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# Nanoparticles in Biomedicine: Advances in Classification, Synthesis, and Emerging Applications

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**Abstract: Nanoparticles revolutionized the field of biomedicine. They have gained significant attention due to their tunable physicochemical characters, nanoscale dimensions, broad applicability across scientific disciplines. This review provides a comprehensive analysis of five principal nanoparticle classes' metal nanoparticles, lipid nanoparticles, polymeric nanoparticles, nanocrystal, and dendrimer emphasizing their synthesis methodologies, structural characteristics, and functional applications. Metal nanoparticles, including gold (Au), silver (Ag)etc., They are used in biosensing, imaging, and therapeutic systems because of their remarkable exhibition of optical, magnetic and catalytic properties. Lipid-based nanoparticles demonstrate superior biocompatibility and are extensively utilized in drug delivery and vaccine formulations. Polymeric nanoparticles offer controlled release capabilities and mechanical flexibility suitable for the treatment of tissue engineering and regenerative medicines. Nanocrystals, characterized due to their high crystallinity and quantum size effects, are highly utilized in the optoelectronic and biomedical applications. Dendrimers, with their monodisperse and highly branched structures, provides efficient carriers for drugs, genes, and imaging agents. Various synthesis routes such as chemical reduction, self-assembly, emulsion polymerization, and green synthesis are evaluated for their influence on nanoparticle morphology, stability, and functionality. This review aims to provide a comprehensive understanding of nanoparticles, facilitating future research and development.**

***Keywords:*** *Nanoparticles: Nanocarrier, Classification, Synthesis, Biomedical Applications.*

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## I. INTRODUCTION

Nanotechnology has emerged as one of the most dynamic and interdisciplinary fields in modern science, providing tools to design and manipulate materials at the manometer scale that is 1 to 100 nm. Dimension of drugs at nano level exhibit unique physical, chemical, electrical, and biological characteristics.[3] These novel characteristics have led to the development of nanoparticles as key components in various technological and biomedical applications. Nanoparticles are specified as particles having nanometre size in one dimension, and they are designed from an inclusion of various materials, including metals, lipids, polymers, and crystalline solids. Their tunable surface functionality, stability, interaction with environment and with the biological system made them indispensable in diagnosis of disease, drug delivery, and electronics.[1]

Among the diverse classes of nanoparticles, metal nanoparticles**,** lipid nanoparticles**,** polymeric nanoparticles**,** dendrimers**,** and nanocrystals have gained particular attention due to their structural versatility and functional diversity.[2] Metal nanoparticles exhibit remarkable optical, electronic, and catalytic properties, enabling applications in biosensing, imaging, photo thermal therapy, and catalysis. Lipid nanoparticles vital in the field of pharmaceutical and biomedical sectors for their ability to enclose both water soluble and lipid soluble drugs, as demonstrated by their use in mRNA vaccine delivery systems.[5] Polymeric nanoparticles**,** synthesized from polymers such as PLGA, chitosan, and PEG, they allow controlled drug release and targeted delivery, offering high advantages to the field of tissue engineering and regenerative medicine. Dendrimers**,** characterized by their monodisperse, branched, and highly defined architecture, are excellent platforms for gene and drug delivery because of precise surface functionality. Meanwhile, nanocrystals which possess highly ordered crystalline structures exhibit enhanced optical, electronic, and mechanical properties that make them suitable for use in photonics, bioimaging, and energy conversion applications.

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Determination of physiochemical and functional characteristics depends on their synthesis. Chemical reduction, sol–gel processing, self-assembly, emulsion polymerization, and green synthesis methods are widely employed to achieve controlled particle size, morphology, and surface modification. Recent advancements in eco-friendly or "green" synthesis have further enhanced the sustainability and safety of nanoparticle production by utilizing biological agents such as plant extracts, enzymes, and microorganisms.[11]

Despite the tremendous progress in nanoparticle research, challenges persist regarding large-scale synthesis, reproducibility, toxicity, and long-term biocompatibility. The aim of this review in to give elaborate details on metal, lipid, polymeric nanoparticles, dendrimers, and nanocrystals emphasizing their synthesis strategies, physicochemical properties, and wide-ranging applications while discussing existing limitations and future perspectives for their safe and effective integration into advanced technologies.

➢ *Metal Nanoparticles*

In the science of nanoparticles, currently developing nanoparticle system is metal nanoparticles or metallic nanoparticles. Noble metals that have beneficial effects on what are known as metallic nanoparticles and employed in the production of nanoparticles include platinum, silver, and gold. Researchers are increasingly focussing on this nano system because of their benefits over catalysis, polymeric preparations, diagnosis, and treatment. There are various methods are used for the synthesis and stabilization of metal nanoparticles such as chemical reduction, photochemical reduction, and electrochemical alteration. Because processes like interaction of metals with the reducing agents and stabilizing agent adsorption with metal nanoparticles occur during the synthesis of nanoparticles, the choice of metallic nanoparticle production technique is equally important. because its stability, physicochemical characteristics, and morphology (size and structure) are greatly influenced by various experimental techniques. Numerous metal particles found in toothpaste, soaps, shampoos, cosmetics, detergents, and pharmaceutical preparations are having direct contact with people.[5] Gold is frequently utilized in Ayurvedic preparations and medications in China and India. Gold nanoparticles are used in numerous medication delivery and diagnostic applications.[10] Additional metal Silver-like nanoparticles additionally, nanoparticles are used in several biological fields, including separation science and innovative medication delivery mechanism. The antibacterial and anti-inflammatory properties of silver are widely recognized. This characteristic is employed specifically to promote quicker wound healing and is widely used in medical implant coating, various pharmaceutical dose formulations, and wound dressings.[4]

➢ *Classification of Metal Nanopartciles*

Metal nanoparticles (MNPs) can be categorised according to their morphology, structure, composition, and usefulness; each category affects the physicochemical characteristics and uses of MNPs. MNPs are classified as single-metal, bimetallic, or multi metallic based on their composition. Gold (Au), silver (Ag), iron (Fe), platinum (Pt), and copper (Cu) are examples of single-metal nanoparticles they possess special optical, magnetic, catalytic qualities that make them useful in industrial and biomedical settings. When compared to their monometallic counterparts, bimetallic nanoparticles which consist of two distinct metals in alloy or core shell forms, such as Au–Ag or Fe–Pt often exhibit improved stability, catalytic activity, and multifunctionality.[2]

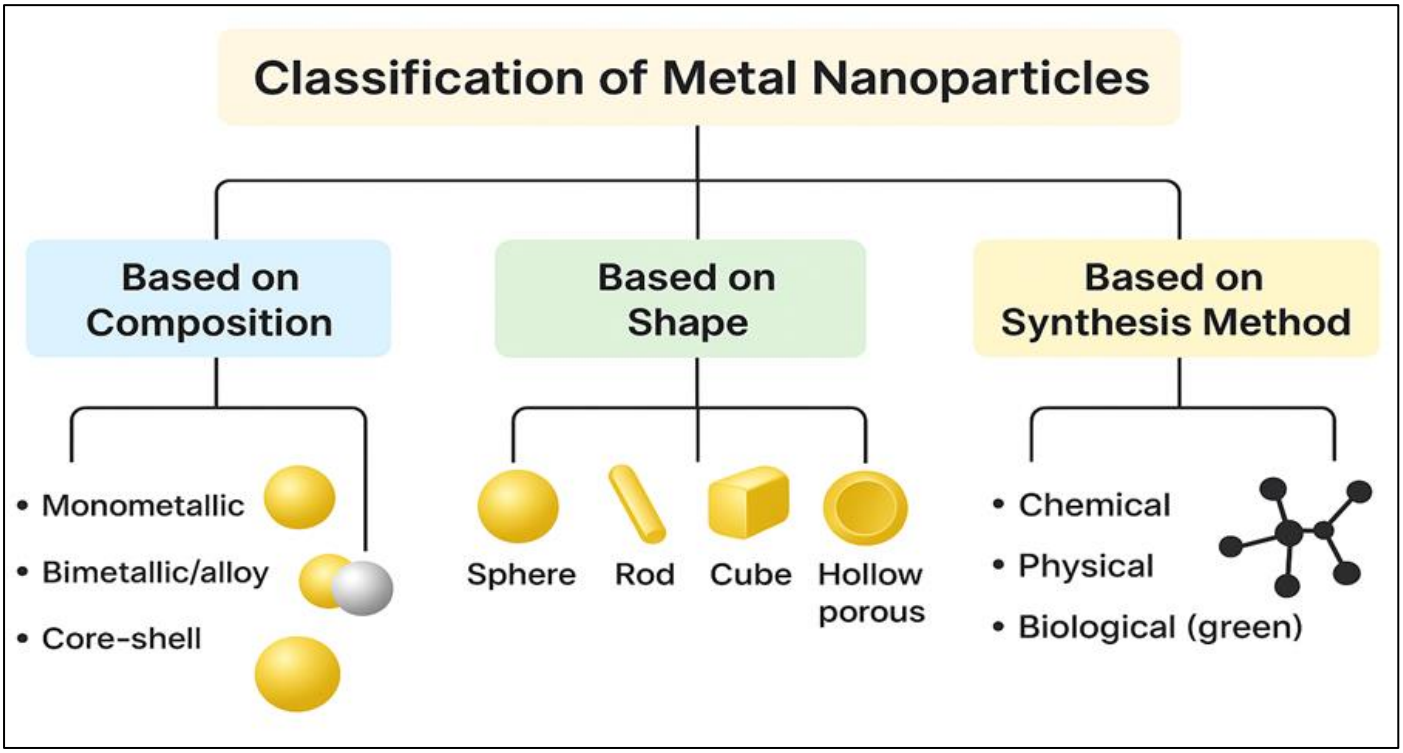


Fig 1 Classification of Metal Nanoparticles

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Three or more metals are incorporated into multimetallic nanoparticles, which provide customisable properties for intricate uses like theranostics. MNPs can be hollow, porous, alloyed, or core-shell based on their morphology and structure. Alloy nanoparticles feature a uniform atomic mixture of metals that enables property optimisation, whereas core-shell nanoparticles have a metallic core coated with another metal or stabilising substance to improve biocompatibility and surface functionality. Large surface areas and interior cavities are provided by hollow and porous nanoparticles, making them perfect for controlled release and drug loading. Furthermore, nanoparticles can have a variety of morphologies, such as spherical, cubic, rod-like, or star-shaped, each of which affects how well they work optically and catalytically.[1] MNPs are further divided into magnetic, plasmonic, and catalytic varieties based on their functioning. Plasmonic nanoparticles employed in biosensing, imaging, and photothermal therapy; magnetic nanoparticles such as iron oxide used in diagnosis and treatment of diseases, and catalytic NPs like platinum, palladium, and copper are effective catalysts in industrial and biomedical reactions.[2]

➢ *Synthesis of Metal Nanoparticles:*

The synthesis of metal nanoparticles mainly based on the reducing the size of the metals into nuclear size. For this synthesis various methods are used like physical, chemical, and biological methods. In physical method there are more chance for contamination due to solvents, and they required more energy for condensation. The temperature and pressure modulation are highly expensive. NPs are synthesised using reducing and protecting agents to prevent agglomeration and Produce highly pure and stable NPs in chemical method.[7] The biological synthesis of NPs is possessed highly efficient, environmentally friendly compared to other two methods. Based on the reducing agent selected, several biological techniques are used in green synthesis, that is employed, including plants and microorganisms like bacteria and fungus.[6]Using plants as NP-producing bio factories is one of the most economical and ecologically friendly ways to create metal nanoparticles.[9]The potential for scaling up metal nanoparticles produced using plants is enormous because of their quantity, accessibility, and capacity to be cultivated in a variety of environmental settings. Furthermore, plant-based synthesis is a safer and more sustainable solution because it does not require the costly and dangerous chemicals that are usually employed in conventional procedures.

➢ *Metal Nanoparticles can be Produced Using Two Primary Strategies:*

- Top-Down Approach: Metals are broken down by physical methods into nanoscale particles using mechanical, laser, or chemical methods. This allows control over particle size but may introduce defects on the surface.
- Bottom-up Approach: Metal ions are chemically or biologically reduced to form nanoparticles, allowing better control over shape, size, and crystallinity.

Almost all metals can be converted into nanoparticles they have high stability, availability, and functional properties.[8]

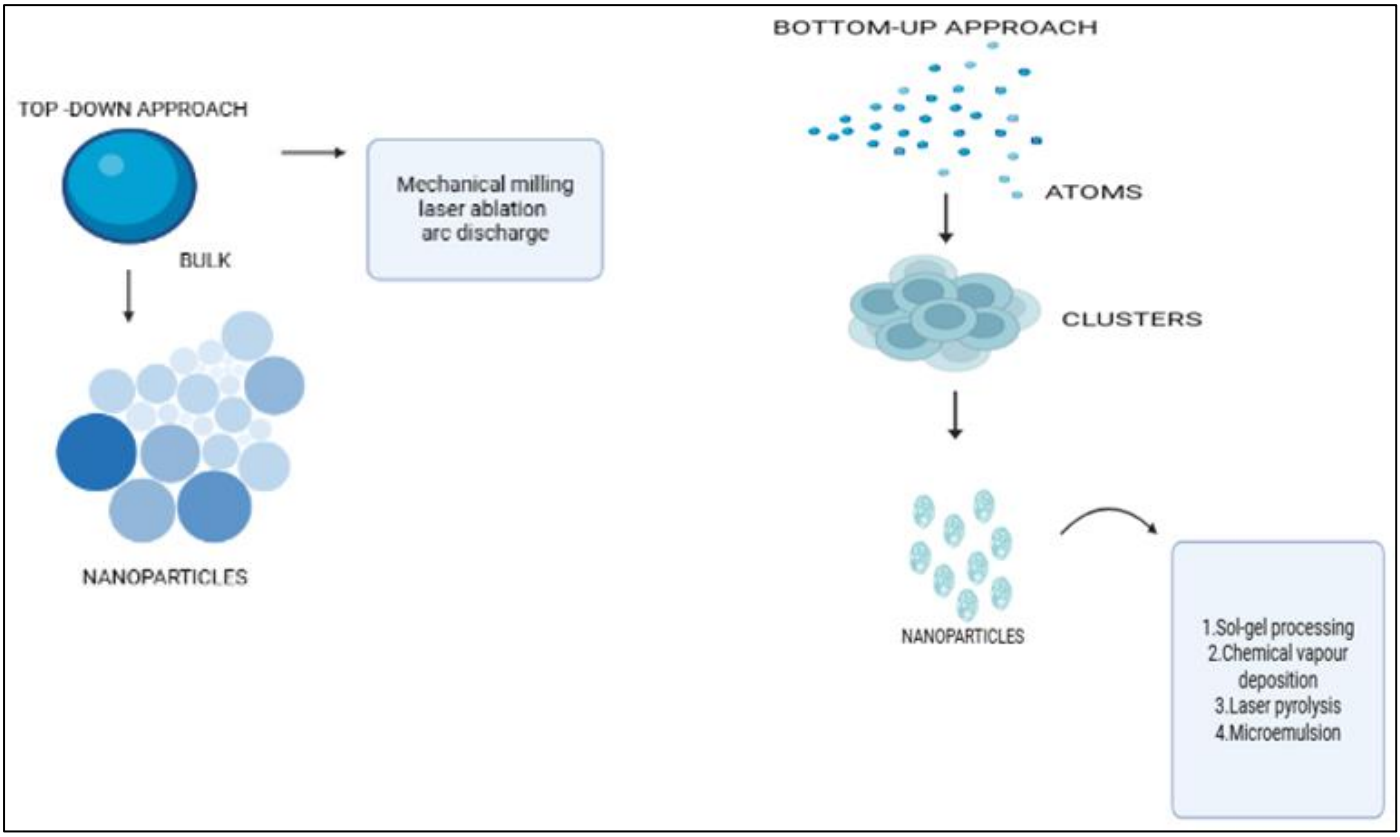


Fig 2 Synthesis Approaches of Metal Nanoparticles

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➢ *Applications*

- *Anti-Infective Agents*

AgNPs' antiviral qualities outperform those of chemically produced silver nanoparticles. In one study, it has been shown that metallic nanoparticles can prevent HIV. They attack the virus and produce the action. Consequently, this binding stops the HIV-1's infectivity is effectively reduced by CD4-dependent virion binding. Additionally, reports have stated that metallic Nanoparticles have demonstrated efficacy against respiratory syncytial viruses, influenza, and herpes simplex virus.[5]

- *Anti-Angiogenicactivity*

The new blood vessels formation is known as angiogenesis, and it happens both in normal foetal development and illness. Numerous illnesses, including cancer and rheumatoid arthritis, are significantly influenced by it. Under normal circumstances, the anti-angiogenic factors and pro-angiogenic growth factors are strictly controlling the angiogenesis. Angiogenesis is activated in pathological conditions. These drugs have major toxicities such thrombosis, hypertension, and deadly bleeding.[11]

- *Tumour Therapy*

Naked gold nanoparticles have been shown to suppress heparin-binding proteins like bFGF and VEGF165 in vitro as well as VEGF-induced angiogenesis in vivo. Moreover, according to research in this field, the absorption of the heparin-binding proteins into the surface silver nanoparticles and subsequently denatured. They also demonstrated that the therapeutic impact of AuNPs is mostly dependent on surface size. [4]

## II. DENDRIMERS

Dendrimers are nanoscale synthetic macromolecules featuring a branched, or dendritic, architecture. Dendrimers generally have a nucleus, repetitive branch point, or generations, along with many terminals' boundary groups. This three-dimensional globular structure gives dendrimers many unique attributes, such as their monodispersed, nanoscale size, internal cavities, and high surface-density functionalities for modification and conjugation.[12] Dendrimers have progressed from synthetic novelties, since their original discovery in the late 1970s and early 1980s (e.g. early 'cascade' dendritic structures and Tomalia's work), to versatile, ubiquitous platforms across chemistry, nanotechnology, materials science and biomedicine.[13] Dendrimers provide a robust bridge from well-defined size, shape, internal cavities, and surface-modifiable chemistry, polymers to biomolecules - enabling much flexibility in molecular architecture for specialized use in drug delivery, imaging, diagnostics, also catalysis.[14]As applied to the following sections, we will consider the structural features of dendrimers, their synthetic strategies, and discuss major and emerging applications - with a focus on their biomedical uses and then material science uses more broadly.

➢ *Structure of Dendrimers:*

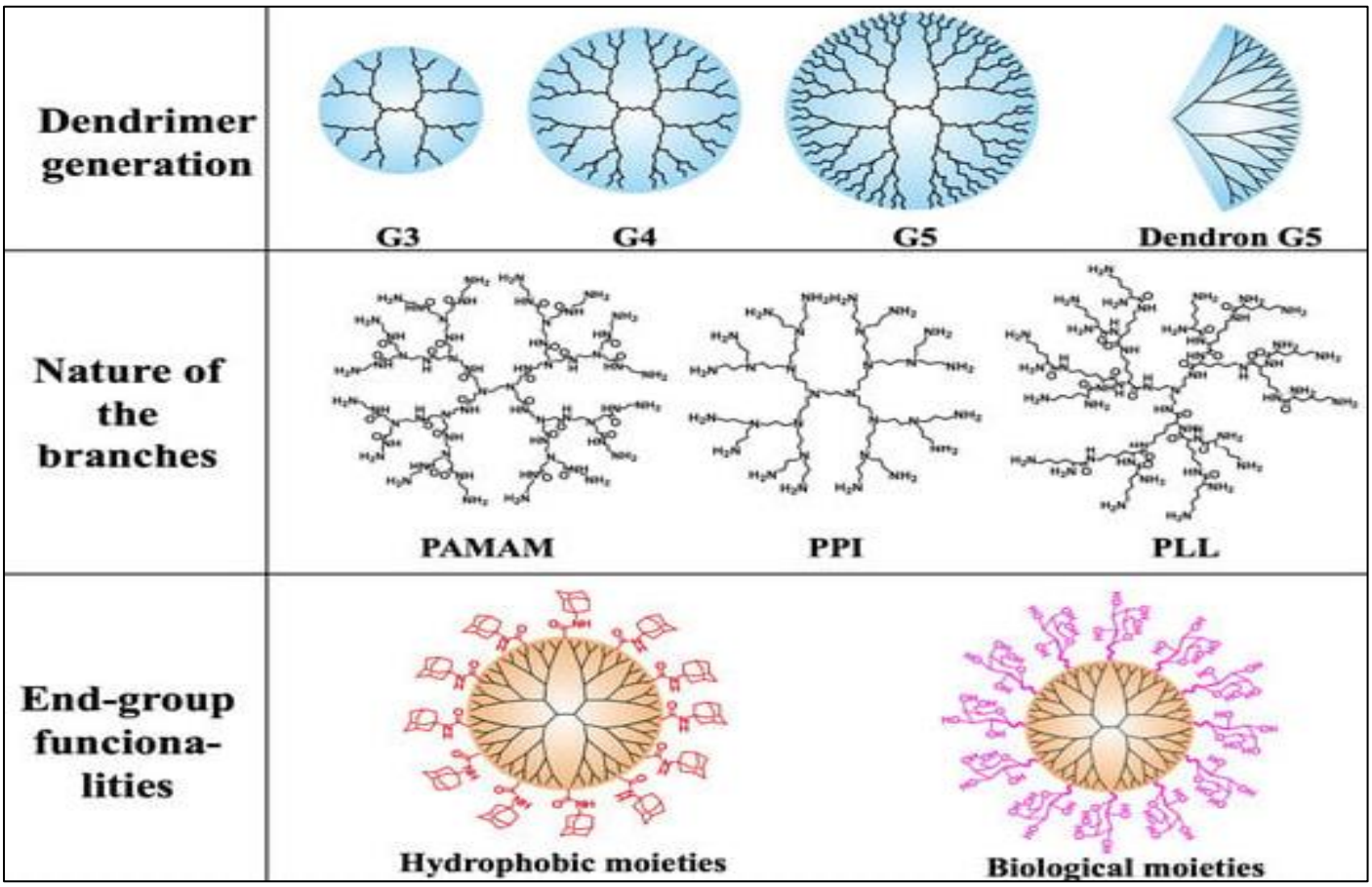


Fig 3 Structure of Dendrimer

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Typically, a dendrimer is designed in three main domains: (1) the core can be either a single atom or a multifunctional molecule; (2) the repeating branching units (which represent the "generations" of the dendrimer structure, such as G1, G2, G3…); and (3) the terminal groups on the periphery, which provide the surface properties of the dendrimer (solubility, charge, reactivity).[14] Each time a generation is added, the molecular weight increases, the diameter typically increases, the number of end groups increases exponentially (in an ideal synthetic case), and the internal cavity volume increases stepwise.[13] Because branching is highly controlled in dendrimers, they tend to have very low polydispersity with highly defined shapes, which is not the case with typical linear or random branched polymers.[12] Dendrimers are also classified by composition (e.g., poly(amidoamine) or PAMAM, poly(propyleneimine) or PPI, polyester dendrimers, carbosilane dendrimers etc.), by topology (symmetric vs. Janus vs. supramolecular), and by functionalization (neutral, cationic, anionic, pegylated, ligand-targeted) of the terminal groups.[14] All these characteristics will influence key properties of dendritic systems, such as solubility, biocompatibility, accessibility of an internal volume/cavity, surface charge, and potential for conjugation and, ultimately, functionality in application.[14] In conclusion, dendrimers' modular architecture allows for a high level of tunability: the designer can tune size, shape, internal structure, surface chemistry, and ultimately application-specific performance via the rational choice of core, branch type, generation number, and terminal functionality.

➢ *Synthesis*

An important synthetic advancement in dendrimer chemistry is the development of efficient “click”-type reactions (i.e., alkyne-azide cycloadditions) for the assembly and functionalisation of dendrimers. For example, Arseneault et al.'s review indicates that the advent of click chemistry around 2001 enabled new dendrimer architectures and a new level of functionalisation possibilities, illustrating high levels of chemo selectivity, atom-economy and modulated growth.[15] Ladd et al. described a divergent synthetic pathway where in dendrimers of generations 1-3 were generated from a tetrafunctional core using Cu(I)-catalysed alkyne-azide cycloaddition (CuAAC), generating surface-terminated dendrimers with 8-32 end groups followed by post-synthesis modification attaching cationic amino groups.[16] They showed generation-one dendrimers with $NH_3^+$ terminal groups possessed significant bactericidal activity, showcasing how synthesis regulates size, surface functionality and hydrophilicity, which, in turn, regulates performance.[16] Overall, these work flows exemplify several important synthetic considerations for dendrimers in the following order: (i) selection of a core (i.e., tetrafunctional vs multi-functional), (ii) generation control through stepwise addition or coupling, (iii) use of highly efficient coupling chemistries (click, CuAAC, thiolene, etc.) to facilitate growth and purification, and (iv) post-synthesis surface functionalisation (i.e., to modify properties like cationic + charge for antimicrobial activity).[15] Overall, while classical convergent/divergent strategies remain foundational, modern dendrimer synthesis increasingly leverages modular “click” approaches, orthogonal chemistries and post-synthetic tailoring enabling more complex, multifunctional dendritic architectures with improved scalability, functional control and application-specific surfaces.

➢ *Role of Dendrimers as Targeted Drug-Delivery Nanocarriers*

Dendrimer-based nanocarriers represent an attractive platform for targeted drug delivery since they offer many features that can be advantageous: tight size control (usually 2–20 nm), high surface-functionality (many terminal groups per molecule), and internal cavities that can encapsulate therapeutics.[17] Dendrimers implement both physiological and ligand mediated targeting mechanism for targeted delivery:

- Physiological targeting: Many dendrimers fall within the optimal size range [typically several tens of nanometers] to exploit the tumor - selective accumulation phenomenone enabling preferential accumulation in tumor tissue due to compromised vasculature and inefficient lymphatic clearance.[18]
- Active (ligand-mediated) targeting: Dendrimers have rich surface chemistry, allowing conjugation of ligands (e.g. folacin, protein fragments, immunoglobulins) that link to over-expressed docking site on cellular targets (e.g. oncogenic cell).
- This improved specificity within the delivery methods greatly improved specificity in targeting and uptake.[19]

For example, in one study, dendrimers modified with folic acid were utilized to deliver methotrexate to KB-cells with overexpression of the folate receptor, which resulted in higher uptake and slower release kinetics than non-targeted systems.[19] Another review cites that a generation of PAMAM dendrimers that were surface modified to achieve desired release kinetics (i.e., neutral acetylated versus amine-terminated) offered controllable release and targeting behaviours for the tumour microenvironment (e.g., acidic pH).[17] Dendrimers also supported-or-multi-functional delivery, as they can encapsulate hydrophobic drugs, conjugate hydrophilic drugs or biologics, and include imaging or diagnostic moieties.[20]

Further, branched architectures allow for high drug-loaded amount and multi-valency (i.e., many drug molecules per carrier, many targeting ligands per carrier) to improve the probability of binding and uptake in target cells.[17] However, design considerations (e.g., size, generation number, surface charge, ligand density, and in active release mechanism (e.g., cleavable linkers responsive to intracellular triggers) directly impact pharmacokinetics, biodistribution, toxicity and therapeutic efficacy. For example, cationic dendrimers may have high uptake, but may also yield high cytotoxicity or interactions with untargeted tissues or serum proteins; thus, surface modification should be considered (e.g., PEGylation, acetylation) to decrease nonspecific binding, clearance, and improve viability for the in vivo delivery.[17] To summarise, dendrimers are targeted drug-delivery nanocarriers that combine modular construction, exceptional functionalisation, and tunable chemistry allowing for both passive and active targeting strategy, controlled payload loading and release, as

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well as opportunities for multifunctional theranostics applications. The avenue for research is to optimise the design for safety, scalability, reproducibility and clinical translation.

➢ *Applications*

In addition to simple structural and delivery applications, dendrimers are being used in all kinds of other functional areas. The review, "Applications and Limitations of Dendrimers in Biomedicine," states that dendrimers improve drugs' solvent affinity, sequestration, systemic availability also precision delivery via their encapsulation cavities and functional groups on the periphery. For example, dendrimer-drug conjugates containing cytotoxic drugs (such as doxorubicin, paclitaxel, cisplatin, etc.) have been shown to have a better therapeutic index than free drugs.[21] Dendrimers are being widely used as carriers for drugs, genes, imaging agents and theranostics because their defined architecture (internal cavities + functionalized surface) allows for both guest encapsulation and surface conjugation. For example, the interior of dendrimers can encapsulate hydrophobic drugs, while targeting ligands and therapeutic industrial can be attached to its surface for improved solubility, bioavailability, targeted delivery and controlled release.[21] In vivo, dendrimer–drug conjugates and dendrimer–nanoparticle hybrids have shown promise for enhanced therapeutic efficacy and reduced off-target toxicity in cancer and other.[22] Moreover, surface functionalization of dendrimers can mitigate toxic effects (for example neutralising cationic surfaces, PEGylation) and to improve circulation half-life, biodistribution and targeting to specific tissues or cellular receptors.[21] Applications of dendrimers include:

- Drug delivery, gene delivery, imaging/theranostics.
- Antimicrobial applications (cationic dendrimer surfaces).
- Nanoparticle stabilization for biosensing and diagnostics.
- Catalysis and materials engineering.

However, application translation is mitigated by hurdles such as dendrimer toxicity (especially with respect to cationic surfaces), biodegradability or clearance in vivo, scalable defect-free synthesis, reproducible functionalization, and ensuring safe long-term responses/behavior in biological system.[22]

## III. LIPID NANOPARTICLES

➢ *Types of Lipid Nanoparticles*

- *Liposomes:*

Liposomes are first discovered in 1965. These are spherical entities, it generally composed of an internal aqueous core and an amphipathic phospholipid bilayer. liposomes can carry both hydrophilic and hydrophobic agents because of their core-shell nanostructure. Hydrophilic drugs are usually entrapped in the aqueous phase of the core, while hydrophobic pharmaceuticals are commonly encased in the lipophilic bilayers of the shell. Due to sufficient developments in liposome technology, many therapeutic formulations based on liposomes are currently safe for human use, and many products are in different phases of clinical trials.[23]

- *Solid Lipid Nanoparticles:*

Drug-incorporated highly ordered crystalline structure with emulsifiers is the characteristic of SLNs made up of fully crystallized lipid components. SLNs were initially created in the mid-1990s using lipids such triglycerides, fatty acids and waxes that have melting points greater than body and ambient temperatures.[24]A solid lipid core with a mean photon correlation spectroscopy diameter of roughly 50-1000 nm makes up solid lipid nanoparticles, which are nanospheres. SLN are appealing for their potential to improve pharmaceutical execution because of their intriguing features, which include small size, large surface area, high medicine stacking, and stage communication at the interface.[24]

- *Nanostructure Lipid Carriers:*

At body temperature, NLC's blend of liquid and solid lipids stays solid. The addition of the oil molecule causes flaws that boost the drug's or active ingredient's absorption capacity by distorting the creation of ideal lipid crystals. The drug loading capacity is increased by this "structure." The structure and lipophilicity of the drug itself, in addition to the lipid matrix's structure, determine the drug's localization.[25]Over time, a reduced chance of drug ejection is another benefit of NLCs. A new and improved variety of NLCs with a precise nanostructure are available. Because of these careful nanostructures, formulation stability is enhanced, bioavailability and drug loading.[33]

- *Hybrid Nanoparticles:*

Hybrid lipid-polymeric nanoparticles is a novel medication delivery technology that seems to have a more uses. It is composed of a therapeutic-containing polymeric core encased in an outer layer of PEGylated lipid and an inner layer of lipid. Hybrid lipid-polymeric nanoparticles exhibit excellent stability, prolonged release, and good biocompatibility due to the properties of both lipids and polymers. Besides the development of lipid-polymer hybrid nanoparticles, several other types of hybrid nanoparticles have been developed for different kinds of uses, such as the hybrids of lipid-metal: lipid-coated silver nanoparticles (lipid-AgNPs), lipid-aluminum nanoparticles, and liposome gold nanoparticles (LiposAu NPs).[36]

➢ *Methods of Preparation*

- *Supercritical Fluid:*

The last 20 years have involved the development of supercritical fluid (SCF) technology as a crucial material processing technique. There is a wide range of nanomaterials that are prepared using supercritical CO2 and H2O. Since the properties of nanoparticles change dramatically with size, the most important prerequisite for the application of nanomaterials is the control of their size and morphology, which dictates the potential applications of the particles. There are special thermophysical characteristics of the supercritical fluid.[26] It can be either liquid or gas. The temperature at which liquefaction of a gas is impossible is known as the fluid's critical temperature. The density and the

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fluid's capacity to dissolve substances both rise with increasing pressure, but the viscosity stays essentially unchanged. The fluid can thus dissolve or liquefy the chemical (such as a medicine containing lipid) at high pressure and the right temperature in the supercritical region. The gases employed in this process include CH2FCF3, CO2, and CHCHl2. Due to its low critical point, safety, affordability, non-irritability, and relative inertness, CO2 is among the finest choices.[34]

- *Sonication:*

This dispersion-based technique entails melting the drug-containing lipid matrix at a temperature 5–10°C above its phase transition temperature. Rapid swirling of those molten lipid creates an emulsion, which is subsequently distributed in a water based medium with a surface modifier (at same temperature).[27] The entire mixture is cooled gradually to create the nanoparticle dispersion after being exposed to ultrasonic irradiation to shrink the droplet's size. To obtain lipid nanoparticles, lengthy sonication periods are necessary, which raises the possibility of metal filings from the probe contaminating the emulsion. Additionally, certain lipid nanoparticle-based drug delivery methods may encounter issues when highly polydisperse formulations containing a high number of microparticles are present.[35]

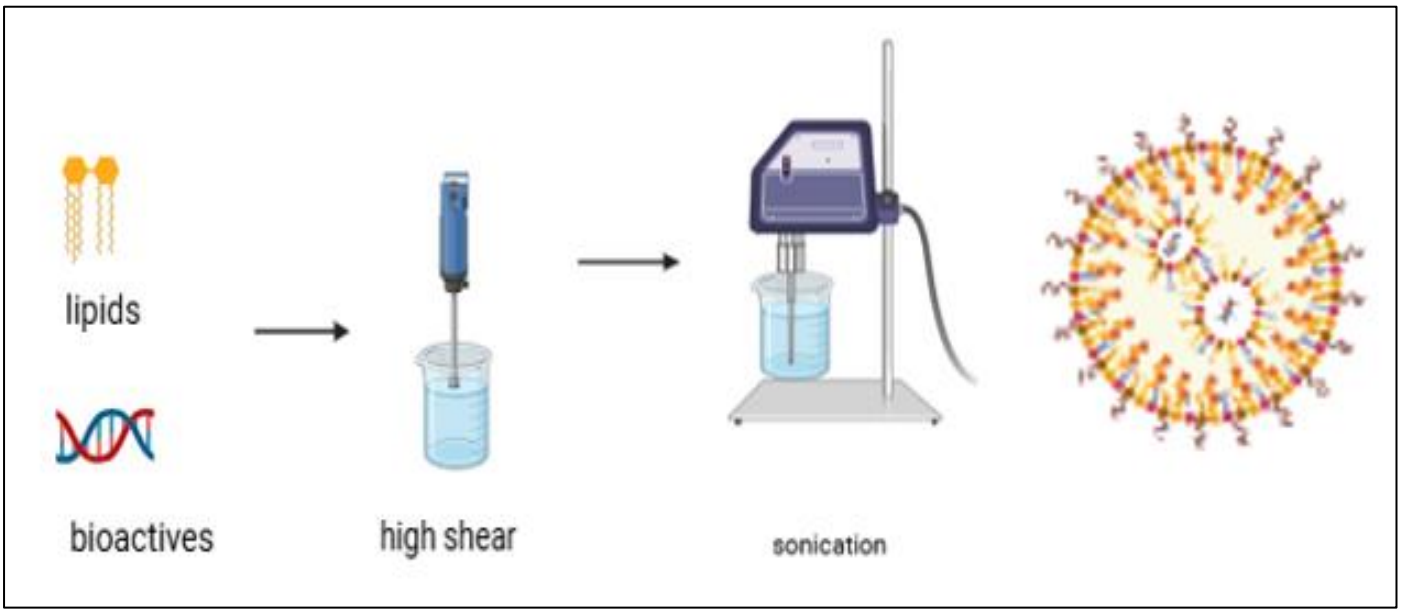


Fig 4 Sonication Method

- *High Pressure Homogenization:*

Using a high pressure (100–200 bars) homogenization process, lipids are forced through a small opening that is only a few microns wide. Shear stress and cavitation, which results from an abrupt drop in pressure, are the forces that cause particles to break down into the submicron range. Lipid contents typically vary from 5 to 10%. It doesn't interfere with homogenization at this concentration. A variety of surfactants, polymers, and their mixtures can stabilize SLN, but lecithin alone stabilizes the emulsion used for parenteral nutrition.[28] High-pressure homogenizers use pressures between 100 to 2000 bar to drive a mixture of lipids, water, surfactant, and the active ingredient through tubes with very small diameters (typically a few microns). The liquid can go above 1000 km/h over short distances. High cavitation and shear stresses cause the liquid lipid particles to break up into sub micrometer pieces. Even at up to 40% by weight lipid concentrations, this technique can produce lipid nano dispersion.[28]

- *Solvent Injection:*

Characterization of the particles it generates. The results indicate that a powerful and versatile technique for the preparation of LNP is represented by solvent injection. As a suitable solvent, ethyl alcohol, isopropyl alcohol, and methyl alcohol are suited because ethyl acetate cannot be used for the preparation of LNP. Particle sizes (z-average) were between 80 and 300 nm, depending on the conditions of preparation. Up to 96.5 Lipid nanoparticles (LNP) may be prepared by rapidly injecting a solid lipid solution in water-miscible solvents or a mixture of water miscible solvents into water. The goal of the present investigation was to investigate the capability of the technique in producing LNP and the physicochemical % of the used lipid was directly transformed into LNP. Diffusion seems to determine the formation of LNP.[29]

➢ *Application:*

- *Lipid Based Nanocarrier for Cancer Therapy:*

Several anticancer drugs have been encapsulated in lipid nanoparticles and there in vitro and in vivo efficacy has been assessed in appropriate investigations. Overall, SLN has been proved to enhance the efficacy and residence time of cytotoxic medicines as well as to decrease the adverse effects.[30]

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- *Gene Therapy:*

Preclinical studies have employed LNP delivery to deliver a range of therapeutic payloads, such as heredit, siRNA, mRNA, antisense oligonucleotide, and micro-RNA. Certain disorders brought on by genetic mutations can be treated by these chemicals by interfering with gene expression. Currently, several clinical trials are being conducted to evaluate how well LNPs transport various payloads.[31]

- *For Treating Lung Disease:*

Tuberculosis is one the most life-threatening disease in the world which leads to death. A system of rifampicin-loaded LNPs with mucoadhesive chitosan was developed for the treatment of tuberculosis. Chitosan- incorporated LNPs shows excellent medication delivery method for the lungs due to their increased cellular absorption and better mucoadhesive strength with mucin.[32]

## IV. POLYMERIC NANOPARTICLES

Because of their great versatility and low toxicity and biodegradability, PNPs are extensively used in the medical field. Generally, a range of therapeutic agents can be encapsulated by polymeric nanoparticles (PNPs), which also improve bioavailability and enable controlled release, leads to increased effectiveness with fewer side effects. Evaluation of the polymer that are used in the preparation of PNP are essential because that has a direct impact on the size, shape, surface charge and drug capacity.[37]Polymeric NPs have properties such as water solubility, biodegradability, nanoparticles, all with different delivery systems.[38] Effective polymeric and intracellular environments. Despite the great number of research works carried out in this domain, only a few designs of polymeric nanoparticles are currently used in a wider clinical practice. This review will give a summary regarding the polymeric nanoparticle for drug targeting, focusing on the most important delivery paths and biological barriers that need to be addressed when designing efficient polymeric nanoparticles.[39] Among the benefit of using polymeric nanoparticle as therapeutic vectors, they also used for controlled release, protection of drugs, and other active molecules from the environment.[40]

➢ *Types of Polymeric Nanoparticle:*

Biomaterials used for the preparation of PNPs include natural and synthetic materials such as chitosan, albumin, gelatin, collagen, polylactic acid, polylactide coglycolic acid. They are stabilized in several ways: as polymeric nano systems, nanoparticles, vesicles, micelles, and dendrimers.[41]

- *Dendrimers:*

Dendrimers are macromolecules composed of three components: an external surface functional group, internal branching, referred to as dendrons, and a central core. Dendrimers have a lower polydispersity index and size range between 1 and 100 nm. The physical and chemical characteristics of dendrimer and rate of encapsulation is mainly determined by the active hydrophobic/hydrophilic surface functional groups.[42] The core molecule contains at least two reactive groups, allowing branches to form in layers called generations. Dendrimers can be synthesized in two ways: divergent, where growth starts from the core and moves outward, and convergent, where branches are made first and then connected toward the core.[43]

- *Nanospheres:*

These nanoparticles and nanospheres are used for many purposes, such as sensing, imaging catalysis, diagnostics, modification of optical property, improvement of chemical and biological properties, and enhancement of catalytic properties.[41]

- *Polymeric Micelle:*

Amphiphilic synthetic copolymers forming polymeric micelles exhibit a wide range of desirable characteristics as drug carriers.[44] The polymer aggregation can be easily removed from the body by complement activation or plasma protein adsorption, which will trigger the RES to eliminate the entire micelle and the medication inside its core. Amphiphilic part of polymers gets assemble in aqueous environment into micelles with hydrophilic outer layer and hydrophobic inner layer. Hydrophilic part is incorporated in the block copolymer to give the polymeric micelles anti-fouling characteristics. The hydrophobic part of block copolymers is designed that controls the drug release from the polymeric micelles and to solubilize the drugs that are poorly soluble in the core.[45]

➢ *Method of Preparation of Polymeric Nanoparticle:*

Method of preparation are divided into two categories; they are one-step and two-step procedures. In two-step procedure, it involves emulsification process followed by formation of nanoparticles by using different mechanisms like precipitation, gelation, or polymerization. In one-step procedure there is a formation of nanoparticles by using nanoprecipitation, desolvation, and drying processes without emulsification process.

- *Nanoprecipitation: One Step Procedure*

Nanoprecipitation is also called as solvent displacement method, having two miscible solvents. In internal phase, the polymer is dissolved in an organic solvent, for example acetone, acetonitrile etc. Since they are immiscible in water, evaporation is a straightforward way of eliminating them. The principle involved in this method is interfacial deposition of polymer that occurs when an organic solvent is transferred into the aqueous phase coming from a lipophilic solution. After the polymer is dissolved in a polar water-miscible solvent, an aqueous phase is added dropwise. Because of the rapid migration of the polymer solution into the aqueous phase to order avoid the formation of water molecules, nanoparticles are formed. When the solvent diffuses out from the nanodroplets, the polymer precipitates as nanospheres.[41] Supersaturation is a driving force for nanoprecipitation method.[46] In order to obtain polymeric nanoparticles ranging 170nm dimensions are prepared by using nanoprecipitation method.[47]

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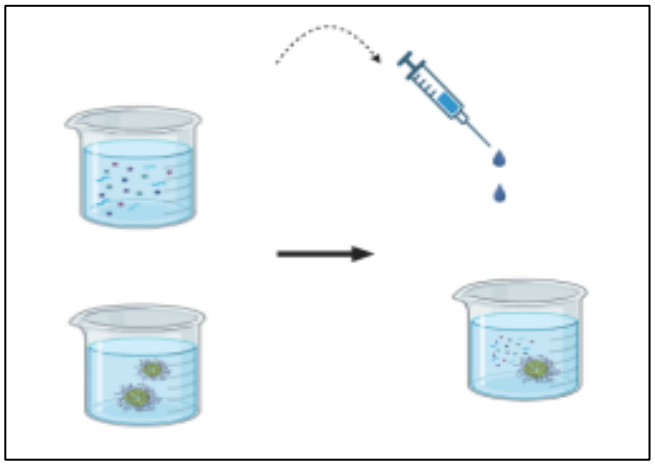

Fig 5 Nanoprecipitation Method

- *Emulsification/Solvent Diffusion:*

In solvent diffusion process, it involves an o/w emulsion formation by dissolving a polymer and a drug in the partially water miscible liquid and surfactant in a aqueous solution. The internal phase of the emulsion has 60 organic solvents such as ethyl acetate or benzyl alcohol. It is previously saturated with water to ensure that the two phase are initially in thermodynamic equilibrium at room temperature. The final process is eliminated based on their boiling point of the organic solvent by using either evaporation or filtration process. Thus, nanoparticles having diameter that ranges from 80-900 nm are obtained.41

- *Salting-Out:*

Acetone is a water-soluble organic solvent selected in the salting-out process due to its non-toxicity and approval by the pharmaceutical companies. In this method, a water-soluble polyvinyl acetate is added into a highly concentered salt solution of distilled water this is considered as aqueous phase and a polymer solution in acetone solution is considered as organic phase. Although acetone and distilled water can mix at any ratio, but the high concentration of salt in the aqueous phase inhibits the mixing process. Upon sufficient addition of the distilled water after emulsification process, acetone diffuses into the aqueous phase, forming nanoparticles.[48]

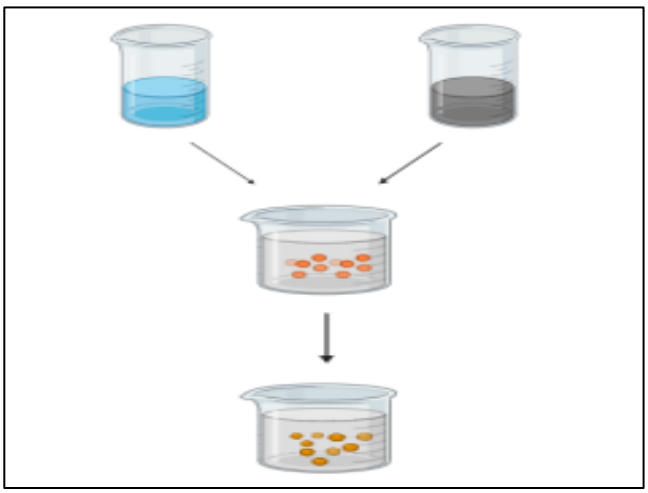

Fig 6 Salting Out Method

➢ *Applications:*

- *Targeted Delivery of Polymeric Nanoparticle:*

✓ Polymeric nanoparticles are very useful as drug carriers in cancer treatment because they are safe for the body (biocompatible), break down naturally (biodegradable), do not cause harmful effects (non-toxic), stay longer in the bloodstream (extended circulation), and can carry many types of drugs (wide drug-loading capacity). Their distinct size and shape allow both passive and active targeting, cellular and subcellular transport mechanisms, and simple payload release management that favors tissue penetration. Controlling the release of medications, preventing the degradation of labile materials like proteins, peptides, and DNA, and precise targeting of drugs at given locations are some of their roles.[41]

✓ Nanoparticles in size ranges from 10–200 nm has the advantage to penetrate and retain in the tumor tissue and allowing to stay longer period inside the tumor tissue compared to that in healthy tissues. Thus, polymeric nanoparticles have been emerged as a highly promising drug targeting systems owing to several reasons that includes less immunogenicity, disease transmission, better stability during systemic circulation, and high drug bioavailability.

✓ Polymeric nanoparticles are being a promising strategy for cancer treatment.[49]

- *PNPS in Drug Delivery for Arthritis Treatment:*

Depending on the composition, nanoparticles increase bioavailability and enhance the therapeutic efficacy of drugs such as methotrexate (MTX) and dexamethasone (DXM). The targeting and prolonged retention in inflamed joints is improved with functionalized nanoparticles, for instance, HA-modified carriers. Bioactive compounds, such as curcumin and resveratrol, have enhanced therapeutic efficacy upon delivery using polymeric nanoparticles. The drugs used in the treatment of arthritis can be encapsulated by using the polymeric nanoparticles.[50]

## V. NANOCRYSTALS

Drug nanocrystals are crystalline particles with size range in nanometer. Drug nanocrystals are composed only of drug, in contrast to polymeric nanoparticles no carrier material is present. Unlike "micro suspensions" or "macro suspensions," "nanosuspensions" are created when drug nanocrystals disperse in liquid environments. The scattered particles must be stabilized, for example, using polymeric stabilizers or surfactants. Water, nonaqueous media (such oils or liquid polyethylene glycol [PEG]), and aqueous solutions are examples of dispersion media. [51] For technical uses in both industry and science, nanocrystals are of great interest. For a variety of uses, the nanocrystals which has stability, well defined structure with distribution is highly challenge in the repeatable production.[52] Drug nanocrystal preparation techniques come in two varieties: top-down approach and bottom-up approach. Top-down techniques based on the reduction of bigger particles into small. whereas bottom-up techniques produce smaller particles from

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individual molecules. The process that gives the development of a crystal from individual molecules is called supersaturation. The supersaturation of drug has occurred in a solution by reducing the temperature or adding an anti-solvent.[53]

*A. Synthesis:*

➢ *Top-Downapproach*

- *Mechanical Milling:*

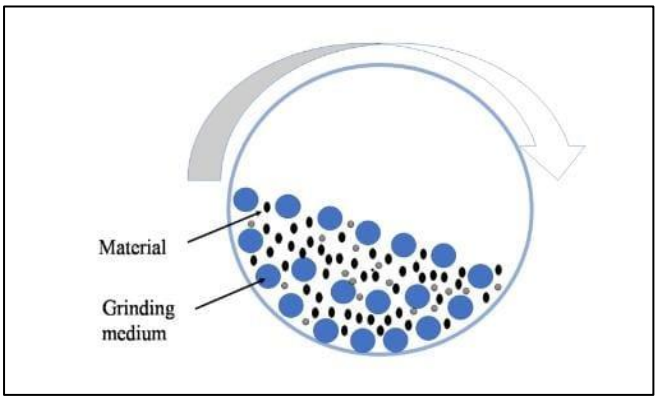


Fig 7 Mechanical Milling

Ball milling, also name for mechanical milling, grinds nanotubes into ultrafine particles. As the name implies, the ball and a milling chamber was used in the ball milling. After that, material powder is placed in a ball milling chamber and ground to a nanoscale using a ball mill that revolves several small irons, ceramic, flint stones, stainless steel, carborundum, Cemented carbide balls inside a stainless-steel chamber. During ball milling, the impact of minuscule hard balls in a hidden tank results in localized high pressure. Particles of a size of two to twenty nanometers are produced as a result. The size of the particles is determined by the speed at which the ball rotates in the milling chamber.[54]

➢ *Limitations:*

- The current method for creating nanoscale materials from bulk resources is inexpensive.
- The uneven form of the particles and the NPs getting polluted by the balls' contents because of the mechanical process are this procedure's main drawbacks.[54]

➢ *Bottom-Up Approach:*

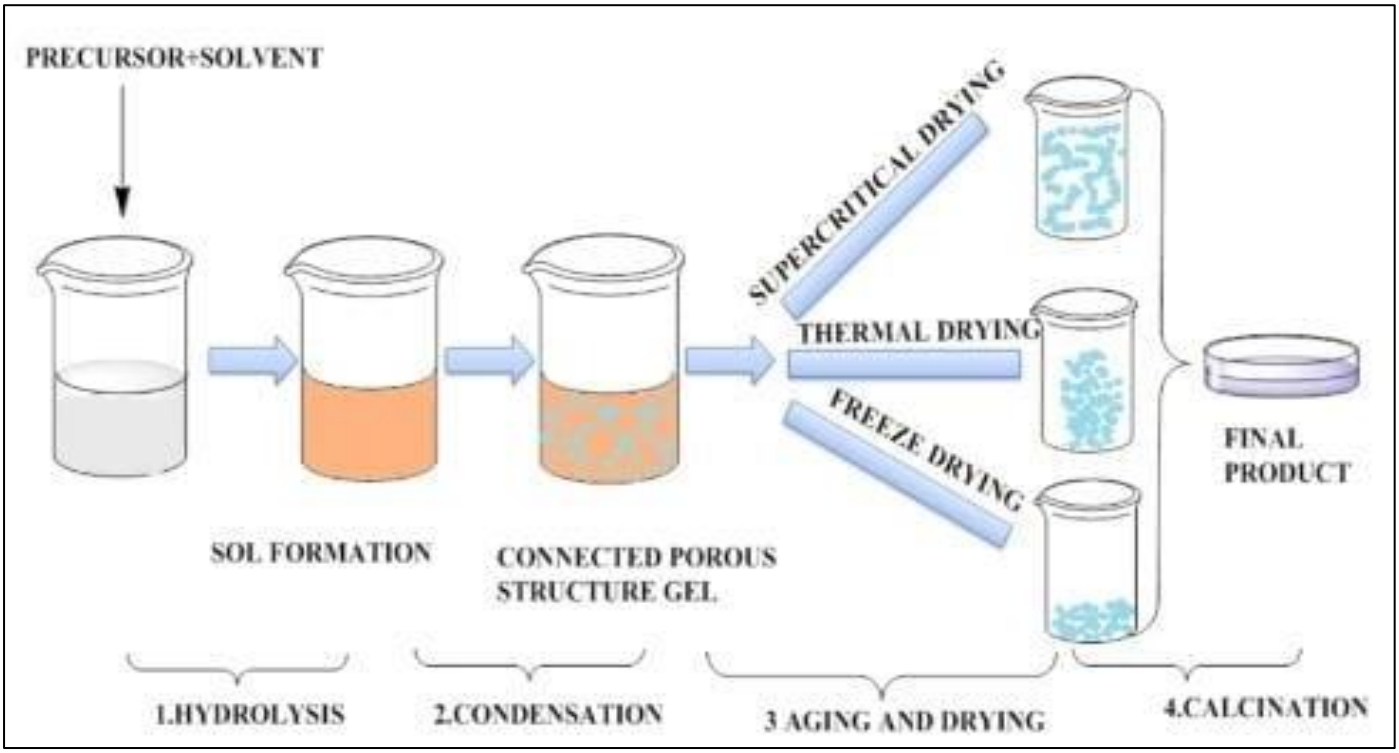


Fig 8 Sol-Gel Method

➢ *Sol-Gel Method*

"Sol-gel" is the combination of "sol" and "gel." Because it is straightforward, it is one of the simplest ways to create nanoparticles. Gel is a solid macromolecule dissolved in liquid, whereas sol is a colloidal solution created with the aid of solid particles suspended in it. Hydrolysis, polycondensation, aging, drying, and finally calcination are the steps involved in this sol gel technology. In the first step, the precursor (metal alkoxides) is hydrolyzed in the presence of water or alcohol to create hydroxide solution. The reaction medium defines the methodology; for instance, an aqueous sol-gel approach is takes place when water used as a medium; in non-aqueous sol-gel approach the organic solvent taken as a medium. Water and alcohol are removed during the second step, and adjacent molecules condense to form metal oxide bonds. Increased solvent viscosity brought on by polycondensation produces porous structures that retain as liquid phase. Third process is called aging because the gel

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network re-precipitates because of ongoing polycondensation inside the localized solution, which decreases the porosity of colloidal particles and increases the thickness between them. After that, the gel is dried, which is somewhat challenging because the separation of the organic and water components upsets the structure. Calcination is the last process, which removes water and contaminants from the sample. [54]

➢ *Combination Method:*

Combination methods, as their name implies, consist of two stages: pretreatment and a high-energy size reduction procedure. Baxter created NANOEDGE technology, in which crystals were first precipitated and then homogenized under high pressure. When a solvent and a non-solvent are mixed in two counter flows as part of a version on NANOEDGE technology, at interface the formation of crystals takes place. This phenomenon is called as counter flow precipitation. The goal of Abbott, USA's Smart Crystal technology is to speed up the size reduction process by combining several medicinal nanocrystal production technologies. Precipitation takes place immediately prior to it's the area where tiny bubbles form and collapse with lots of force, breaking down particles. in the H69 combination technique. H96 combines lyophilization with high shear, whereas H42 combination of spray drying and high shear homogenization. To create drug nanocrystals, CT combines bead milling with high pressure homogenization.[55]

- *Advantage*

Produces more stable crystalline particles.[56]

- *Limitations*

Far more costly than individual techniques. It's not a universal approach. Possibility of organic solvent residual contamination.[56]

*B. Applications:*

➢ *Drug Nanocrystals with Surface Engineering for Specific Cancer Cells:*

Cancer cells often have special markers on their surface, called receptors, that are more abundant than on healthy cells. Researchers can attach molecules called ligands to the nanocrystals, which bind specifically to these receptors. When the nanocrystals reach the cancer cell, they get taken in through a process called receptor-mediated endocytosis, delivering the drug exactly where it's needed.[57]

- *Brain Cancer:*

Treating brain cancer is highly complex because the blood-brain barrier (BBB) blocks most medicines from reaching the tumour cells. Researchers have found a way to sneak drugs past this barrier using special nanocrystals coated with a lipid membrane. These nanocrystals are like tiny crystals that contains the drug straight to the brain. When these nanocrystals reach the brain, they disrupt the cancer cells' ability to create new blood vessels, starving them of nutrients, and ultimately killing them. This new approach could be a game-changer for treating brain cancer.[57]

➢ *Drug Delivery Using Nanocrystals:*

- *Oral:*

Oral medication is the most convenient way to take medicine, and nanocrystalline-based medicines are making it even better. These medicines come in various forms like liquids, tablets, and capsules, making it easier for patients to take them. A great example is Rapamune, a nanocrystalline form of sirolimus, a medicine used to prevent organ rejection. It was the first nanocrystalline product comes to the market and is available as tablets and oral suspension. The original formulation of sirolimus was a liquid solution that was tricky to handle and store, but the nanocrystalline version solved these problems. Rapamune tablets are not only easier to take, but they also increase the medicine's effectiveness by 27% compared to the old liquid solution. This means patients get the right amount of medicine with fewer hassles, leading to better treatment outcomes.[58]

➢ *Cellulose Nanocrystals in Pharmaceutical Industry:*

- *Drug Delivery Carrier:*

Scientists have found new ways to control how medicines are released in the body using special materials called cellulose nanocrystals (CNCs). These CNCs are made from microcrystalline cellulose, a common ingredient in medicines, and have a negative charge on their surface. To make them work better, researchers added a special molecule called CTAB, which neutralizes the negative charge. This allows CNCs to bind to cancer-fighting medicines like docetaxel and paclitaxel and release them slowly over a few days. They also created a new material called polyelectrolyte macro-ion complex (PMC) by attaching chitosan, a natural polysaccharide, to CNCs. This PMC has potential uses in delivering medicines to the right place in the body.[59]

- *Doped Nanocrystals in Imaging:*

When it comes to seeing inside the body, doctors use techniques like CT scans, MRI, and fluorescence imaging. But these methods need special helpers called contrast agents to make things visible. For fluorescence imaging, materials need to be excited by specific light wavelengths. Quantum dots are tiny particles that shine brightly when exposed to UV light, making them super useful for bioimaging. The cool thing about quantum dots is that their emission wavelength can be tuned, meaning they can produce different colors of light. By tweaking things like the Cu/In ratio or adding silver, scientists can make quantum dots emit light from visible to near-infrared, making them perfect for spotting tiny details in the body.[60]

## VI. CONCLUSION

Nanoparticles have emerged as a transformative platform in biomedical science, offering unique physicochemical properties that enable advances in diagnostics, targeted drug delivery, imaging, and therapeutic interventions. The continuous development of novel synthesis techniques ranging from chemical and physical methods to eco-friendly biological approaches has enhanced control over particle size, morphology, and surface

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functionality, thereby improving their biocompatibility and clinical potential. Despite remarkable progress, challenges such as large-scale reproducibility, long-term toxicity was remaining as a hurdle to clinical translation. Further research should be precise on integrating interdisciplinary strategies to optimize nanoparticle design, ensure safety, and harness their full potential in precision medicine. As our understanding deepens, nanoparticles are playing important role in shaping the biomedical innovation greatly.

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