Journal of Physical Chemistry and Functional Materials

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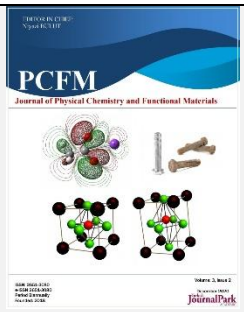

Nano Pharmaceuticals: A Comprehensive Review on Chemistry, Nanostructures, and Advanced in Drug Delivery Applications

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ABSTRACT

This review provides an in-depth analysis of nanopharmaceuticals, focusing on their chemistry, nanostructures, and advanced drug delivery applications. Its highlights molecular design, synthesis techniques, synthesis techniques, and functionalization strategies that enable nano pharmaceuticals to revolutionize therapeutic delivery, The review also outlines key challenges such as stability, scalability, and regulatory compliance. In conclusion, nano pharmaceuticals hold transformative potential in advancing personalized medicine through controlled and targeted drug delivery. Future developments will depend on innovation in overcoming current limitations and ensuring clinical translation.

This review presents a comprehensive overview of nanopharmaceuticals, emphasizing their chemistry, nanostructures, and advancements in drug delivery applications. It highlights molecular design, synthesis methods, and functionalization strategies that empower nanopharmaceuticals to revolutionize therapeutic delivery. Additionally, the review addresses critical challenges such as stability, scalability, and regulatory compliance, which must be navigated for successful clinical implementation. Nanopharmaceuticals represent a promising frontier in personalized medicine by enabling precise, controlled, and targeted drug delivery. In summary, nanopharmaceuticals have the potential to significantly enhance drug efficacy and patient outcomes. Continued research and innovation are essential to overcome current barriers and translate laboratory advancements into safe and effective clinical solutions. The future of drug delivery lies in the integration of smart nanomaterials, interdisciplinary collaboration, and rigorous regulatory frameworks.

ARTICLE INFO

Keywords:
Nano pharmaceuticals, Drug Delivery, Nanostructures, Chemistry Applications, Molecular Design

Received: January 31, 2025
Accepted: May 2, 2025
ISSN: 2651-3080
DOI: 10.54565/jphcfum.1630835

1. INTRODUCTION

Nanopharmaceuticals represent a cutting edge intersection of nanotechnology and pharmaceutical sciences, focusing on the creation of nano-sized drug delivery systems, which these materials typically ranges between 1 and 100 nanometers, possess unique characteristic that can make them highly effective for medical applications, like drug delivery, diagnostics, and therapeutics [1, 2]. Nanotechnology involves manipulating materials like atomic or molecular scale, has revolutionized drug design and delivery [3]. By operating at the nanoscale, these materials exhibit distinct physical, chemical, and biological characteristic that traditional formulations cannot match, these properties enable enhanced drug localization, controlled release, improved solubility, and increased

bioavailability [4]. The integration of nanotechnology into pharmaceuticals has been transformative. Nanopharmaceuticals can target specific sites within the body more precisely, reducing side effects and improving therapeutic outcomes [5]. This precision is particularly beneficial for treating complex diseases such as cancer, where targeted drug delivery can significantly enhance treatment efficacy, Nanopharmaceuticals can cross biological barriers that traditional drugs cannot, such as the blood-brain barrier, opening new avenues for treating neurological disorders [2]. The ability to engineer these materials at the nanoscale allows for the development of multifunctional systems that can diagnose, deliver therapy, and monitor treatment progress simultaneously. Overall, Nanopharmaceuticals hold great promise for advancing medical science by providing more effective, targeted, and safer therapeutic options. As research in this field progresses, we can expect to see even more innovative applications that will further enhance the capabilities of modern medicine[6].

2. MATERIAL AND METHOD

2.1. Chemistry of Nano pharmaceuticals

The Chemistry of Nano Pharmaceuticals is a fascinating blend of molecular precision and technological innovation, holding immense potential to transform health care. The makeup characteristics of chemicals of nanoscale material used in drug delivery can include: organic molecules, polymers, lipids, and inorganic compounds. Each possesses distinct features that make them ideal for therapeutic use.

2.2. Molecular Design and Functionalization

Nanostructures (NSs) have good character due to their small size, which ranges from 1 to 100 nanometers. Their chemical composition significantly impact their action for example , the surface chemistry of Nano Particles (NPs) affects their reactivity, stability, and interactions with other materials and they exhibit unique electrochemical character because of their high surface area, Understanding their redox behavior is critical for applications in batteries, sensors, and catalysis [7].

There are several chemical properties that affect (NSs) formations which are:

a) Size Effects on Properties: NSs exhibit unique quantum confinement outcome, leading to separate electronic states and changes of the optical band gap. This affects the chemical reactivity of oxides, which generally possess wide band gaps and low reactivity in their bulk state [8].

b) Surface Properties: NSs have modified surface properties compared to their bulk coequal. The presence of under coordinated atoms and vacancies enhances chemical activity. The modification greatly alter surface properties such as sorption and acid\base behavior [8, 9].

c) Chemical Reactivity and Stability: The surface reactivity of NPs is essential for their use in catalysis, environmental control and sensor devices .The chemical reactivity of NPs is greatly influenced by their high surface to volume ratio and modified local geometries at their surface sites [8]. Attaching stabilizing agents and functional groups to NPs helps prevent them from aggregation [7].

d) Intermolecular Interactions: The self-assembly process is influenced by various interactions such as van der waals forces, electrostatic interactions, and hydrogen bonding. The equilibrium among these forces dictates the ultimate structure of the NPs assembly [7, 9].

e) Self-Assembly of NPs: Creating molecular components that naturally form into specific nanostructures is essential. The selection of these components, based on their chemical characters and the conditions under which they assemble is critical in defining the final structure and function of the NPs [7]. The figure shows that the self-assembly process of NPs. At First, the individual NPs come together to form intermediate structures, after that, they encapsulate into a completely NPs structure assembly.

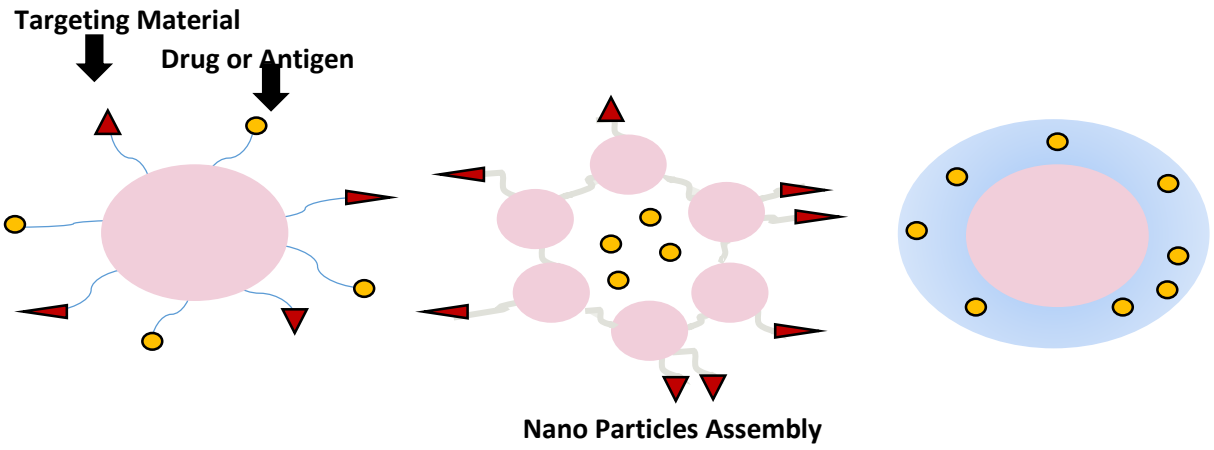

Figure 1. Nanoparticles self-assembly

To enhance tissue targeting and cellular uptake NPs can be functionalized by modifying their surface character with specific molecules, key methods include:

a) Ligand Attachment: By attaching ligands such as antibodies or peptides to NPs, they can be directed to specific cells or tissues. These ligands bind to receptors on target cells, ensuring precise delivery of drug payload [10].For example ligands can be linked to polymer chains using N-hydroxysuccinimide (NHS) chemistry, studies have shown that increasing the local density of ligands can improve integrin binding and promote osteogenic differentiation [11].

b) Polymer Coating: coating NPs with polymers like polyethylene glycol(PEG) enhance their stability and biocompatibility, reduce immunogenicity, and extend their circulation time in bloodstream [12], The processes involved in polymer coating, such as activation of functional groups with EDC/NHS and the use of initiators for polymerization [13].

c) Cationic Polymers and Peptides: These substances can be utilized to alter the surface characteristics of NPs, facilitating endosomal escape and improving drug delivery efficiency by exploiting the proton sponge effect [10].

d) Chemical Conjugation: Reactive groups such as NHS (N-hydroxysuccinimide) and EDC(1-ethyl-3-(3dimethylaminopropyl)carbodiimide)can be utilized for conjugate therapeutic agents and targeting ligands to nanoparticles under mild conditions, preserving the activity of sensitive biological molecules [10, 12]. Figure 2 shows how nanoparticles can be customized with different ligands to target specific cells.

Nano pharmaceuticals are designed to enhance drug delivery by exploiting the unique properties of nanoparticles. One key application is controlled drug release, which aims to achieve specific release kinetics for therapeutic benefits while minimizing side effects. Figure 3 shows how a drug is gradually released over time from a controlled delivery system. The y-axis represents the percentage of drug released, while the x-axis corresponds to time. This controlled release ensures therapeutic effectiveness without harmful toxicity.

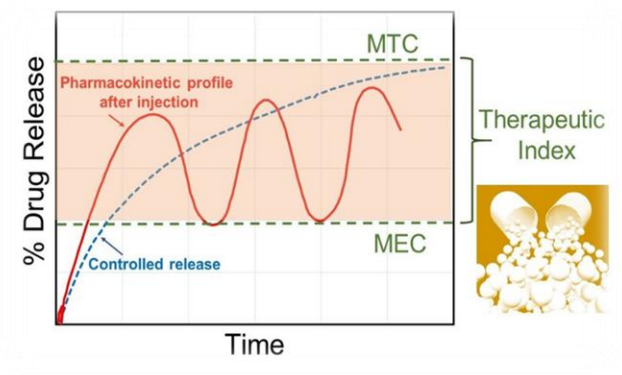

Figure 2. Time dependent drug release profile

e) Surface properties: The surface character of NPs, like surface charge, hydrophobicity, and the presence of targeting ligands, significantly influence drug release kinetics and targeting efficacy:

• Surface Modification: (PEG) polyethylene glycol can minimize opsonization and extend circulation time (a process known as PEGylating) [16].

• Targeting Ligands: By attaching ligands that interact with specific receptors on target cells, the precision of drug delivery can be improved leading to better therapeutic results [15].

Figure 4 shows that Nanoparticles impact drug release profiles through factors like size, surface chemistry, shape, and structure.

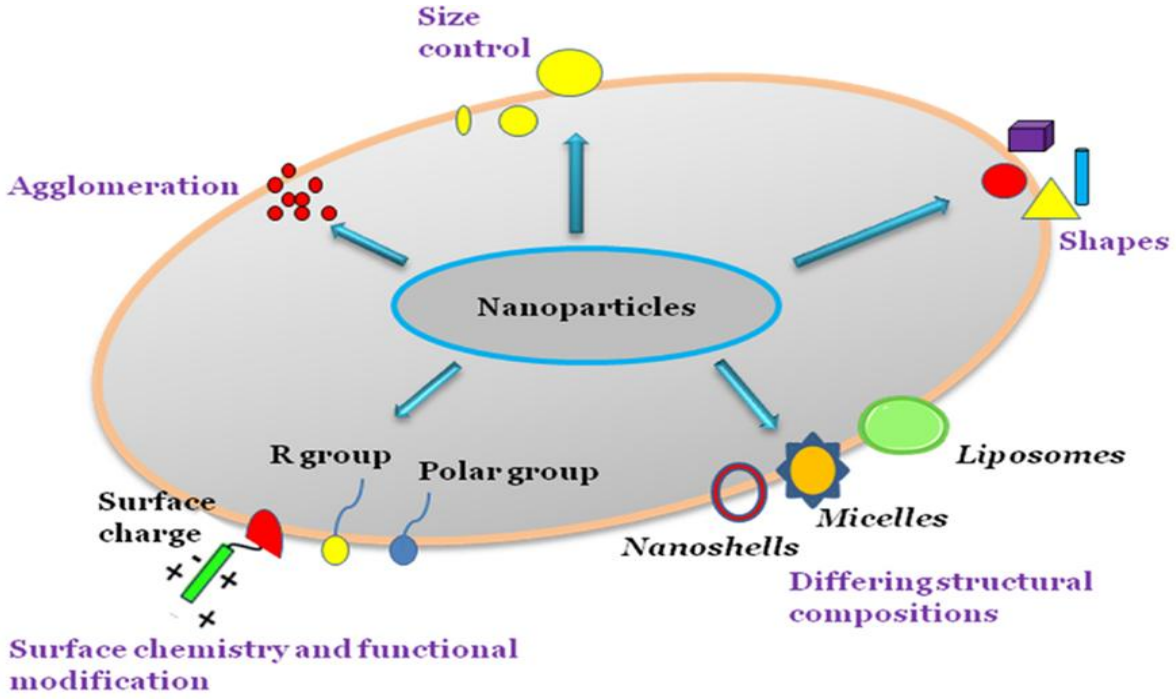

Figure 3. Controlled Drug release profile

There are strategies for controlled drug release which are:

1) Sustained Release: Achieving sustained drug release involves designing nanoparticles that release their payload over extended periods. This can be accomplished through:

- Biodegradable Polymers: Employing polymers such as PLGA, which slowly break down and dispense the medication in a regulated fashion [17].
- Matrix Systems: Embedding the drug in a polymer structure that gradually breaks down or expends to release medication [17].

2) Triggered Release: Triggered drug release utilizes external or internal stimuli to control the release of drug at specific periods or locations:

- Exogenous Triggers: Such as temperature changes (thermoresponsive polymers), light (light-responsive materials), or ultrasound [18].
- Endogenous Triggers: Like changes in pH, redox conditions, or enzymatic activity within the target tissue (e.g., tumor microenvironment) [18].

3) Site-Specific Release: Site-specific drug release aims to concentrate the drug at the desired location, reducing systemic side effects:

- Targeting Moieties: Employing antibodies, peptides, or small molecules that selectively attach to markers on the target tissue [19].
- Environmental Sensitivity: Designing nanoparticles that respond to the unique biochemical environment of the target site, such as acidic pH in tumors or inflamed tissues [19].

f) Modification of Nanoparticles by Schiff base

Schiff bases are intriguing organic compounds characterized by an azomethine group (-C=N), formed when a primary amine reacts with aldehyde or ketone. These compounds can form stable complexes with metal ions, leading to applications in antimicrobial agents, antioxidants, and catalysts [20].

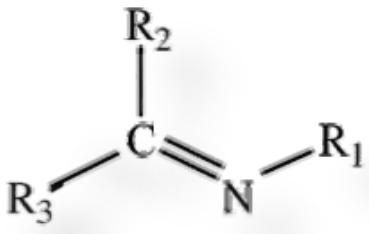

Figure 4. General structure of Schiff Base

When Schiff bases are combined with nanoparticles, they exhibit enhanced properties. For example, $Fe_3O_4.SiO_2$ core-shell nanoparticles functionalized with Schiff bases and copper (II) ions show increased apoptosis in cancer cells. The synthesis involves coating Fe_3O_4 nanoparticles with a SiO_2 shell, functionalizing with (3-aminopropyl)

triethoxysilane (APTS), and reacting with an aldehyde to form Schiff base ligands [21]. These Schiff base-functionalized nanoparticles also find use in catalysis. Their metal-Schiff base complexes create robust, recyclable catalytic systems. Overall, integrating Schiff bases and nanoparticles offers exciting possibilities in biomedical applications and catalysis [22].

2.2. Nanoparticle Synthesis Techniques

Synthesis techniques are important for creating nanoparticles(NPs) for drug delivery in general there are two categories , which are top-down and bottom-up approaches [23]. Figure 5 shows the classification of NPs Synthesis based on physical and chemical approaches.

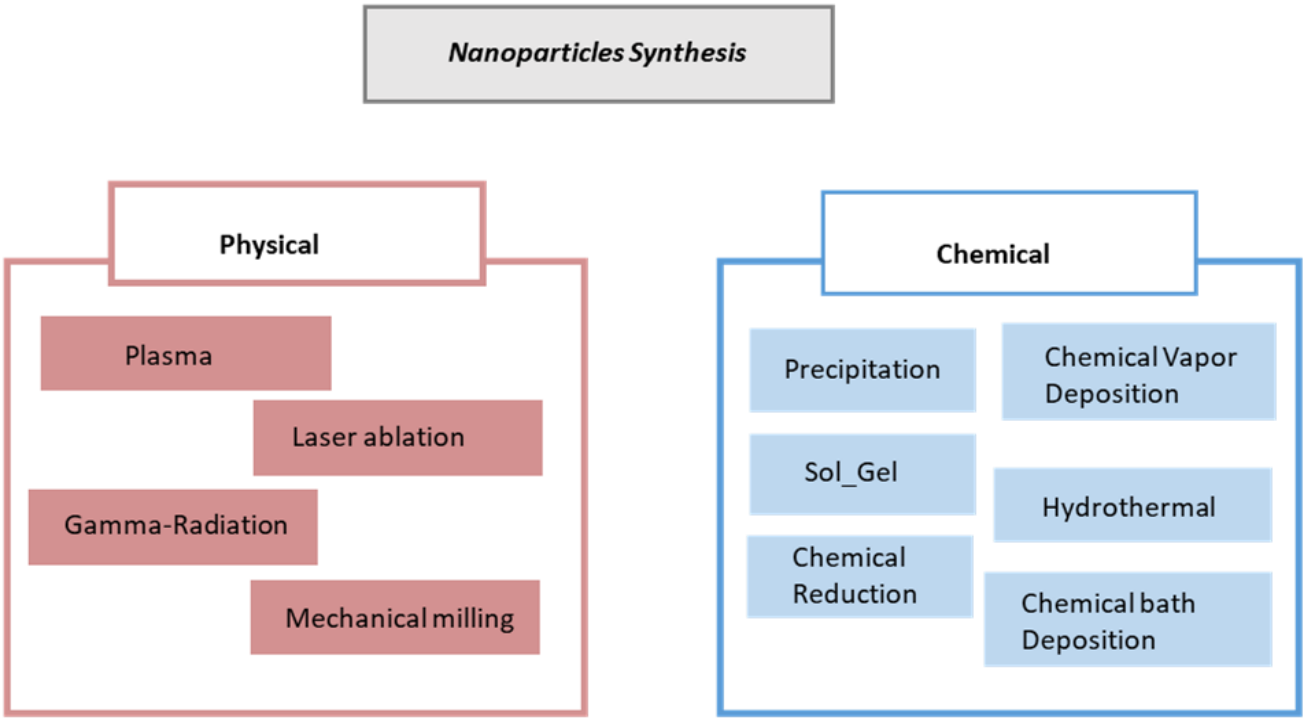

Figure 5. Classification of synthesis NPs, including physical and chemical routs

In top-down synthesis, nanoparticles are made by breaking down larger molecules. this can cause surface imperfections, which affect the nanoparticles surface chemistry and physical properties [3], the techniques include:

a) Mechanical Milling (MM): is a process used to create nanomaterials by grinding and blending powders in a high-energy mill, the main goal is to reduce particles size and form new material phases, MM is efficient and cost-effective for producing nano-sized materials on a large scale [24], The efficiency of MM Depends on factors like milling speed, ball size, and milling duration, high density materials like steel which is alloy of Carbon and iron or Tungsten carbide are preferred by milling balls due to their higher kinetic energy [25], Temperature also influences the milling outcome, affecting phase transformations. Higher temperatures promote phases needing high atomic mobility, while lower temperatures favor amorphous phase formation [25].

However, mechanical milling often results in non-uniform size distribution and achieving a uniform size can be challenging because high mechanical energy applied during process of milling [26].

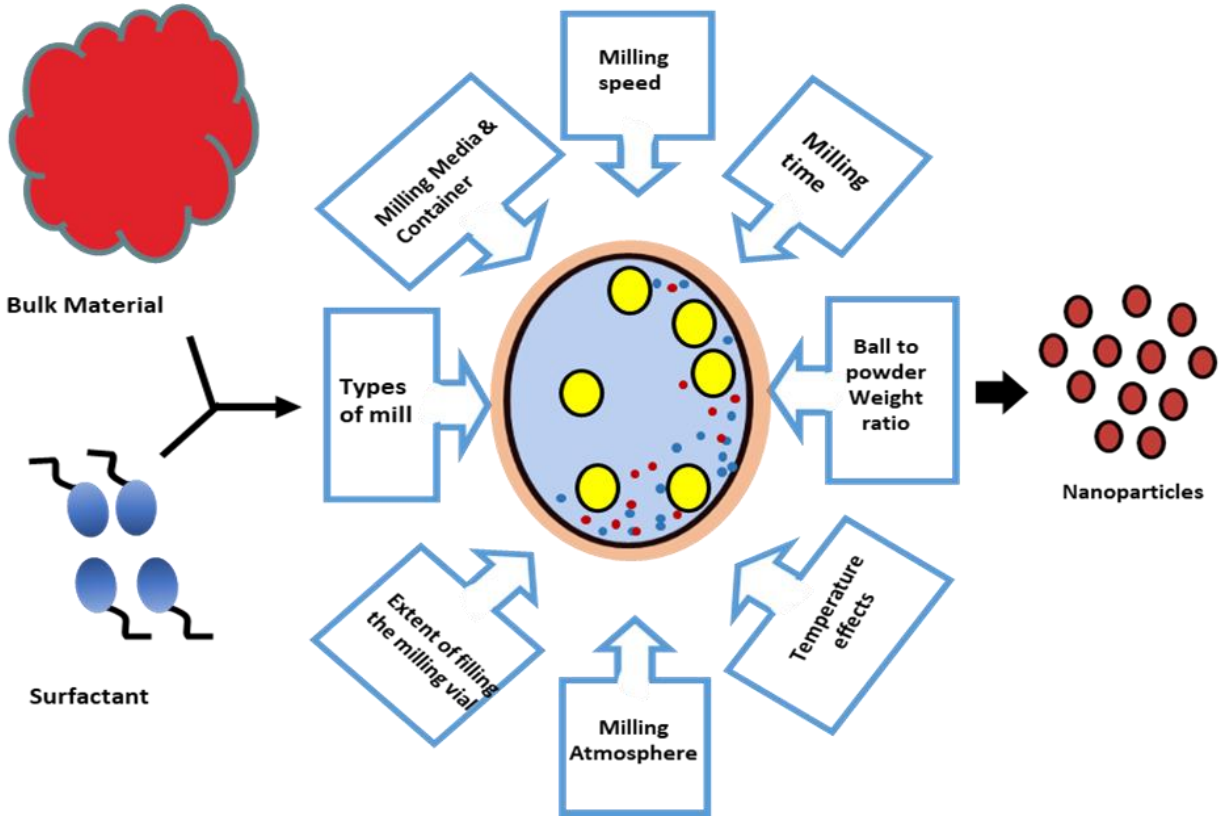

Figure 6. Factors affecting NPs synthesis by mechanical milling technique

b) Laser Ablation: is a method for creating nanoparticles by directing a laser beam at a solid target which acts as stationary phase in a gas or liquid medium serves as mobile phase [27], the laser heat vaporize the target forming a plasma plume of atoms and clusters, the plume properties such a size and emission spectrum are influenced by the target(Solid) material surrounding medium , pressure , and laser settings. Laser ablation creates high-purity NPs with precise control over their sizes and shapes [28].

However Synthesis of (NPs) by laser ablation method needs high energy consumption, limited production scale, equipment costs are expensive, difficult particle size control and material waste [29].Figure 6 shows that Nps synthesis by laser ablation process which include first, evaporation of targeted material by heat of laser to form of plasma then nucleation process occurs and finally agglomeration which means the primary particles can clump together to form larger structure into NPs.

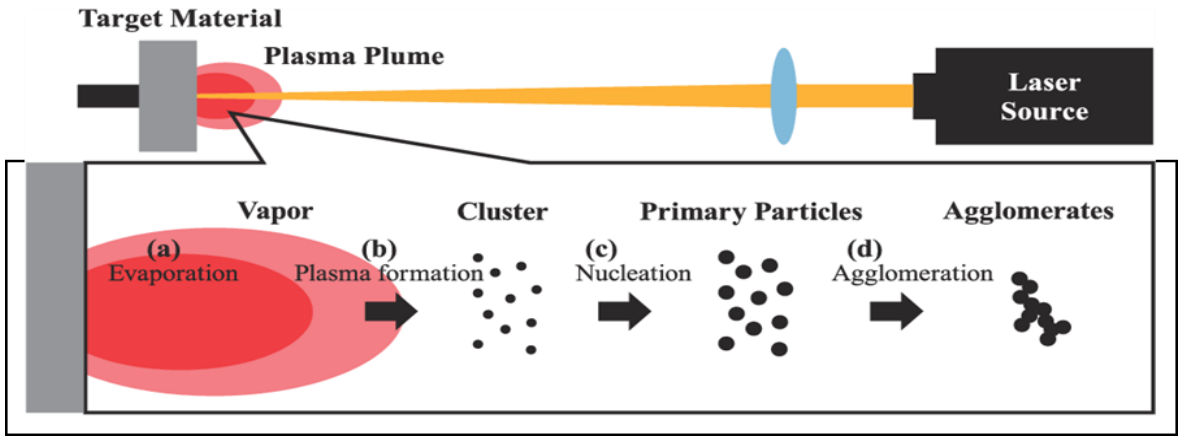

Figure 7. Diagrammatic of particle generation procedure in the laser ablation process

c) Thermal Decomposition: It is common approach for synthesizing nanoparticles like iron(II)oxide FeO, a metal complex like iron(III)acetyl acetone decomposes in the midst of high-boiling organic solvent and surfactants, this method is recognized for producing high-grade NPs with small size, narrow distributions of size and high crystallinity NPs which is very stable in organic solvents [30]. The thermal decomposition method has some drawbacks, including the requirement of working under stable atmosphere, very high reaction temperatures, and long time needed, leading to highest energy and time consumption and Non-uniform Particle Size Distribution [31].

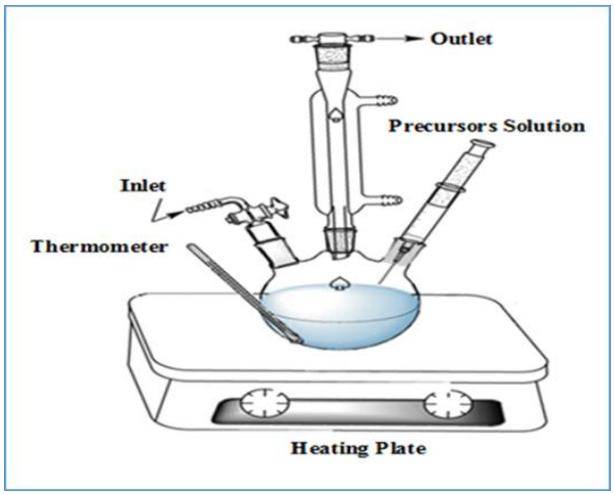

Figure 8. NPs Synthesis by thermal decomposition process

In bottom-up synthesis nanomaterial are created by assembling from atoms or molecules through chemical reactions , this method enables particles of the precursor to grow in size while minimizing structural defects , resulting High-quality nanomaterials [3] , techniques include :

a) Green synthesis: it is an eco-friendly method using plant extracts or microbial agent , converts metal ions into nanoparticles this technique avoids toxic chemical and harsh physical condition , green synthesis typically involves plant extracts or microbial enzymes that acts as reducing agents, which results unique properties of the nanoparticles , green synthesis occurs as in-vitro [32-34]. However bacteria may be not a very sufficient way to synthesis NPs due to Toxicity Concerns of NPs to plants, animals, and humans requires comprehensive toxicological studies to ensure safety in various applications [35].

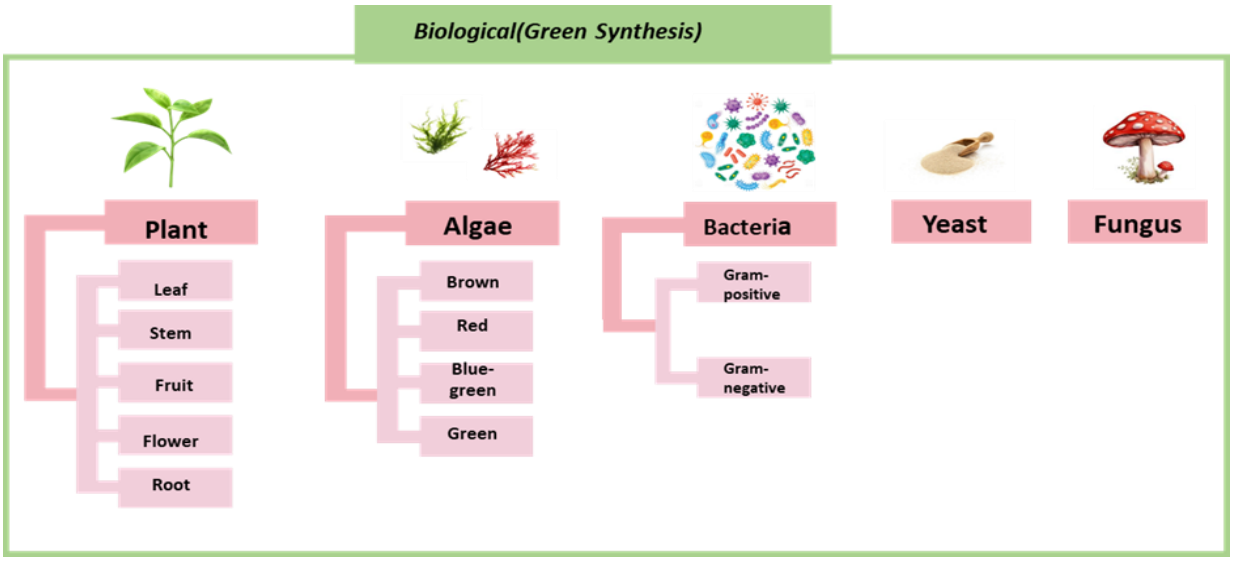

Figure 9. Biological synthesis

a) Sol-Gel method: The wet chemical method entails transforming a system from liquid to sol which is typically colloidal into a solid gel phase ,it is widely used chemical synthesis approach to prepare high-quality metal oxide nanoparticles (MONPs) and mixed oxide composites which the process involves (Hydrolysis, polycondensation, Aging, Drying and Thermal decomposition) [36] , In the sol-gel method first, metal alkoxide can be dissolved in water or alcohol then converted to a gel through hydrolysis or alcoholysis with heating and stirring, finally, The wet gel is dried, often by burning off the solvent, and the resulting dried gels are powdered and calcined [37].However drying process is comprehensive in sol gel method because water and organic components must be removed from the gel, which can disturb its structure [36].

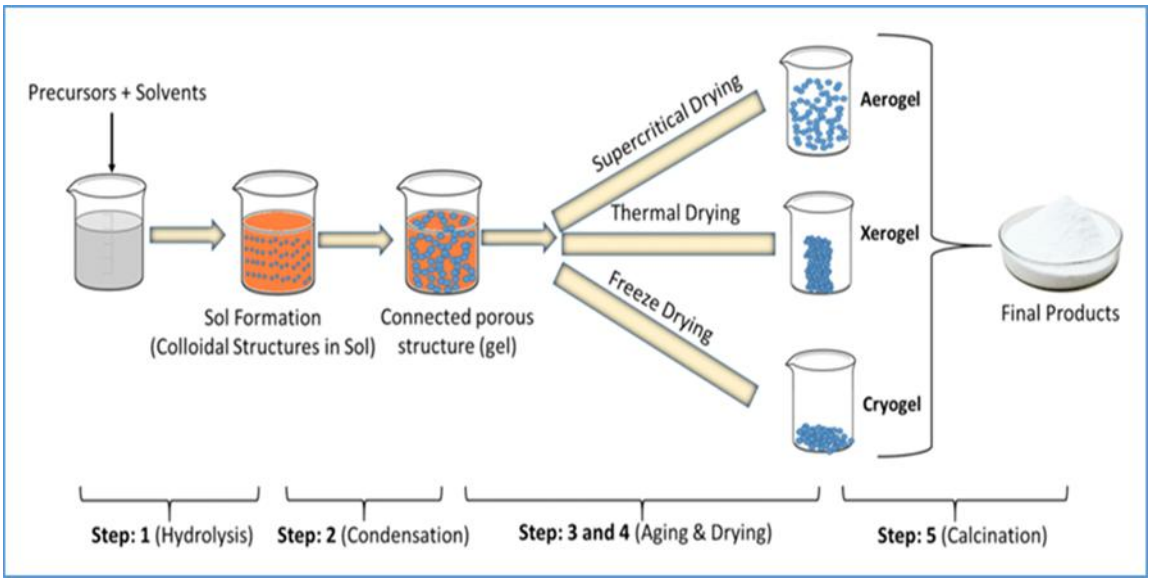

Figure 10. Steps involved in sol-gel method

b) Hydrothermal Synthesis: This technique uses high- temperature and high- pressure water to crystallize materials from solution. It's particularly useful for producing NPs with shape and size controlled , and is often used for synthesizing metal oxides and other inorganic materials [38], The reaction temperature strongly influenced the particle. Higher temperatures lead to bigger particle sizes because of the changes in the growth rate between different crystallographic planes, The hydrothermal synthesis method offers several advantages, including the ability to obtain nanometer-sized powders under moderate conditions, control over particle morphology and properties by adjusting reaction parameters, and a simple, cost-effective, and environmentally-friendly process, However hydrothermal process is difficult to control due to inert required conditions [26].

Each technique presents unique benefits and obstacles, particularly in managing the size, shape, and surface features of nanoparticles. These factors significantly influence their interactions within biological systems. Therefore, it is essential to customize nanoparticles with precise attributes to suit various applications, such as drug delivery.

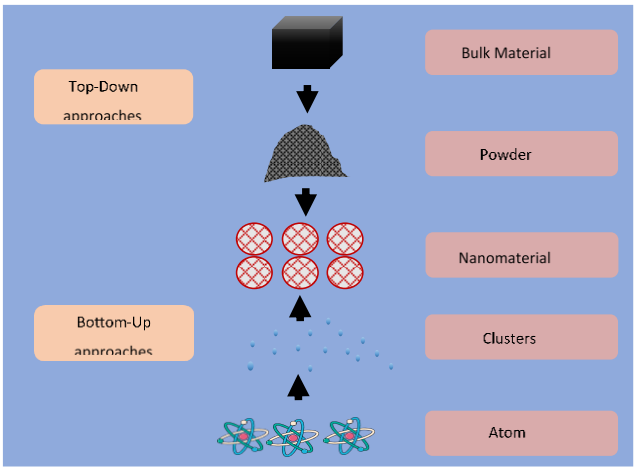

Figure 11. Common NPs synthesis approaches

3. RESULTS AND DISCUSSIONS

3. Nanostructures in Drug Delivery:

NSs (Nanostructures), leading the charge in contemporary medical advancements, hold immense promise for targeted drug delivery. These minuscule carriers ranging from liposomes to polymeric nanoparticles initiate a groundbreaking phase in precision medicine. By encapsulating therapeutic agents, they enhance solubility, reduce toxicity, and ensure drug delivery to designated areas within the body. In this exploration, we unravel the secrets of these tiny allies and their pivotal role in revolutionizing pharmaceutical science [39, 40].

3.1. Lipid-Based Nanocarriers

Lipid-based nanoparticles have shown potential as an effective delivery method in recent years, with liposomes being a standout option due to their versatility and unique properties. These lipid-based structures provide several benefits for drug delivery, possessing the capability to

precisely control drug release duration, improve bio distribution, and improve permeability. However, safety considerations remain crucial when exploring the anticipated applications of these Nano carriers in the pharmaceutical and food industries [41-43] describes so many types let's divine into this here:

3.1.1. Liposome

Nano carriers are versatile class of delivery systems, and liposomes are a particularly promising type of Nano carriers, as a nanotechnology-based approach, liposomes Due to their distinctive structural characteristic and potential benefits they have attracted considerable interest in drug delivery. Liposomes are a remarkable type of drug delivery vehicles that have captured the consideration of researchers and clinicians alike [44] ,These tiny spherical vesicles exhibit distinctive structural and functional characteristics which can make them promising platform for the controlled and targeted delivery of different therapeutic agents [43]. Liposome can be prepared through a series of steps. Initially, phospholipids and cholesterol can be dissolved in organic solvent, forming a thin lipid film. Hydration with aqueous solution leads to multilamellar vesicles (MLVs). Ultrasonic energy reduces the MLVs to small unilamellar vesicles (SUVs). Extrusion through polycarbonate membranes ensures uniform size distribution. Finally, detergent removal yields liposomes [45, 46].

a) Structure and Composition: Liposomes consist of phospholipid bilayers, mimicking natural cell membranes, The hydrophilic heads face outward, while the hydrophobic tails form the inner core, This structure allows liposomes to encapsulate drugs, proteins, or nucleic acids [47].

b) Evolution and Enhancements: Early liposomes primarily used natural phospholipids like phosphatidylcholine, Challenges included stability issues and rapid clearance from the bloodstream Researchers introduced modifications [48]:

- PEGylating: Applying polyethylene glycol (PEG) to the surface of NPs grants them stealth properties.
- Cholesterol: Enhancing membrane stability.
- Targeting Ligands: Adding molecules for tissue-specific delivery.

Overall liposomes provide an innovative approach for drug delivery, with tunable properties and applications for the treatment of conditions such as cancer and infections. Their stability and altering the surface properties is essential for optimizing drug release and targeting specificity [49, 50].

3.1.2. Solid lipid nanostructures (SLNs)

SLNs are microscopic particles created from safe and biodegradable lipids. They act as an innovative method to transport drugs [51]. taking the benefits of traditional liposomes and polymeric NPs while reducing their drawbacks, they have ability to enclose a variety of drugs, safeguarding them from breakdown and enhancing the stability and effectiveness of the enclosed drug [52]. SLNs can be synthesized using several techniques. Solvent Emulsification-Diffusion Method. These techniques encompass High Pressure Homogenization (HPH), Ultra sonication/High-Speed Homogenization, Solvent Evaporation, Solvent Emulsification-Diffusion, Supercritical Fluid method, Microemulsion-Based approaches, Spray Drying, and Double Emulsion processes. Each method has its own advantages and limitations, the choice is based on factors such as drug solubility, lipid type, and intended administration route [46].

Structure and Composition: The core of an SLN is made up of a solid lipid material, which can include a variety of lipids like triglycerides, partial glycerides, fatty acids, waxes, and sterols this solid lipid core encapsulates the drug that is to be delivered. Surrounding the solid lipid core is a stabilizing layer of surfactants [53]. These surfactants can be non-ionic, ionic, or amphiphilic. Aim of this surfactant layer is to offer stability on the whole SLN structure and prevent aggregation [54]. The combination of the solid lipid core, the stabilizing surfactant layer, and any additional layers or coatings results in the exceptional structure and composition of SLNs, so that it can be tailored to meet the specific requirements of a given drug delivery application [55].

3.1.3. Nano Emulsion

Nano Emulsions (NEs) are formed by dispersing oil and water with help of satiable surfactant, resulting in very small droplet size. These emulsions, which usually have droplets between 20 to 200nms, are used in various fields such as drug delivery, food, cosmetics, and material synthesis. In NEs, the immiscible liquid is dispersed within another, forming tiny droplets [56], NEs can be synthesized through various techniques, which are two methods high-energy methods and low-energy methods. One way to synthesize NEs is through High-Pressure Homogenization (HPH). This process first, starts with a coarse oil-in-water (O/W) emulsion, then passed through a narrow valve at high pressures, typically ranging from 50 to 100 MPa, or even up to ultra-high pressures of 400 MPa [57]. The basic components of a Nano emulsion are:

a) Oil Phase: This phase exists in oil-in-water (O/W) NEs or serves as the continuous phase in water-in-oil (W/O) NEs [58].

b) Aqueous Phase: In O/W Nano emulsions, this phase is continuous, while in W/O NEs, it is dispersed [58].

c) Surfactants: These surface-active agents stabilize the NEs by reducing the tension between the oil and water phases [59].

d) Co-surfactants: Often combined with surfactants, co-surfactants enhance formulation stability and help achieve desired droplet size [59].

The specific structure of NEs varies based on component types, ratios, and preparation methods. High-energy methods like high-pressure homogenization, ultra-sonication and low-energy methods like phase inversion temperature, spontaneous emulsification influence their properties [60].

3.1.4. Nano capsule

Nano capsules, featuring a central core enveloped by a polymeric shell, acts as carriers for active substances such as drugs, enzymes, or bioactive compounds. Their structure allows for controlled release and targeted delivery, making them highly promising for pharmaceutical drug delivery application [61]. NanoCapsule can be produced through several methods, with nanoprecipitation being one of the most efficient. This method involves forming a colloidal suspension by mixing two distinct phases. Researchers can precisely control the particle size by tweaking parameters like polymer concentration and agitation speed. This technique is especially beneficial for bioimaging and targeted drug delivery applications[62].

Structure and Composition

1. Core: the core of the Nano capsule is its innermost part, which can exist in liquid, solid, or even a gaseous state. It houses the active ingredient or drug intended for delivery [63].

2. Shell: The outer layer or coating of the Nano capsule is crafted from biodegradable substances such as polyalkylcyanoacrylate, poly-e-caprolactone, or proteins like bovine serum albumin (BSA) and silk fibroin [64].The material used for shell plays a crucial role in determining the release rate of encapsulated substance and overall stability of NanoCapsule [65].

The core-shell design of Nano capsules ensures efficient encapsulation and targeted delivery of active ingredients. By adjusting the shell material [61, 66].

Over all Nano capsules present a promising method for improving drug delivery system by enabling controlled release and targeted delivery.

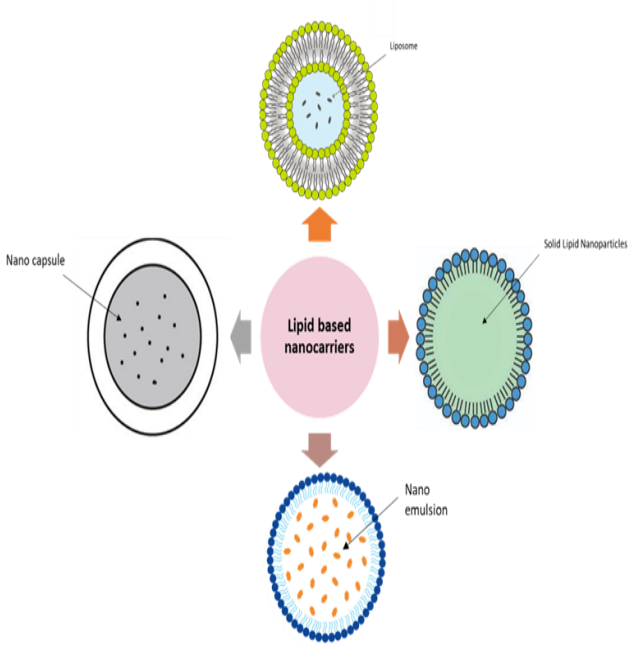

Figure 12. Lipid based nanocarriers

3.2. Polymeric Nanoparticles

Polymer nanoparticles are a remarkable class of nanomaterials composed of polymers that self-assemble into particles in the nanometer range. These tiny particles possess unique characteristic that can make them highly valuable in biomedical applications. One key advantage it is ability to encapsulate and transport therapeutic payloads, improving drug delivery and efficacy. Polymer NPs function as diagnostic contrast mediums for medical imaging, enhancing visualization and enabling earlier disease diagnosis [72]. These nanomaterials can provide scaffolds for promoting cell growth and aiding tissue regeneration, which plays a crucial role in the progress of regenerative medicine. As a versatile platform, polymer nanoparticles show great promise in improving patient outcomes across various healthcare applications [73].

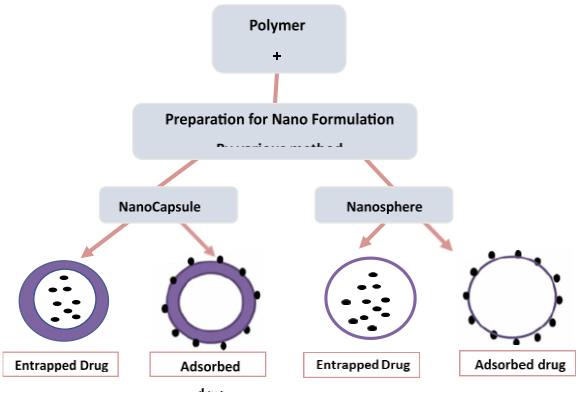

Figure13. Preparation for Nano Formulation by various method

3.2.1. Poly Lactic-co-glycolic-acid (PLGA) Nanoparticles

PLGA stands out as a remarkable biodegradable polymer in drug delivery. Its unique characteristic which make it an attractive choice for designing nanostructures that can efficiently transport therapeutic agents [73]. Emulsification-Solvent Evaporation Technique in this process PLGA can be synthesis first, by making oil-in-water (O/W) emulsion, then by mixing PLGA which dissolved in an organic solvent (e.g., dichloromethane) after that, with an aqueous phase containing a surfactant (e.g., polyvinyl alcohol, PVA) then Sonicate the mixture to form Nano droplets finally ,Evaporate the solvent, leading to PLGA NPs [74].

Key properties of PLGA are:

•**Degradation Rate:** PLGAs degradation across different duration, it depends on the molar ratio of lactide to glycol ide. With ratio 50:50 results the fastest and highest degradation, while ratios like 85:15 or 75:25 lead to slower degradation [75].

•**Biocompatibility and Safety:** PLGA is highly biocompatible, ensuring minimal adverse effects when used in biomedical applications. Also it is degradation products like lactic acid and glycolic acid which are metabolized and then excreted by the body [76, 77].

•**Physicochemical Properties:** Functional carboxylic end groups in PLGA allow covalent bonding with therapeutic agents. This property enables precise control over drug release rates. Additionally, PLGA can form block copolymers with polyethylene glycol (PEG), enhancing shelf stability and altering release kinetics [78].

3.2.2. Chitosan Nanoparticles

Chitosan, resulting from chitin which found in crustacean exoskeletons, has gained attention in biomedical fields. Its biocompatibility, biodegradability, and unique properties make it valuable [79]. Ionotropic gelation is a method for synthesizing chitosan nanoparticles , which start from Preparing a chitosan solution first, dissolving chitosan in an acidic aqueous medium (e.g., acetic acid) and Gradually adding a poly anion solution (e.g., sodium tripolyphosphate) to the chitosan solution while stirring, This ionic interaction leads to chitosan nanoparticle formation [80].After separation, characterize the NPs using methods like dynamic light scattering (DLS) and electron microscopy.

Key properties of Chitosan Nanoparticles are:

•**Biocompatibility:** Chitosan is safe for medical and pharmaceutical use, which is Non-toxic and compatible with the human body [76, 81].

•**Biodegradability:** Chitosan naturally breaks toxic into non-toxic products (glucosamine and N-acetyl glucosamine) [82] .

•**Antimicrobial Properties:** its anti-microbial activity against bacterial and fungi, aiding wound healing and other medical applications [83].

3.2.3. Polymeric Micelles

Polymeric micelles are nanoscale structures which are formed from the self-assembly of an amphiphilic block copolymers in an aqueous solution. These micelles exhibit a core shell architecture, made up of hydrophobic core and a hydrophilic shell. Their unique characteristic make them excellent for drug delivery systems [84]. One method for synthesizing polymeric micelles involves the core first approach. In this method, small gel particles are first formed by polymerizing a bis-unsaturated monomer (such as divinylbenzene) using BuLi in a hydrocarbon solvent. The surface of these particles is then modified with metal organic functions to create a polystyrene shell structure. This results in core-shell polymeric micelles [85].

Key properties of Polymeric Micelles are:

•**Enhanced Solubility:** Hydrophobic core of polymeric micelles can be encapsulate poorly in water soluble drugs, by solubilizing hydrophobic compounds, micelles improve drug bioavailability. This property is important for enhancing therapeutic efficacy of hydrophobic drugs [86].

•**Stability in Biological Fluids:** The hydrophilic shell surrounding the core provides stability to polymeric micelles. In biological environments (such as blood or interstitial fluid), micelles remain intact and prevent aggregation. Stable micelles ensure controlled drug release and prolonged circulation duration [87].

•**Controlled Drug Release:** Polymeric micelles allow achieving meticulous regulation of drug release rates. Factors influencing release include polymer composition, micelle size, and environmental conditions, external stimuli (e.g., pH, temperature, light) can also modulate drug release from micelles [88].

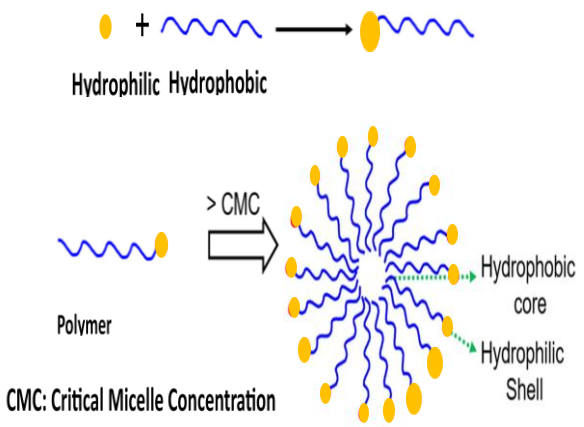

Figure14.Polrymeric Micelles

3.2.4. Polymeric Nanogels

Polymeric Nano gels are hydrogels submicron-dimensions that can form through either physically or chemically cross-linked polymeric chains. These Nano gels develop a three-dimensional (3D) tunable porous structure than can absorb water with a high capacity while remaining intact in an aqueous medium [89]. To synthesize Nanogels Inversion Emulsion Polymerization can be used which in this method involves a water-in-oil polymerization process. The resulting Nanogels exhibit specific surface properties, which can be tailored for targeted interactions [90].

•**High Drug Loading Capacity:** Because of their porous structure and surface area which is large, Nano gels can encapsulate a significant amount of drugs, it is essential for efficient drug delivery systems [91].

•**Biocompatibility and Biodegradability:** Nano gels are created from biocompatible and biodegradable polymers. As a result, they have safety to use in the human body and suitable for in vivo applications [92].

•**Responsive Behavior:** Nano gels can sense the changes in their medium, such as changes in pH or temperature variations. This responsiveness can allow controlled drug release at specific site, which can enhance therapeutic efficacy [93].

Over all Polymeric Nanoparticles, including PLGA and chitosan-based nanoparticles, as well as polymeric micelles and Nano gels, exhibit diverse characteristic that make them suitable for different biomedical applications. PLGA is versatile in drug delivery and tissue engineering because of controlled degradation. Chitosan's mucoadhesiveness and antimicrobial properties are ideal for drug delivery and wound healing. Polymeric micelles can enhance both stability and solubility of drugs, while polymeric Nano gels offer drug loading capacity high and responsive release. These NPs are advancing Nano medicine, providing solutions for gene therapy, drug delivery, and diagnostic imaging.

4. Advanced Applications

1)Targeted Drug Delivery

Referring to a specialized approach where pharmacologically active agents (medicaments) are selectively delivered to targeted locations within the body. The goal is to maximize drug concentration at the intended location of action while minimizing exposure to non-target organs and tissues. By doing so, targeted drug delivery improves treatment effectiveness and minimize side effects associated with systemic drug administration [94].

Figure 15. Targeted Drug Delivery system

•**Basic Principles and Mechanisms and Applications:**

a) Pharmaceutical Carrier: The medication is paired with a uniquely designed molecule or system that guarantees efficient delivery to the targeted sites. This carrier must be non-toxic, non-immunogenic, biochemically inert, biodegradable, and biocompatible [95].

b) Controlled Release: The drug-targeting system must exhibit a predictable and controllable release of the drug, be readily eliminated from the body, and minimize drug leakage during transport [96].

c) Controlled Bio distribution: Targeted delivery helps in modulating pharmacokinetics and controlling bio distribution, which ensures that the drug is concentrated in the target area without affecting non-target compartments [95].

d) Nanoparticles (NPs): NPs are often employed as drug carriers because of ability to deliver higher doses of drugs without increasing toxicity. These carriers can be directed to specific tissues or cells passively or actively, which improves accuracy and efficiency of drug delivery.

f) Cancer Treatment: Targeted drug delivery is especially beneficial in cancer therapy, as it can focus anticancer medications on tumor sites. This approach minimize harm to healthy tissues and addresses issues such as multidrug resistance [97].

•Nanoparticle-Mediated Drug Delivery: Nanomedicine has transformed drug delivery by introducing a variety of innovative techniques to enhance the effectiveness and safety of treatments. Utilizing the unique characteristics of nanomaterials, NPs based drug delivery systems have become a promising solution to overcome the challenges associated with conventional drug formulations[96].

NPs utilized in drug delivery can be divided into three primary categories: liposomes, polymer-based carriers, and inorganic nanoparticles. Liposomes, which are vesicles composed of phospholipid bilayers, can encapsulate both water-soluble and fat-soluble drugs, thereby improving their bioavailability and stability. Polymer-based carriers, such as PLGA. Inorganic nanoparticles, including those made of metals and metal oxides, possess distinctive optical and magnetic properties, making them ideal for theranostic applications, which combine diagnosis and therapy [98].Nps can be infused with medications through methods like adsorption, encapsulation, and surface attachment. Once loaded, these nanoparticles can be directed to specific cells or tissues using passive strategies, such as the enhanced permeability and retention (EPR) effect, or active strategies, which involve ligand-receptor interactions [99].

2) Theranostic Nanosystem

Theranostic nanosystems are at the forefront of personalized medicine, offering a sophisticated blend of therapeutic and diagnostic functions. These advanced nanoparticles are designed to deliver cancer treatments directly to tumors while simultaneously providing real-time monitoring of the treatment's effectiveness. By integrating therapeutic agents, such as chemotherapy drugs, with imaging markers like fluorescent dyes, these systems enable precise targeting of cancer cells. This targeted approach not only enhances the efficacy of the treatment but also reduces side effects by limiting the exposure of healthy tissues to the drugs. Consequently, theranostic nanosystems improve treatment outcomes and minimize adverse effects for patients [102].

•Multifunctional Design: Theranostic NPs are intentionally designed to serve multiple functions simultaneously. They integrate both therapeutic and diagnostic functions into single system. The therapeutic component delivers drugs (such as chemotherapy agents) to the tumor site, while the diagnostic component provides real-time imaging feedback [102].

•Targeted Drug Delivery: These nanoparticles are engineered to specifically target cancer cells. They can be modified with ligands or antibodies that can recognize tumor receptors. By increasing the drug concentration payload at the tumor site, Theranostic nanosystems reduce exposure to healthy tissues, minimize side effects [103].

•Imaging Modalities: Various imaging techniques can be incorporated into theranostic nanosystems:

a) Magnetic Resonance Imaging (MRI): Nanoparticles containing paramagnetic or superparamagnetic materials enhance contrast in MRI scans [104].

b) Computed Tomography (CT): NPs with elements which have high atomic number (e.g., gold) enhance CT imaging [105].

c) Nuclear Imaging (PET/SPECT): Radioactive isotopes can be incorporated for molecular imaging [106].

•Real-Time Monitoring: During treatment, clinicians can monitor the nanoparticles' behavior in real time using the chosen imaging modality. This monitoring helps assess drug delivery efficiency, tumor response, and potential adverse effects [103, 107].

•Personalized Medicine: Theranostic nanosystems enable personalized treatment strategies. Clinicians can adjust drug dosages based on the individual patient responses.

•Challenges and Future Directions: Challenges include ensuring biocompatibility, scalability and stability, of these nanoparticles, Researchers do continue to explore novel materials, surface modifications [108].

In summary, theranostic nanosystems offer a powerful combination of targeted therapy and real-time imaging. Their potential impact on personalized medicine is immense Theranostic nanosystems leverage the advantages of Nano medicine to revolutionize cancer treatment [108].

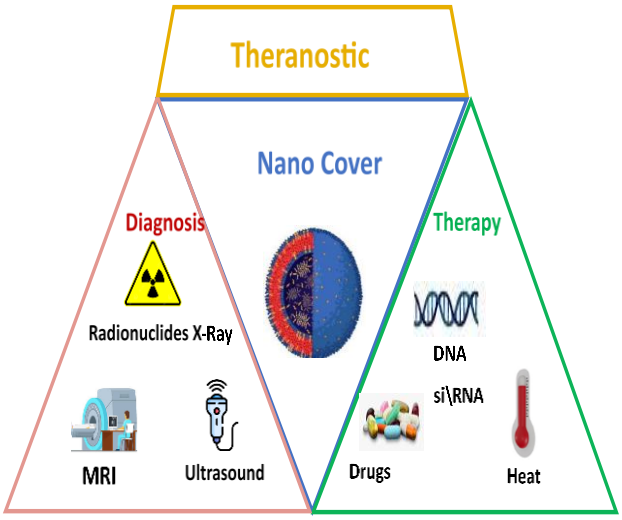

Figure16. Theranostic System

5. Challenges and Future Perspectives:

This section discusses current challenges in the field, including toxicity concerns, regulatory barriers, and issues related to mass production, and future perspectives which delves into the future prospects of Nanomedicine, examining new trends, possible advancements, and the changing landscape of this vibrant field.

Key challenges associated with Nps (Nano pharmaceutical), particularly for cancer treatment:

a) Stability and Formulation Challenges

•**Self-Aggregation and Size Control:** Nps often face significant stability issues because of their propensity to self-aggregate when the drug concentration low. For instance, the Nano-formulated version of the chemotherapeutic agent doxorubicin has demonstrated this problem, where the aggregation of nanoparticles has resulted in a decrease in its anticancer effectiveness [106, 109].

•**Swelling Mechanism in Drug Delivery:** Some Nps utilize a swelling mechanism to facilitate the release of the drug at the targeted location. While this approach can enhance the precision of targeted drug delivery, it also poses challenges. Larger NPs may have difficulty passing through tight biological barriers, hindering ability of drug to successfully deliver to target cells [4, 110].

•**Stability Under Physiological Conditions**: improving the stability of Nps under various physiological situations critical for their efficacy. NPs need to maintain their stability in the bloodstream and within tissues to effectively deliver drugs to the desired location. However, changes in pH, ionic density, and proteins can lead to the aggregation or disintegration of nanoparticles, reducing their overall therapeutic effectiveness [111].

b) Drug Delivery Challenges

•**Targeted Drug Delivery Issues:** Nps are frequently designed to transport drugs directly to specific cells or tissues, like cancer cells, to enhance effectiveness and minimize side effects. Achieving precise targeting is a significant challenge because of complex tumor microenvironment, which consists of surrounding blood vessels, immune cells, and extracellular matrix, can act as a barrier, preventing nanoparticles from reaching the tumor cells effectively. Moreover, the heterogeneity of tumors, meaning the variation in tumor cell types and structures, makes it difficult for a single nanoparticle formulation to be universally effective [112].

•**Tumor Microenvironment and Drug Resistance:** The complex and often hostile tumor microenvironment presents a significant hurdle in cancer treatment. The environment can feature irregular blood vessels that hinder NPs penetration, elevated interstitial pressure that obstructs drug entry, and proteins that actively expel drugs from cancer cells, causing drug resistance. NPs must be designed to navigate these obstacles, but current technologies are not always effective in overcoming these challenges [113].

c) Regulatory and Manufacturing Hurdles

•**Compliance with FDA Regulations:** Manufacturing NPs that comply with FDA (Food and Drug Administration) regulations is a significant challenge. The FDAs and cGMPs (Current Good Manufacturing Practices) are stringent, and many Nps struggle to meet these quality-related standards. Due to the intricate nature of nanotechnology, even minor changes in the manufacturing process can result in variations in the final product, potentially impacting its safety and effectiveness. Ensuring uniformity in particle size, surface characteristics, and drug loading in large-scale production is essential for regulatory approval but remains a significant challenge [4].

•**Cost and Complexity of Manufacturing:** The production of Nps is not only complex but also costly, Scaling up the production of these drugs while ensuring they meet quality and consistency standards demands substantial financial and technical resources , which can pose a considerable challenge. The nanoscale nature of these drugs often requires the adaptation or complete re-engineering of traditional pharmaceutical manufacturing processes, further adding to the complexity and cost of production. These factors can limit the widespread adoption of Nps.

d) Cancer Treatment-Specific Challenges

•**Innovations in Antitumor Agents:** Nanotechnology has brought about significant innovations in the development of antitumor agents. Nps can be engineered to insure the delivery and effectiveness of these agents, potentially leading to better outcomes for patients.

However, despite these advances, the challenges of drug delivery in the complex tumor environment persist. The variability in tumor biology and the adaptive nature of cancer cells often result in less than optimal therapeutic results, even with the use of nanoparticle-based formulations [109, 111].

•Overcoming Biological Barriers: Effectively crossing biological barriers like the blood-brain barrier (BBB) or the intestinal barrier is essential for nanoparticles (NPs) to treat diseases in these regions. Delivering therapeutic agents across the BBB remains a major obstacle, particularly in the context of certain cancers that affect the brain. Nps must be small enough and have the right surface characteristics to cross these barriers without being recognized and removed by the body's defense mechanisms [114].

Over all challenges associated with Nano pharmaceuticals, notably in cancer care, are multifaceted and interconnected. Problems related to stability, drug delivery, manufacturing, and regulatory compliance must be addressed to fully realize potential of nanotechnology in developing effective and safe pharmaceutical therapies. Ongoing research and technological advancements are essential to overcome these barriers and bring more Nps to clinical use, ultimately improving patient outcomes in cancer treatment and other medical applications.

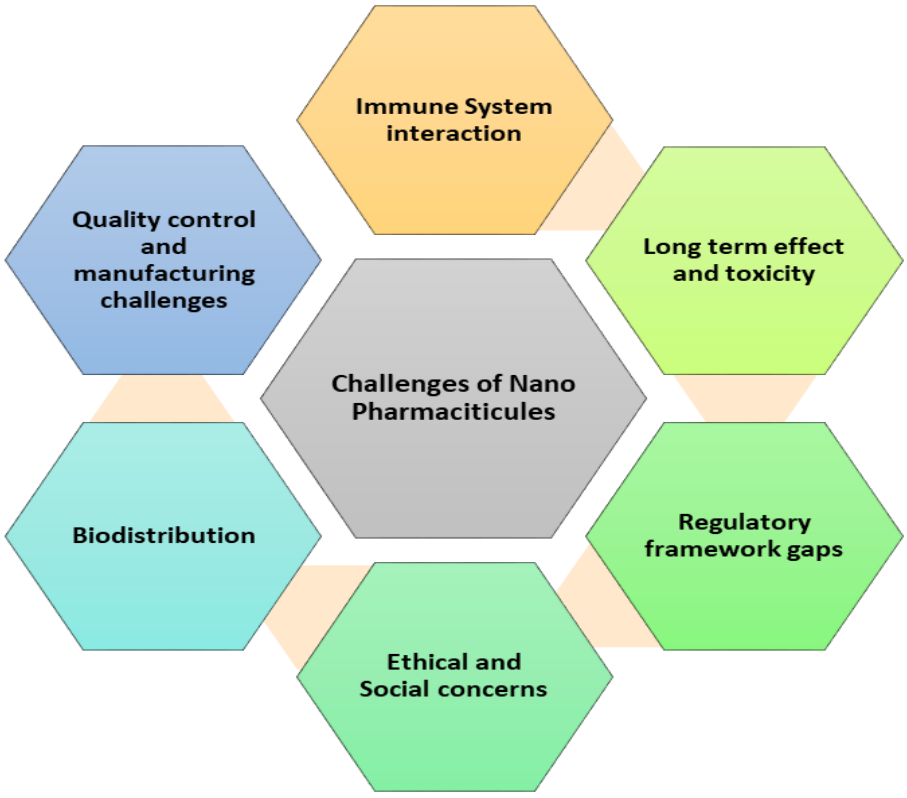

Figure17. Challenges of Nano Pharmaciticules

a) Multifunctional Nanocarriers

Creating advanced nanocarriers that integrate therapeutic, diagnostic, and monitoring capabilities into one platform is a promising development. These versatile nanoparticles can improve targeting, regulate drug release, and monitor treatment effectiveness. For instance, some NPs can identify specific biomarkers, release drugs based on environmental triggers like pH or temperature, and provide real-time updates on treatment progress [115, 116].

b) Precision Medicine

Nanotechnology is anticipated to be pivotal in advancing precision medicine by facilitating treatments tailored to the specific disease characteristics of individual patients. Personalized Nanomedicine might involve creating nanoparticles designed to deliver drugs that target unique tumor markers or genetic mutations in patients. This strategy could result in more effective and precise therapies, particularly in oncology, where the diversity of tumors presents a significant challenge [116].

c) Nanotechnology in Gene Therapy

Nps hold significant promise for advancing gene therapy by enabling the direct delivery of DNA, RNA, or CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) components to specific cells. This approach could enhance the precision and efficiency of genetic material delivery, paving the way for new treatments for genetic disorders, the development of nanoparticles capable of bypassing biological barriers, such as the cell membrane and nuclear envelope, is crucial for the successful delivery of these genetic payloads [117].

d) Nano pharmaceuticals in Regenerative Medicine

Nanotechnology holds great promise in regenerative medicine, particularly through the use of nanoparticles to deliver growth factors or other therapeutic agents that aid in tissue repair and regeneration. These nanoparticles can be engineered to replicate the extracellular matrix, creating an optimal environment for stem cell differentiation and tissue regeneration. This approach could significantly advance treatments for various conditions, including organ damage and neurological disorders [117].

e) Stimuli-Responsive Drug Delivery Systems

Researchers are creating nanoparticles that can react to external triggers, like magnetic fields, or internal ones, such as the acidic conditions found in tumors. These responsive nanoparticles can release their therapeutic contents in a controlled way, enhancing the precision and effectiveness of drug delivery, for example , pH-sensitive liposomes can discharge their cargo in the acidic environment of a tumor, while magnetic nanoparticles can be directed to a specific location using an external magnetic field [115].

f) Combination Therapies

The information anticipates the increased use of NPs to deliver combination therapies, where multiple therapeutic agents are delivered in a coordinated manner to enhance treatment efficacy. NPs can be engineered in order to carry and release different drugs simultaneously, leading to synergistic effects, especially for addressing intricate conditions such as cancer. This approach could help address drug resistance and enhance patient outcomes by simultaneously targeting multiple biological pathways or mechanisms [115, 118].

g) Global Impact

As manufacturing techniques improve and costs decrease, Nano pharmaceuticals could become more widely available, potentially revolutionizing healthcare across the globe, especially in resource-limited settings the enhanced targeting, controlled drug release, and improved bioavailability offered by Nano pharmaceuticals could make lifesaving treatments more accessible to underserved populations. This global impact could help address disparities in healthcare and improve patient outcomes worldwide [119].

Over all future prospects of Nano pharmaceuticals and drug delivery systems are remarkably promising to transform the landscape of modern medicine. From personalized treatments to regenerative therapies, the integration of nanotechnology into the pharmaceutical industry holds the promise of improved patient outcomes, enhanced therapeutic efficacy, and a more equitable global healthcare system.

4. DISCUSSION

NPs mark a major advancement in drug delivery, providing unparalleled opportunities to enhance the precision, efficacy, and safety of therapeutic interventions. The complex chemistry and NS design of these agents enable the development of highly specialized drug delivery systems that can target specific tissues or cells, thereby reducing side effects and improving therapeutic outcomes. This review explores various aspects of NPs, from their molecular design and synthesis techniques to their use in targeted drug delivery and therapeutic. Each area presents unique challenges but also offers significant potential for innovation and improvement. The review underscores the importance of understanding the chemical characteristics and functionalization strategies essential for the successful deployment of NPs. These strategies include the use of lipid-based carriers, polymeric nanoparticles, and stimuli-responsive systems, each providing distinct advantages depending on the therapeutic context. However, the development and application of these systems face challenges such as stability, scalability, and regulatory hurdles, which remain significant barriers to their widespread adoption. Overcoming these challenges will require dedicated research and development efforts focused on improving the biocompatibility, effectiveness, and manufacturability of these systems.

REFERENCES

[1] A. K. Deshantri, A. V. Moreira, V. Ecker, S. N. Mandhane, R. M. Schiffelers, M. Buchner and M. H. Fens. Nanomedicines for the treatment of hematological malignancies. Journal of Controlled Release. 2018;287:194-215.

[2] A. M. Elbadry and H. H. Mohamed. Introduction to Nanomedicine, Nanotechnology, and Nanopharmaceuticals.

Nanocarriers in Neurodegenerative Disorders. CRC Press. p. 75-83.

[3] R. Sood and D. S. Chopra. Metal–plant frameworks in nanotechnology: an overview. Phytomedicine. 2018;50:148-156.

[4] F. Rodríguez, P. Caruana, N. De la Fuente, P. Español, M. Gámez, J. Balart, E. Llurba, R. Rovira, R. Ruiz and C. Martín-Lorente. Nano-based approved pharmaceuticals for cancer treatment: present and future challenges. Biomolecules. 2022;12(6):784.

[5] V. K. Yata, S. Ranjan, N. Dasgupta and E. Lichtfouse. Nanopharmaceuticals: Principles and Applications Vol. 2. Springer; 2020.

[6] S. P. Gangapure and O. G. Bhusnure. Nanopharmaceuticals. Journal of Drug Delivery and Therapeutics. 2019;9(4):676-687.

[7] G. D. Moon, S. Ko, Y. Min, J. Zeng, Y. Xia and U. Jeong. Chemical transformations of nanostructured materials. Nano Today. 2011;6(2):186-203.

[8] M. Fernandez-Garcia, A. Martinez-Arias, J. Hanson and J. Rodriguez. Nanostructured oxides in chemistry: characterization and properties. Chemical reviews. 2004;104(9):4063-4104.

[9] Y. Wang. Nanogeochemistry: Nanostructures, emergent properties and their control on geochemical reactions and mass transfers. Chemical Geology. 2014;378:1-23.

[10] M. Prato, K. Kostarelos and A. Bianco. Functionalized carbon nanotubes in drug design and discovery. Accounts of chemical research. 2008;41(1):60-68.

[11] F. Karimi, A. J. O'Connor, G. G. Qiao and D. E. Heath. Integrin clustering matters: a review of biomaterials functionalized with multivalent integrin-binding ligands to improve cell adhesion, migration, differentiation, angiogenesis, and biomedical device integration. Advanced Healthcare Materials. 2018;7(12):1701324.

[12] C. Sahlgren, A. Meinander, H. Zhang, F. Cheng, M. Preis, C. Xu, T. A. Salminen, D. Toivola, D. Abankwa and A. Rosling. Tailored approaches in drug development and diagnostics: from molecular design to biological model systems. Advanced Healthcare Materials. 2017;6(21):1700258.

[13] L. Stillger and D. Müller. Peptide-coating combating antimicrobial contaminations: a review of covalent immobilization strategies for industrial applications. Journal of Materials Science. 2022;57(24):10863-10885.

[14] N. Kamaly, B. Yameen, J. Wu and O. C. Farokhzad. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chemical reviews. 2016;116(4):2602-2663.

[15] J. H. Lee and Y. Yeo. Controlled drug release from pharmaceutical nanocarriers. Chemical engineering science. 2015;125:75-84.

[16] M. Rawal, A. Singh and M. M. Amiji. Quality-by-design concepts to improve nanotechnology-based drug development. Pharmaceutical research. 2019;36(11):153.

[17] H. M. Mansour, M. Sohn, A. Al-Ghananeem and P. P. DeLuca. Materials for pharmaceutical dosage forms: molecular pharmaceutics and controlled release drug delivery aspects. International journal of molecular sciences. 2010;11(9):3298-3322.

[18] O. Dumitriu Buzia, A. M. Păduraru, C. S. Stefan, M. Dinu, D. I. Cocoș, L. C. Nwabudike and A. L. Tatu. Strategies for Improving Transdermal Administration: New Approaches to Controlled Drug Release. Pharmaceutics. 2023;15(4):1183.

[19] A. Raza, T. Rasheed, F. Nabeel, U. Hayat, M. Bilal and H. M. Iqbal. Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release. Molecules. 2019;24(6):1117**.**

[20] F. Li, C. Zheng, J. Xin, F. Chen, H. Ling, L. Sun, T. J. Webster, X. Ming and J. Liu. Enhanced tumor delivery and antitumor response of doxorubicin-loaded albumin nanoparticles formulated based on a Schiff base. International journal of nanomedicine. 2016:3875-3890.

[21] M. Esmaeilpour, A. R. Sardarian and J. Javidi. Schiff base complex of metal ions supported on superparamagnetic Fe3O4@ SiO2 nanoparticles: An efficient, selective and recyclable catalyst for synthesis of 1, 1-diacetates from aldehydes under solvent-free conditions. Applied Catalysis A: General. 2012;445:359-367.

[22] S. Peng, X. Yuan, W. Lin, C. Cai and L. Zhang. pH-responsive controlled release of mesoporous silica nanoparticles capped with Schiff base copolymer gatekeepers: Experiment and molecular dynamics simulation. Colloids and surfaces B: biointerfaces. 2019;176:394-403.

[23] S. Verma, R. Gokhale and D. J. Burgess. A comparative study of top-down and bottom-up approaches for the preparation of micro/nanosuspensions. International journal of pharmaceutics. 2009;380(1-2):216-222.

[24] H. Panjiar, R. Gakkhar and B. Daniel. Strain-free graphite nanoparticle synthesis by mechanical milling. Powder Technology. 2015;275:25-29.

[25] T. P. Yadav, R. M. Yadav and D. P. Singh. Mechanical milling: a top down approach for the synthesis of nanomaterials and nanocomposites. Nanoscience and Nanotechnology. 2012;2(3):22-48.

[26] P. G. Jamkhande, N. W. Ghule, A. H. Bamer and M. G. Kalaskar. Metal nanoparticles synthesis: An overview on methods of preparation, advantages and disadvantages, and applications. Journal of drug delivery science and technology. 2019;53:101174.

[27] M. Kim, S. Osone, T. Kim, H. Higashi and T. Seto. Synthesis of nanoparticles by laser ablation: A review. KONA Powder and Particle Journal. 2017;34:80-90.

[28] N. Semaltianos. Nanoparticles by laser ablation. Critical reviews in solid state and materials sciences. 2010;35(2):105-124.

[29] M. C. Sportelli, M. Izzi, A. Volpe, M. Clemente, R. A. Picca, A. Ancona, P. M. Lugarà, G. Palazzo and N. Cioffi. The pros and cons of the use of laser ablation synthesis for the production of silver nano-antimicrobials. Antibiotics. 2018;7(3):67.

[30] R. Hufschmid, H. Arami, R. M. Ferguson, M. Gonzales, E. Teeman, L. N. Brush, N. D. Browning and K. M. Krishnan. Synthesis of phase-pure and monodisperse iron oxide nanoparticles by thermal decomposition. Nanoscale. 2015;7(25):11142-11154.

[31] O. Pascu, E. Carenza, M. Gich, S. Estrade, F. Peiro, G. Herranz and A. Roig. Surface reactivity of iron oxide nanoparticles by microwave-assisted synthesis; comparison with the thermal decomposition route. The Journal of Physical Chemistry C. 2012;116(28):15108-15116.

[32] I. Hussain, N. Singh, A. Singh, H. Singh and S. Singh. Green synthesis of nanoparticles and its potential application. Biotechnology letters. 2016;38:545-560.

[33] H. Jahangirian, E. G. Lemraski, T. J. Webster, R. Rafiee-Moghaddam and Y. Abdollahi. A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. International journal of nanomedicine. 2017:2957-2978.

[34] H. Nadaroglu, A. A. Güngör and S. Ince. Synthesis of nanoparticles by green synthesis method. International Journal of Innovative Research and Reviews. 2017;1(1):6-**9.**

[35] P. K. Dikshit, J. Kumar, A. K. Das, S. Sadhu, S. Sharma, S. Singh, P. K. Gupta and B. S. Kim. Green synthesis of metallic nanoparticles: Applications and limitations. Catalysts. 2021;11(8):902.

[36] M. Parashar, V. K. Shukla and R. Singh. Metal oxides nanoparticles via sol–gel method: a review on synthesis, characterization and applications. Journal of Materials Science: Materials in Electronics. 2020;31(5):3729-3749.

[37] D. Bokov, A. Turki Jalil, S. Chupradit, W. Suksatan, M. Javed Ansari, I. H. Shewael, G. H. Valiev and E. Kianfar.

Nanomaterial by sol-gel method: synthesis and application. Advances in materials science and engineering. 2021;2021(1):5102014.

[38] J. A. Darr, J. Zhang, N. M. Makwana and X. Weng. Continuous hydrothermal synthesis of inorganic nanoparticles: applications and future directions. Chemical reviews. 2017;117(17):11125-11238.

[39] H. Lu, J. Wang, T. Wang, J. Zhong, Y. Bao and H. Hao. Recent progress on nanostructures for drug delivery applications. Journal of Nanomaterials. 2016;2016(1):5762431.

[40] E. Andronescu and A. M. Grumezescu. Nanostructures for drug delivery. Elsevier; 2017.

[41] D. Patel, B. Patel and H. Thakkar. Lipid based nanocarriers: promising drug delivery system for topical application. european Journal of lipid science and technology. 2021;123(5):2000264.

[42] M. R. Shah, M. Imran and S. Ullah. Lipid-based nanocarriers for drug delivery and diagnosis. William Andrew; 2017.

[43] A. Abbasi. TiO2-Based nanocarriers for drug delivery. Nanocarriers for Drug Delivery. Elsevier; 2019. p. 205-248.

[44] D. Lombardo, P. Calandra, D. Barreca, S. Magazù and M. A. Kiselev. Soft interaction in liposome nanocarriers for therapeutic drug delivery. Nanomaterials. 2016;6(7):125.

[45] D. K. Mishra, R. Shandilya and P. K. Mishra. Lipid based nanocarriers: a translational perspective. Nanomedicine: Nanotechnology, Biology and Medicine. 2018;14(7):2023-2050.

[46] N. Naseri, H. Valizadeh and P. Zakeri-Milani. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Advanced pharmaceutical bulletin. 2015;5(3):305.

[47] H. Nsairat, D. Khater, U. Sayed, F. Odeh, A. Al Bawab and W. Alshaer. Liposomes: Structure, composition, types, and clinical applications. Heliyon. 2022;8(5).

[48] M. Ashtikar, K. Nagarsekar and A. Fahr. Transdermal delivery from liposomal formulations–Evolution of the technology over the last three decades. Journal of Controlled Release. 2016;242:126-140.

[49] L. W. Allahou, S. Y. Madani and A. Seifalian. Investigating the application of liposomes as drug delivery systems for the diagnosis and treatment of cancer. International journal of biomaterials. 2021;2021(1):3041969.

[50] Y. Malam, M. Loizidou and A. M. Seifalian. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends in pharmacological sciences. 2009;30(11):592-599.

[51] P. Ghasemiyeh and S. Mohammadi-Samani. Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: Applications, advantages and disadvantages. Research in pharmaceutical sciences. 2018;13(4):288-303.

[52] G. Yoon, J. W. Park and I.-S. Yoon. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs): recent advances in drug delivery. Journal of Pharmaceutical Investigation. 2013;43:353-362.

[53] A. Gordillo-Galeano and C. E. Mora-Huertas. Solid lipid nanoparticles and nanostructured lipid carriers: A review emphasizing on particle structure and drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2018;133:285-308.

[54] H. Bunjes. Structural properties of solid lipid based colloidal drug delivery systems. Current Opinion in Colloid & Interface Science. 2011;16(5):405-411.

[55] S. Khatak and H. Dureja. Structural composition of solid lipid nanoparticles for invasive and non-invasive drug delivery. Current Nanomaterials. 2017;2(3):129-153.

[56] R. P. Patel and J. R. Joshi. An overview on nanoemulsion: a novel approach. International Journal of Pharmaceutical sciences and research. 2012;3(12):4640.

[57] P. J. Espitia, C. A. Fuenmayor and C. G. Otoni. Nanoemulsions: Synthesis, characterization, and application in bio-based active food packaging. Comprehensive Reviews in Food Science and Food Safety. 2019;18(1):264-285.

[58] Y. Singh, J. G. Meher, K. Raval, F. A. Khan, M. Chaurasia, N. K. Jain and M. K. Chourasia. Nanoemulsion: Concepts, development and applications in drug delivery. Journal of Controlled Release. 2017;252:28-49.

[59] P. Bhatt and S. Madhav. A detailed review on nanoemulsion drug delivery system. International Journal of Pharmaceutical sciences and research. 2011;2(10):2482.

[60] M. Jaiswal, R. Dudhe and P. Sharma. Nanoemulsion: an advanced mode of drug delivery system. 3 Biotech. 2015;5:123-127.

[61] M. Somiya and S. i. Kuroda. Development of a virus-mimicking nanocarrier for drug delivery systems: The bio-nanocapsule. Advanced Drug Delivery Reviews. 2015;95:77-89.

[62] K. C. Bentz and D. A. Savin. Hollow polymer nanocapsules: synthesis, properties, and applications. Polymer Chemistry. 2018;9(16):2059-2081.

[63] C. E. Mora-Huertas, H. Fessi and A. Elaissari. Polymer-based nanocapsules for drug delivery. International journal of pharmaceutics. 2010;385(1-2):113-142.

[64] D. Urimi, M. Hellsing, N. Mahmoudi, C. Soderberg, R. Widenbring, L. Gedda, K. Edwards, T. Loftsson and N. Schipper. Structural characterization study of a lipid nanocapsule formulation intended for drug delivery applications using small-angle scattering techniques. Molecular pharmaceutics. 2022;19(4):1068-1077.

[65] U. Shimanovich, G. J. Bernardes, T. Knowles and A. Cavaco-Paulo. Protein micro-and nano-capsules for biomedical applications. Chemical Society Reviews. 2014;43(5):1361-1371.

[66] C. Mayer. Nanocapsules as drug delivery systems. The International journal of artificial organs. 2005;28(11):1163-1171.

[67] A.-L. Robson, P. C. Dastoor, J. Flynn, W. Palmer, A. Martin, D. W. Smith, A. Woldu and S. Hua. Advantages and limitations of current imaging techniques for characterizing liposome morphology. Frontiers in pharmacology. 2018;9:80.

[68] L. Sercombe, T. Veerati, F. Moheimani, S. Y. Wu, A. K. Sood and S. Hua. Advances and challenges of liposome assisted drug delivery. Frontiers in pharmacology. 2015;6:286.

[69] M. Nishitani Yukuyama, E. Tomiko Myiake Kato, R. Lobenberg and N. Araci Bou-Chacra. Challenges and future prospects of nanoemulsion as a drug delivery system. Current pharmaceutical design. 2017;23(3):495-508.

[70] C. Viegas, A. B. Patrício, J. M. Prata, A. Nadhman, P. K. Chintamaneni and P. Fonte. Solid lipid nanoparticles vs. nanostructured lipid carriers: a comparative review. Pharmaceutics. 2023;15(6):1593.

[71] P. Ganesan and D. Narayanasamy. Lipid nanoparticles: Different preparation techniques, characterization, hurdles, and strategies for the production of solid lipid nanoparticles and nanostructured lipid carriers for oral drug delivery. Sustainable Chemistry and Pharmacy. 2017;6:37-56.

[72] B. Begines, T. Ortiz, M. Pérez-Aranda, G. Martínez, M. Merinero, F. Argüelles-Arias and A. Alcudia. Polymeric nanoparticles for drug delivery: Recent developments and future prospects. Nanomaterials. 2020;10(7):1403.

[73] J. M. Chan, P. M. Valencia, L. Zhang, R. Langer and O. C. Farokhzad. Polymeric nanoparticles for drug delivery. Cancer nanotechnology: Methods and protocols. 2010:163-175.

[74] Y. Sun, A. Bhattacharjee, M. Reynolds and Y. V. Li. Synthesis and characterizations of gentamicin-loaded poly-lactic-co-glycolic (PLGA) nanoparticles. Journal of Nanoparticle Research. 2021;23:1-15.

[75] P. Narvekar, P. Bhatt, G. Fnu and V. Sutariya. Axitinib-loaded poly (lactic-co-glycolic acid) nanoparticles for age-related macular degeneration: formulation development and in vitro characterization. Assay and drug development technologies. 2019;17(4):167-177.

[76] A. Kumari, S. K. Yadav and S. C. Yadav. Biodegradable polymeric nanoparticles based drug delivery systems. Colloids and surfaces B: biointerfaces. 2010;75(1):1-18.

[77] N. Jan, A. Madni, S. Khan, H. Shah, F. Akram, A. Khan, D. Ertas, M. F. Bostanudin, C. H. Contag and N. Ashammakhi. Biomimetic cell membrane-coated poly (lactic-co-glycolic acid) nanoparticles for biomedical applications. Bioengineering & Translational Medicine. 2023;8(2):e10441.

[78] D. Pandita, S. Kumar and V. Lather. Hybrid poly (lactic-co-glycolic acid) nanoparticles: design and delivery prospectives. Drug discovery today. 2015;20(1):95-104.

[79] E. Nagarajana, P. Shanmugasundarama, V. Ravichandirana, A. Vijayalakshmia, B. Senthilnathanb and K. Masilamanib. Development and evaluation of chitosan based polymeric nanoparticles of an antiulcer drug lansoprazole. Journal of Applied Pharmaceutical Science. 2015;5(4):020-025.

[80] A. Grenha. Chitosan nanoparticles: a survey of preparation methods. Journal of drug targeting. 2012;20(4):291-300.

[81] S. Naskar, S. Sharma and K. Kuotsu. Chitosan-based nanoparticles: An overview of biomedical applications and its preparation. Journal of drug delivery science and technology. 2019;49:66-81.

[82] K. Divya and M. Jisha. Chitosan nanoparticles preparation and applications. Environmental chemistry letters. 2018;16:101-112.

[83] A. Pramanik, D. Laha, S. K. Dash, S. Chattopadhyay, S. Roy, D. K. Das, P. Pramanik and P. Karmakar. An in-vivo study for targeted delivery of copper-organic complex to breast cancer using chitosan polymer nanoparticles. Materials Science and Engineering: C. 2016;68:327-337.

[84] Z. Ahmad, A. Shah, M. Siddiq and H.-B. Kraatz. Polymeric micelles as drug delivery vehicles. Rsc Advances. 2014;4(33):17028-17038.

[85] X. Wang, J. E. Hall, S. Warren, J. Krom, J. M. Magistrelli, M. Rackaitis and G. G. Bohm. Synthesis, characterization, and application of novel polymeric nanoparticles. Macromolecules. 2007;40(3):499-508.

[86] S. Movassaghian, O. M. Merkel and V. P. Torchilin. Applications of polymer micelles for imaging and drug delivery. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2015;7(5):691-707.

[87] J. Gong, M. Chen, Y. Zheng, S. Wang and Y. Wang. Polymeric micelles drug delivery system in oncology. Journal of Controlled Release. 2012;159(3):312-323.

[88] U. Kedar, P. Phutane, S. Shidhaye and V. Kadam. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;6(6):714-729.

[89] J. Kousalová and T. Etrych. Polymeric nanogels as drug delivery systems. Physiological research. 2018;67.

[90] J. Ramos, J. Forcada and R. Hidalgo-Alvarez. Cationic polymer nanoparticles and nanogels: from synthesis to biotechnological applications. Chemical reviews. 2014;114(1):367-428.

[91] S. Rigogliuso, M. A. Sabatino, G. Adamo, N. Grimaldi, C. Dispenza and G. Ghersi. Polymeric nanogels: Nanocarriers for drug delivery application. Chem Eng. 2012;27:247-252.

[92] R. T. Chacko, J. Ventura, J. Zhuang and S. Thayumanavan. Polymer nanogels: a versatile nanoscopic drug delivery platform. Advanced Drug Delivery Reviews. 2012;64(9):836-851.

[93] S. Hajebi, N. Rabiee, M. Bagherzadeh, S. Ahmadi, M. Rabiee, H. Roghani-Mamaqani, M. Tahriri, L. Tayebi and M. R. Hamblin. Stimulus-responsive polymeric nanogels as smart drug delivery systems. Acta biomaterialia. 2019;92:1-18.

[94] P. V. Devarajan and S. Jain. Targeted drug delivery: concepts and design. 2015.

[95] K. Rani and S. Paliwal. A review on targeted drug delivery: Its entire focus on advanced therapeutics and diagnostics. Sch. J. App. Med. Sci. 2014;2(1C):328-31.

[96] A. Tewabe, A. Abate, M. Tamrie, A. Seyfu and E. Abdela Siraj. Targeted drug delivery—from magic bullet to nanomedicine: principles, challenges, and future perspectives. Journal of Multidisciplinary Healthcare. 2021:1711-1724.

[97] A. I. Freeman and E. Mayhew. Targeted drug delivery. Cancer. 1986;58(S2):573-583.

[98] P. Y. Liyanage, S. D. Hettiarachchi, Y. Zhou, A. Ouhtit, E. S. Seven, C. Y. Oztan, E. Celik and R. M. Leblanc. Nanoparticle-mediated targeted drug delivery for breast cancer treatment. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2019;1871(2):419-433.

[99] S. Titu, C. M. Grapa, T. Mocan, O. Balacescu and A. Irimie. Tetraspanins: physiology, colorectal cancer development, and nanomediated applications. Cancers. 2021;13(22):5662.

[100] N. Ponnappan and A. Chugh. Nanoparticle-mediated delivery of therapeutic drugs. Pharmaceutical Medicine. 2015;29:155-167.

[101] C. Yang and D. Merlin. Nanoparticle-mediated drug delivery systems for the treatment of IBD: current perspectives. International journal of nanomedicine. 2019:8875-8889.

[102] H. Kang, S. Hu, M. H. Cho, S. H. Hong, Y. Choi and H. S. Choi. Theranostic nanosystems for targeted cancer therapy. Nano Today. 2018;23:59-72.

[103] B. Massoumi, N. Poorgholy and M. Jaymand. Multistimuli responsive polymeric nanosystems for theranostic applications. International Journal of Polymeric Materials and Polymeric Biomaterials. 2017;66(1):38-47.

[104] X. Chen, J. Song, X. Chen and H. Yang. X-ray-activated nanosystems for theranostic applications. Chemical Society Reviews. 2019;48(11):3073-3101.

[105] W. Lin, X. Zhang, L. Qian, N. Yao, Y. Pan and L. Zhang. Doxorubicin-loaded unimolecular micelle-stabilized gold nanoparticles as a theranostic nanoplatform for tumor-targeted chemotherapy and computed tomography imaging. Biomacromolecules. 2017;18(12):3869-3880.

[106] A. Polyak and T. L. Ross. Nanoparticles for SPECT and PET imaging: towards personalized medicine and theranostics. Current medicinal chemistry. 2018;25(34):4328-4353.

[107] S. Khizar, N. M. Ahmad, N. Zine, N. Jaffrezic-Renault, A. Errachid-el-salhi and A. Elaissari. Magnetic nanoparticles: from synthesis to theranostic applications. ACS Applied Nano Materials. 2021;4(5):4284-4306.

[108] D. Wei, Y. Sun, H. Zhu and Q. Fu. Stimuli-responsive polymer-based nanosystems for cancer theranostics. ACS nano. 2023;17(23):23223-23261.

[109] S. Berkner, K. Schwirn and D. Voelker. Nanopharmaceuticals: tiny challenges for the environmental risk assessment of pharmaceuticals. Environmental toxicology and chemistry. 2016;35(4):780-787.

[110] J. Jeevanandam, Y. San Chan and M. K. Danquah. Nano-formulations of drugs: recent developments, impact and challenges. Biochimie. 2016;128:99-112.

[111] F. Farjadian, A. Ghasemi, O. Gohari, A. Roointan, M. Karimi and M. R. Hamblin. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine. 2019;14(1):93-126.

[112] M. N. Hafeez, C. Celia and V. Petrikaite. Challenges towards targeted drug delivery in cancer nanomedicines. Processes. 2021;9(9):1527.

[113] B. S. Pattni and V. P. Torchilin. Targeted drug delivery systems: Strategies and challenges. Targeted drug delivery: Concepts and design. 2015:3-38.

[114] A. A. Halwani. Development of pharmaceutical nanomedicines: from the bench to the market. Pharmaceutics. 2022;14(1):106.

[115] J. K. Patra, G. Das, L. F. Fraceto, E. V. R. Campos, M. d. P. Rodriguez-Torres, L. S. Acosta-Torres, L. A. Diaz-Torres, R. Grillo, M. K. Swamy and S. Sharma. Nano based drug delivery systems: recent developments and future prospects. Journal of nanobiotechnology. 2018;16:1-33.

[116] A. Badar, S. Pachera, A. Ansari and N. Lohiya. Nano based drug delivery systems: present and future prospects. Nanomed Nanotechnol J. 2019;2(1):121.

[117] P. Agrawal. Potential prospects of future medicine: Nano medicine. Journal of Pharmacovigilance. 2016;4(1):1000-1149.

[118] S. Çalış, K. Ö. Atar, F. B. Arslan, H. Eroğlu and Y. Çapan. Nanopharmaceuticals as Drug-Delivery Systems: For, Against, and Current Applications. Nanocarriers for Drug Delivery. Elsevier; 2019. p. 133-154.

[119] R. K. Thapa and J. O. Kim. Nanomedicine-based commercial formulations: Current developments and future prospects. Journal of Pharmaceutical Investigation. 2023;53(1):19-33.