]

7. Sol-Gel Method:

The sol-gel method is a versatile chemical technique used in pharmacy to synthesize nanoparticles, involving the conversion of a liquid precursor (sol) into a solid gel network through hydrolysis and polycondensation reactions, offering control over size, shape, and composition.

The sol-gel process is a wet chemical method widely used for synthesizing various nanostructures, particularly metal oxide nanoparticles. In this approach, a molecular precursor, typically a metal alkoxide, is dissolved in water or alcohol and undergoes hydrolysis or alcoholysis through heating and stirring, leading to gel formation. Since the resulting gel retains moisture, it must be dried using techniques suited to its intended properties and applications. For instance, in the case of an alcoholic solution, drying is achieved by burning off the alcohol. Following the drying stage, the gel is ground into a fine powder and subjected to calcination to enhance its structural and functional properties.[63]

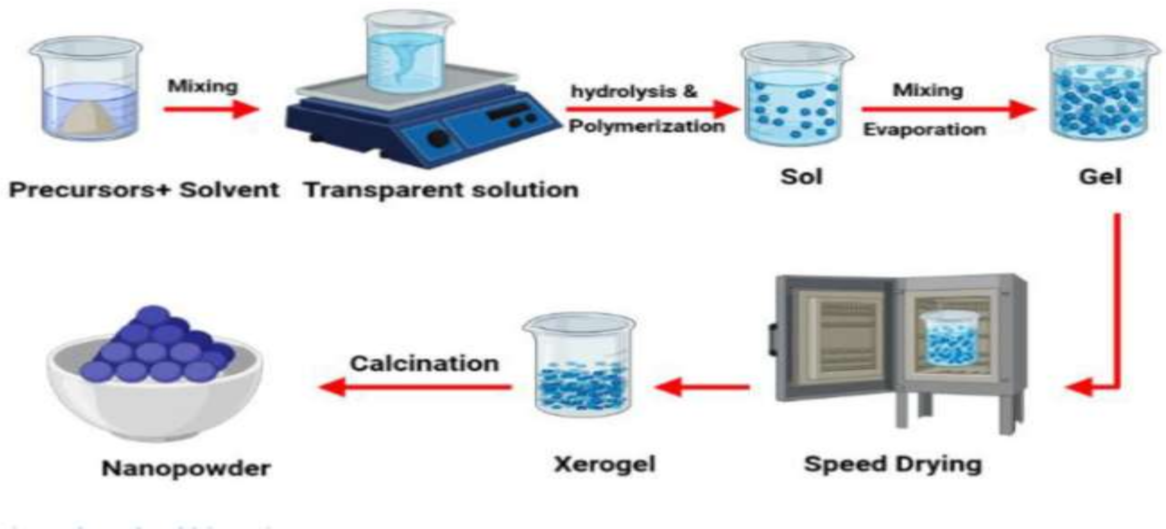

Figure 28. Sol-Gel Method[64]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

8. Solvothermal Synthesis:

Solvothermal synthesis in pharmacy involves reactions of precursors in a solvent under high temperature and pressure, leading to the formation of nanoparticles with controlled size and morphology, useful for drug delivery and other applications.

Most hydrothermal and solvothermal reactions take place in a sealed reactor, commonly referred to as an autoclave, pressure vessel, or high-pressure bomb. These methods facilitate material synthesis through a crystallization process that typically involves two stages: initial crystal nucleation followed by subsequent growth.Nanostructured materials with controlled size, shape, crystallinity, and surface functionalities have gained significant research interest due to their distinctive optical, electronic, magnetic, mechanical, and chemical properties. These unique characteristics primarily arise from the quantum confinement effect and the high surface-to-volume ratio of nanomaterials.

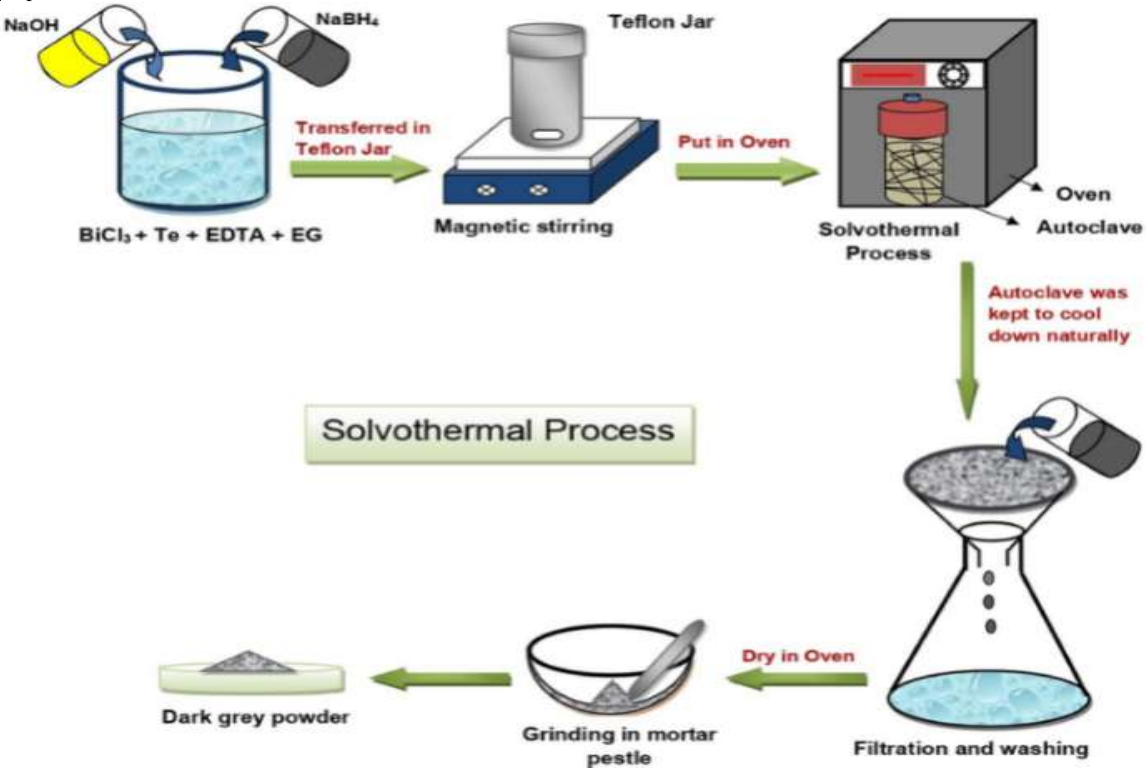

Figure 29. Synthesis by solvothermal method [65]

These methods have many advantages, such as manufacturing a large amount of nanomaterials at a relatively low cost and yielding highly crystalline nanocrystals (NCs). Hydrothermal and solvothermal methods can be enhanced by integrating microwaves and magnetic fields, enabling semicontinuous synthesis of materials with significantly improved reproducibility and high quality. This combination allows for better control over reaction kinetics, leading to more uniform nanoparticle properties and increased efficiency in material production.

Quantum dots can be synthesized by the solvothermal route in many shapes including spheres, rods, tetrapod's, and teardrops by controlling the temperature, concentration, and reaction time.[66]

Biological Methods

Plant extract-mediated synthesis of nanoparticles offers a green and eco-friendly approach in pharmacy, utilizing plant compounds as reducing and stabilizing agents to produce nanoparticles with potential applications in drug delivery and other therapeutic areas.

Microorganism-mediated nanoparticle synthesis in pharmacy involves culturing microbes, exposing them to metal ions, and monitoring color changes

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

to indicate nanoparticle formation, followed by purification and characterization.

Algae-mediated synthesis of nanoparticles, particularly silver nanoparticles (AgNPs), involves using algal extracts as reducing and stabilizing agents to form nanoparticles from metal ions, offering a green and eco-friendly approach. Algae contain compounds like polysaccharides, proteins, and pigments that can reduce metal ions (like silver ions) and stabilize the formed nanoparticles, preventing them from aggregating.

Enzyme-mediated synthesis of nanoparticles, a "green" approach in pharmacy, utilizes enzymes and biomolecules as reducing and stabilizing agents, offering a biocompatible and environmentally friendly alternative to traditional chemical methods.

- Enzymes, like α-amylase, laccase, and others, can act as both reducing and capping agents, facilitating the formation of nanoparticles.
- Some enzymes catalyze the formation of nanoparticles, while others, upon denaturation, release amino acids that act as reducing and stabilizing agents.
- This method is gaining popularity due to its biocompatibility and eco-friendliness, making it suitable for pharmaceutical applications.

Synthesizing nanoparticles from industrial and agricultural waste offers a sustainable approach, using waste materials like rice husk, sugarcane bagasse, and fruit peels as precursors for eco-friendly nanoparticle production, reducing waste and promoting circular economy.

Mechanism of Drug Delivery Using Nanoparticle

With the advancement of nanomedicine, drug discovery, and drug delivery systems, numerous therapeutic strategies have been developed, alongside the evaluation of traditional clinical diagnostic methods to enhance drug specificity and diagnostic accuracy.

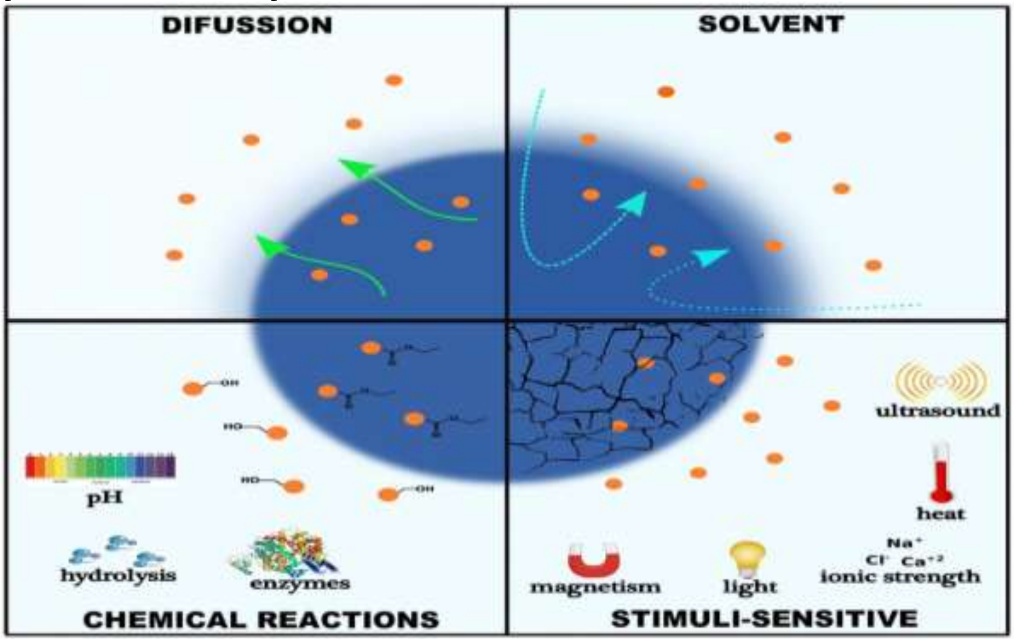

Figure 30. Mechanisms for controlled release of drugs using different types of nanocarriers [67]

Various mechanisms govern drug release from nanocarriers, including diffusion, solvent interaction, chemical reactions, and stimuli-responsive release, allowing for controlled and targeted therapeutic delivery.[68]

Targeted Delivery

Active targeting involves conjugating a therapeutic agent or its carrier system to a tissue- or cell-specific ligand, ensuring precise delivery to the target site. In contrast, passive targeting relies on incorporating the therapeutic agent into a macromolecule or nanoparticle, which naturally accumulates in the target organ.

Drugs encapsulated in nanoparticles or linked to macromolecules can passively target tumors via the enhanced permeability and retention (EPR) effect. Additionally, catheters can facilitate the direct infusion of nanoparticles to specific organs or tissues. For instance, the localized delivery of drug-loaded nanoparticles to areas of vascular restenosis can enable sustained drug release at precise arterial sites, enhancing therapeutic efficacy.[69]

Nanoparticles (NPs) offer a promising strategy for crossing the blood-brain barrier (BBB) and delivering targeted therapies to brain tumors. Their unique physical and chemical properties enable precise drug delivery while minimizing toxicity and allowing controlled release. Additionally, NPs can be surface-modified with proteins to target specific receptors, further enhancing localization to tumor sites.

In some malignant brain tumors, BBB disruptions facilitate improved NP transport compared to larger molecules. Electrostatic interactions also play a crucial role in NP permeability, as the negatively charged proteoglycans on endothelial cells create a dense anionic surface that influences NP movement across the BBB.[70]

Controlled and Sustained Release

When a nanoparticle is coated with a polymer, drug release is primarily governed by diffusion through the polymeric membrane. This membrane acts as a barrier, making drug solubility and diffusion across the polymer key factors in determining the release rate.

The method of drug incorporation also influences the release profile. If the drug is loaded using the incorporation method, the system exhibits a lower initial burst release and provides a more sustained drug release over time.[69]

Applications of nanoparticle systems in drug delivery

Nanotechnology has revolutionized the treatment of cancer, AIDS, and various other diseases while also advancing diagnostic testing. By integrating nanotechnology into medicine, nanoparticles have been engineered to replicate or modify biological processes, enhancing therapeutic effectiveness.

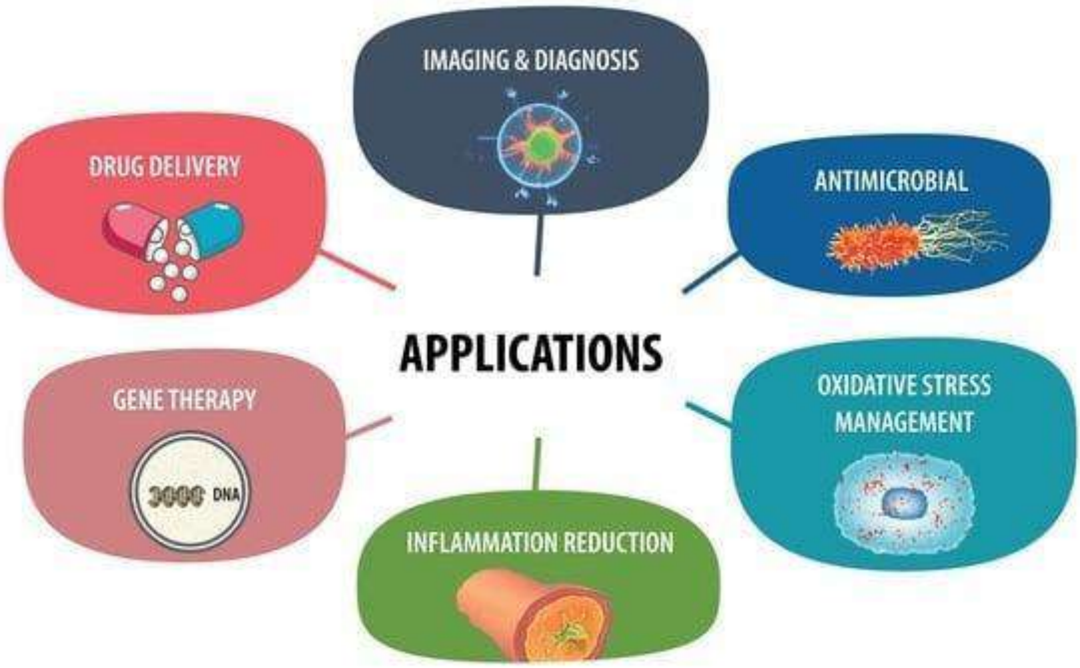

Figure 31. Applications of nanoparticle systems [71]

The development of nanoparticles has introduced a novel approach to chemotherapy. Smartly designed nanoparticles enable targeted drug delivery to tumor sites or specific cell groups, significantly reducing toxic effects on healthy tissues and organs. Micelles and liposomes provide additional options for delivering chemotherapeutic agents, with micelles particularly useful for solubilizing insoluble drugs due to their hydrophobic core and hydrophilic shell.

Furthermore, nanoparticles serve as highly efficient carriers for therapeutic molecules such as microRNAs (miRNAs), showing promise in treating various respiratory disorders, including cancer, ischemic stroke, and pulmonary fibrosis. Upon reaching target sites, they demonstrate effective aerosol behavior by evading local clearance mechanisms such as sneezing, swallowing, mucociliary transport, surfactant layers, and macrophage phagocytosis at the alveolar level.

Nanomaterials possess distinctive optical, electrical, and magnetic properties at the nanoscale, making them valuable in fields such as electronics and medicine. Their large surface area-to-volume ratio enhances their effectiveness across applications. These materials are widely used in everyday products, including sunscreens, cosmetics, sporting goods, tires, and electronic devices.

Nanotechnology holds immense potential in medicine, contributing to imaging techniques, diagnostic tools, advanced drug delivery systems, tissue engineering, implants, and pharmaceutical therapeutics. It has also significantly improved treatments for various diseases, including cardiovascular conditions, cancer, musculoskeletal disorders, psychiatric and neurodegenerative diseases, bacterial and viral infections, and diabetes.[71, 72, 73]

Chronic airway inflammation, bronchial hyperresponsiveness, and reversible airway blockage are the hallmarks of asthma, an inflammatory lung disease. Prolonged exposure to allergens triggers an inflammatory reaction in the lungs, which leads to lung tissue destruction and constriction of the tiny airways. Nanoparticles enhance therapeutic effectiveness by facilitating targeted drug transport and improving deposition in the lungs. Various in vivo and in vitro studies have demonstrated their potential impact on asthma treatment.

In cardiovascular nanomedicine (CVN), research has primarily focused on innovative solutions to address the limitations of current cardiovascular disease (CVD) treatments, aiming to improve therapeutic outcomes and patient care.

The original goal of CVN's nano systems was to improve the bioavailability, stability, and safety of already-approved medications. Nanomaterials vary from ordinary materials in their physicochemical characteristics, as their high surface energy enhanced surface area to volume ratio, which affect biological activity and protein adhesion. Therefore, the regulated and targeted administration of different functional components for the management of lipid metabolism disorders and other illnesses associated to CVD is made possible by nanotechnology, which offers a safe and effective platform.

Long-term stability while use is absent from traditional UV protection sunscreens. There are several benefits to using sunscreen that contains nanoparticles, including titanium dioxide. Certain sunscreens incorporate titanium oxide and zinc oxide nanoparticles due to their dual ability to absorb and reflect UV radiation while remaining transparent to visible light, providing effective sun protection without leaving a white residue on the skin.[74]

Advantages and Challenges of Nanoparticles.

Advantages

Drug loading plays a vital role in preserving pharmaceutical activity, as drugs can be incorporated into delivery systems without triggering chemical reactions, ensuring high drug-loading efficiency.

The therapeutic efficacy of a drug can be enhanced by regulating or sustaining its release, allowing for controlled and prolonged effects. Due to their small size, nanoparticles can penetrate tiny capillaries, facilitating efficient drug accumulation at targeted sites.

Liposomes and polymeric nanoparticles, being biodegradable, do not accumulate in the body, minimizing potential risks. Additionally, improved bioavailability enhances a drug's solubility, enabling more precise and effective drug administration.

Disadvantages

It is possible that the solvent system used in the preparation technique may have harmful effects.

Prescription leaks and unscheduled releases may be a significant issue.

The production expenses are significant and the efficiency of encapsulation is low.

Manipulating nanoparticles in both their wet and dry states is a significant challenge.[74]

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2192-2223 www.ijprajournal.com ISSN: 2456-4494

Table 1. Limitations[74]

Nanomaterial	Limitations
Silica-based nanomaterials(mesoporous silica and zeolites)	1. Limited selectively and adsorption capacity 2. poor recovery 3. Weak thermal, chemical, and mechanical stabilities 4. extensive cycling 5. Aggregation
Carbonaceous nanomaterials	1. Hydrophobicity 2. Aggregation (negligible suspension into aqueous solution) 3. Low reactivity of carbon 4. High cost of carbon nanotubes 5. Possible health risk (direct toxicity) 6. poor recovery of materials after treatment
Nanoparticles (metals, oxides, and quantum dots)	1. Lack of chemical stability and mechanical strength(corrosion) 2. Propensity to aggregate 3. Lack Of for reactions in complex systems 4. Limited selectivity to organics and heavy metals 5. Limited activity under visible light (Ti02, ZnO) 6. Fast recombination of photogenerated charge carriers (semiconductor nanoparticles)

Future Perspectives and Emerging Trends of Nanoparticles in Pharmacy

Nanoparticles hold immense promise for revolutionizing pharmaceutical applications, with future trends focusing on enhanced drug delivery, targeted therapies, and improved diagnostics, while also addressing challenges like safety and scalability.

Emerging Trends:

- **Nanovaccines:** Nanoparticles are being explored as delivery vehicles for vaccines, offering enhanced immunogenicity and stability.
- **Nanozymes:** Synthetic nanostructures that mimic the function of natural enzymes are being investigated for therapeutic and diagnostic applications.
- **Bioinks:** Nanoparticles can be incorporated into bioinks for 3D bioprinting, enabling the creation of complex tissues and organs for regenerative medicine.
- **Point-of-Care Diagnostics:** Nanomaterials are being used in point-of-care (POC) devices to enable rapid and accurate diagnosis of diseases in resource-limited settings.

II. CONCLUSION

Nanoparticles have revolutionized the field of pharmacy, offering advanced drug delivery systems, improved bioavailability, and targeted therapeutic applications. Their ability to enhance drug solubility, stability, and controlled release has positioned them as a vital tool in modern medicine. Various types of nanoparticles, including liposomes, polymeric nanoparticles, dendrimers, and metal nanoparticles, each offer unique benefits for pharmaceutical applications.

The synthesis of nanoparticles involves multiple methods such as chemical reduction, sol-gel processes, hydrothermal and solvothermal techniques, and green synthesis using plant extracts. These methods allow precise control over particle size, shape, and functionality, making them highly adaptable for different therapeutic needs.

Recent advancements in nanomedicine have expanded the applications of nanoparticles in areas such as cancer therapy, cardiovascular treatment, respiratory disorders, and vaccine development. The integration of nanotechnology with imaging, diagnostics, and biosensing has further enhanced disease detection and monitoring.

Despite their immense potential, challenges such as toxicity concerns, large-scale production, and regulatory approvals remain key hurdles in nanoparticle-based drug development.

Ongoing research aims to overcome these barriers and refine nanoparticle technology for safer and more effective pharmaceutical applications. As innovations continue, nanoparticles are set to redefine the future of medicine, making treatments more precise, efficient, and personalized.

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