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NANOTECHNOLOGY IN DRUG DELIVERY SYSTEM

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ABSTRACT

Nanoparticles play an essential role in biomedical applications, such as drug delivery, bio sensing, and tissue engineering. They guarantee the delivery of drugs to the target tissues. The controlled release mechanisms improve the efficacy and safety of the treatments. Further, Nano-based methods have been developed where cancer therapies are integrated with diagnostic imaging techniques, offering hope for combined or integrated treatments in the future. Over the past decade, tremendous research has revolutionized drug delivery systems by focusing on delivering therapeutic agents and natural active compounds directly to the targeted site for the treatment of various diseases. Although the prevailing drug delivery systems have found immense applications, problems including drug stability, bioavailability, and precise targeting continue to persist. Such limitations open up avenues for more advanced technologies to emerge to discover higher efficacy and safety of the therapy. Nano-based drug delivery systems have emerged as promising options in improving the solubility and controlled-release delivery of drugs and targeted site delivery. By encapsulating therapeutics within Nano carriers, it shields therapeutic agents from degradation while ensuring their delivery to the target site and thereby minimizing the side effects with maximum effectiveness. Nanotechnology is now in the pipeline day by day in search of the precise aspect of its potential in medicine, promising to make a revolution in chronic and complex diseases into more efficient and personalized therapies. This bolds a promising treatment of vast diseases as medicine is destined for further progressions in NDDS.

Nanotechnology shall thus be able to revolutionize the delivery method in a way that drugs would be administered in more effective manner, personalized, and therefore reachable to patients all over the world.

KEYWORDS: Nanotechnology, Nanoparticles, medicine, drug delivery, controlled release.

INTRODUCTION

Nanotechnology has emerged as one of the most trans-formative interdisciplinary fields of the twenty-first century, integrating principles from physics, chemistry, biology, materials science, and engineering to manipulate matter at the atomic and molecular level. The term nanotechnology, first conceptualized by physicist Richard Feynman in his landmark 1959 lecture titled 'There's Plenty of Room at the Bottom,' refers to the design, synthesis, characterization, and application of materials and devices at the nanoscale (1-1000 nm).[1] In the context of medicine and pharmacy, nanotechnology has opened revolutionary avenues for improving the diagnosis, prevention, and treatment of disease through the development of sophisticated nanoscale drug delivery systems (nano-DDS).[2]

Conventional drug delivery methods are frequently associated with significant pharmacokinetic limitations such as poor bioavailability, rapid systemic clearance, non-specific tissue distribution, and dose-dependent toxicity. Many pharmacologically potent compounds - particularly those in BCS Class II and Class IV - suffer from poor aqueous solubility, which severely hampers their therapeutic potential.[3] Similarly, highly toxic chemotherapeutic agents used in cancer therapy exert severe side effects on healthy tissues due to their non-selective distribution. The development of nano-sized drug carriers addresses these fundamental limitations by providing controlled, targeted, and site-specific drug delivery.[4]

A nanoparticle-based drug delivery system can improve drug solubility, protect labile drugs from premature degradation in biological environments, extend circulation half-life, facilitate receptor-mediated endocytosis, and allow stimuli-responsive drug release at the pathological site.[5] The surface of nanocarriers can be engineered with functional groups, polymers such as polyethylene glycol (PEG), and targeting ligands such as antibodies, aptamers, or folate to enhance selectivity and reduce non-specific interactions.[6]

The global nanomedicine market was valued at approximately USD 207.5 billion in 2023 and is projected to exceed USO 450 billion by 2030, reflecting the enormous clinical and commercial interest in nanotechnology-based therapeutics.[7] The successful clinical translation of liposomal doxorubicin (Doxia®). albumin-bound paclitaxel (Abraxane®}, and mRNA-lipid nanoparticle COVID-19 vaccines (Comirnaty®, Spikevax®) has validated the immense therapeutic potential of nanomed1cme and propelled further investment in this domain.[8]

This Project report provides a comprehensive review of nanotechnology in drug delivery systems, encompassing the classification and structural characteristics of nanocarriers, methods of preparation and characterization, mechanisms of drug release, passive and active targeting strategies, and applications across cancer therapy, gene delivery, brain drug delivery, oral delivery, and transdermal delivery. Additionally, toxicological safety profiles, regulatory frameworks, and recent advances are discussed, along with future perspectives for field.[9,10]

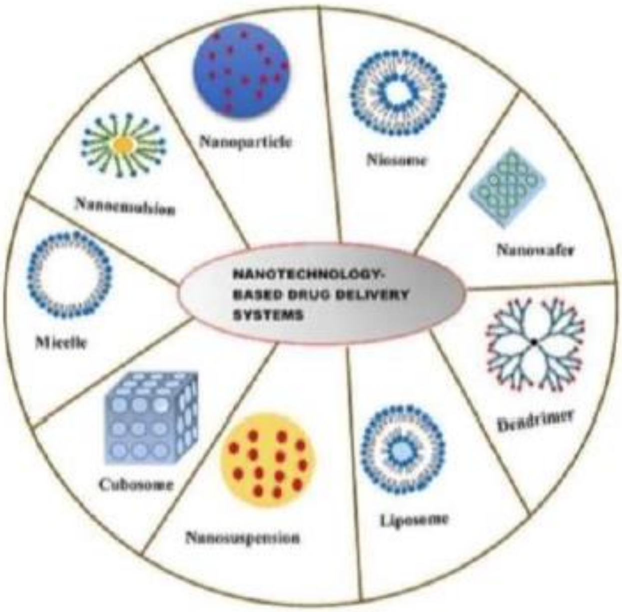


Fig. 01: Nanotechnology In Drug Delivery system.

2. OVERVIEW OF DRUG DELIVERY SYSTEMS

A drug delivery system (DDS) is defined as a formulation or device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of drug release.[11] The primary objective of any DD is to deliver the right amount of drug to the right site at the right time, while minimizing undesirable side effects.

Conventional drug delivery systems include tablets, capsules, solutions, suspensions, creams, and injections. While these are widely used, they are associated with several limitations including erratic absorption, first-pass metabolism, short half-life necessitating frequent dosing, poor patient compliance, and potential toxicity due to high peak plasma concentrations.[12] These challenges have driven the development of novel drug delivery systems (NOD).

2.1 Classification of Drug Delivery systems

Drug delivery systems can be broadly classified based on the route of administration (oral, parenteral, transdermal, pulmonary, ocular, nasal, buccal), the release mechanism (immediate release, sustained release, controlled release, delayed release), and the carrier type (conventional, vesicular, particulate, polymeric, nano-based) [131 The evolution from first-generation conventional formulations to third-generation advanced targeted nano systems represents a paradigm shift in pharmaceutical science.

2.2 Limitations of conventional Drug Delivery

Conventional drug delivery systems are subject to significant pharmacokinetic and pharmacodynamic lim1tat1ons. Drugs with poor water solubility, particularly BCS Class II and IV compounds, exhibit erratic and complete absorption after oral administration.[14] Drugs with short biological half-lives require frequent dosing leading to oscillating peak-trough plasma concentration profiles. Systemic distribution of cytotoxic agents damages healthy tissues indiscriminately. The blood-brain barrier (BBB) prevents most drugs from reaching the central nervous system.[15]

2.3 Need for Novel Drug Delivery systems

The growing complexity of therapeutic targets and the emergence of biologics, peptides, nucleic acids, and poorly soluble small molecules has necessitated the development of sophisticated drug delivery platforms Novel drug delivery systems such *as* m1crosphercs, 11posomes, mestomes. nanoparticles, transdermal patches, implants, and hydrogels have been developed to overcome these limitations[16] Among these, nanotechnology-based drug delivery systems stand out for their unique ability to overcome biological barriers, improve pharmacokinetics, and enable targeted therapy.

3. INTRODUCTIO TO ANOTECIINOLOGY

Nanotechnology is the science, engineering, and application of materials, structures, devices, and systems having novel properties and functions resulting from their small nanoscale size (I to I 00 nm, though in pharmaceutical sciences up to I 000 nm is considered).[17] At the nanoscale, materials exhibit unique physicochemical properties- include quantum effects, dramatically increased surface-area-to-volume ratios, enhanced reactivity, and altered mechanical, optical, and electrical characteristics - that are distantly different from their bulk counterparts.[18]

The fundamental premise of nanotechnology in medicine (nanomedicine) is the utilization of nanoscale materials and devices to diagnose, monitor, treat, prevent, and understand disease at the molecular and cellular level.[19] Nanomedicine encompasses a broad spectrum of applications including tnrgeted drug delivery, molecular imaging, biosensors, tissue engineering, regenerative medicine, and theranost1cs (simultaneous therapy and diagnostics).[21]

The multidisciplinary nature of nanotechnology is drawn from biology, chemistry, physics, medicine, engineering, and materials science. Modern nanomedicine leverages advance in polymer chemistry, lipid science, protein engineering, and materials synthesis to design nanocarriers with precisely tuned properties for optimal therapeutic performance.[21]

3.1 The Nanoscale and Its Significance

Materials m the nanoscale range possess extraordinarily high surface-area-to-volume ratio For example, a mmopart1cle of 10 nm diameter has approximately 30% of its atoms on its surface, compared to less than 0.0I% for a l-micrometer particle.[22] This dramatically increased surface area enhances chemical reactivity, drug loading capacity, and interactions with biological membranes and targeting ligands. Additionally, nanoparticles can traverse b1olog1cal barriers - including the cp1thclial lining, endothelial walls, the blood-brain barrier, and tumor vasculature - that arc impenetrable to larger particles.[23]

4. HISTORICAL BACKGROUND OF NANOTECHNOLOGY IN MEDICINE

The concept of nanotechnology was first articulated by Nobel Prize-winning physicist Richard Feynman in his seminal 1959 lecture "There's Plenty of Room at the Bottom," where he proposed the possibility of manipulating individual atoms and molecules.[24] The term "nanotechnology" was coined in 1974 by Norio Taniguchi to describe precision machining at the nanometer level.[25]

In the pharmaceutical sciences, the history of nanotechnology-based drug delivery is closely linked to the development of liposomes. In 1965, Alec Bangham and colleagues at the Babraham Institute in Cambridge first described phospholipid vesicles (liposomes) as potential drug carriers.[26] This discovery laid the foundation for lipid-based drug delivery systems. In 1976, Peter Speiser and colleagues at ETH Zurich described the first polymeric nanoparticles for drug delivery, using polyacrylamide-based nanospheres.[27]

The 1980s witnessed major advances in targeted drug delivery. The concept of the "magic bullet"—first proposed by Paul Ehrlich—was revived through the development of antibody-conjugated nanoparticles.[28] In 1986, Matsumura and Maeda described the Enhanced Permeability and Retention (EPR) effect, which provided the mechanistic basis for passive tumor targeting with macromolecules and nanoparticles.[29] This discovery revolutionized the field of anti-cancer nanomedicine.

The 1990s marked the era of clinical translation. The first FDA-approved nanomedicine, Doxil® (PEGylated liposomal doxorubicin), was approved in 1995 for the treatment of Kaposi's sarcoma and later for ovarian cancer and multiple myeloma.[30] The approval of Abraxane® (albumin-bound paclitaxel nanoparticles) in 2005 further validated the clinical utility of nanoparticle-based drug delivery. The 2000s and 2010s saw the proliferation of nanomedicine research with major advances in dendrimers, quantum dots, carbon nanotubes, and metallic nanoparticles.[31] The most recent landmark achievement was the development of lipid nanoparticle (LNP)-mRNA vaccines for COVID-19 (Comirnaty® and Spikevax®), approved in 2021, representing the first clinical application of LNP technology for nucleic acid delivery.[32]

5. ADVANTAGES OF NANOTECHNOLOGY IN DRUG DELIVERY

Nanotechnology-based drug delivery systems offer a multitude of advantages over conventional dosage forms, making them the preferred platform for the delivery of challenging therapeutic agents.[33]

5.1 Improved Bioavailability

Nanoparticle formulations can dramatically improve the oral bioavailability of poorly water-soluble drugs (BCS Class II and IV) by increasing the surface area for dissolution, enhancing mucosal permeability, and inhibiting P-glycoprotein-mediated efflux.[34] Nanosizing increases the dissolution rate of drugs, leading to higher plasma concentrations. Nanoemulsions and self-nanoemulsifying drug delivery systems (SNEDDS) have shown 5–10 fold improvements in bioavailability for hydrophobic drugs.[35]

5.2 Targeted Drug Delivery

One of the most significant advantages of nanotechnology is the ability to deliver drugs specifically to the target tissue, organ, or cell. Passive targeting through the EPR effect and active targeting using surface-conjugated ligands enable preferential accumulation of nanocarriers at tumor sites, inflamed tissues, or specific cell populations.[36] This dramatically enhances therapeutic efficacy while reducing systemic side effects.

5.3 Controlled and Sustained Drug Release

Nanocarriers can be engineered to provide controlled, sustained, or stimuli-responsive drug release profiles. Polymeric nanoparticles based on PLGA, chitosan, or gelatin degrade slowly in physiological environments, providing sustained drug release over days to weeks.[37] Stimuli-responsive nanocarriers release drugs in response to specific triggers such as pH changes (exploiting the acidic tumor microenvironment), redox potential (glutathione in cancer cells), temperature, light, or enzymes.[38]

5.4 Protection of Drug Molecules

Nanoencapsulation protects sensitive drug molecules, including peptides, proteins, nucleic acids, and light-sensitive compounds—from enzymatic degradation, hydrolysis, and immune recognition in physiological environments.[39] Liposomes protect encapsulated drugs from enzymatic degradation in the gastrointestinal tract. Polymeric nanoparticles protect nucleic acids from nuclease degradation for gene therapy applications.

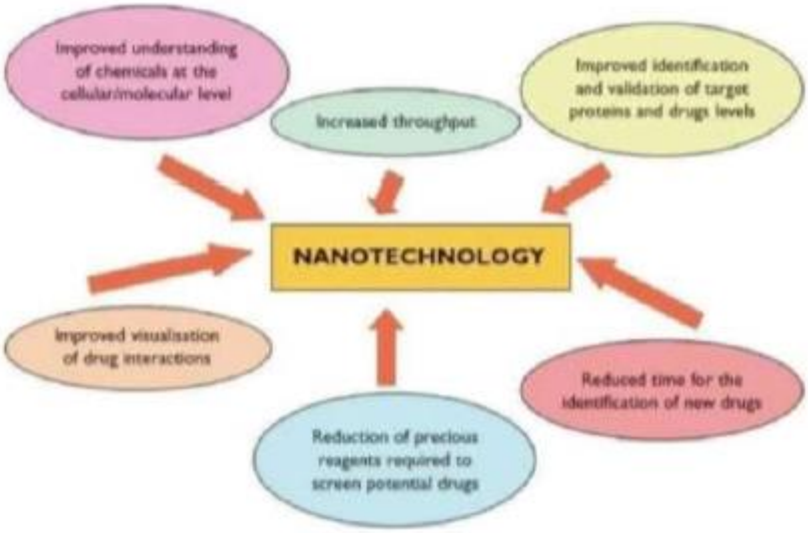
5.5 Multi-Drug Loading

Advanced nanocarriers can simultaneously encapsulate multiple therapeutic agents with different physicochemical properties, enabling combination therapy with synergistic effects.[40] For example, liposomes can co-encapsulate a hydrophilic drug in the aqueous core and a hydrophobic drug in the lipid bilayer, enabling precise ratiometric delivery for combination cancer therapy.

5.6 Reduced Dosing Frequency and Enhanced Compliance

Controlled-release nano formulations reduce the frequency of drug administration, minimizing peak-trough plasma concentration fluctuations and improving patient compliance. Sustained-release PLGA nanoparticles for hormonal therapy or antipsychotic drugs can maintain therapeutic levels for weeks with a single administration.[41]

Fig 02 : Advantages of Nanotechnology



6. LIMITATIONS AND CHALLENGES OF NANOTECHNOLOGY

Despite their enormous promise, nanotechnology-based drug delivery systems face significant technical, biological, toxicological, and regulatory challenges that must be addressed for successful clinical translation.[42]

6.1 Manufacturing Scalability and Reproducibility

Scale-up from laboratory to industrial manufacturing while maintaining consistent particle size, morphology, and drug loading is a major challenge. Many preparation methods (e.g., nanoprecipitation, thin-film hydration) are difficult to scale up reproducibly. Batch-to-batch variability in nanoparticle properties can affect pharmacokinetics and therapeutic outcomes.[43]

6.2 Stability

Nanoparticles are thermodynamically unstable and prone to aggregation, Ostwald ripening, and physical instability during storage and in biological environments. Lipid-based nanoparticles may undergo oxidative degradation, while polymeric nanoparticles may hydrolyze under physiological conditions.[44] Lyophilization (freeze-drying) is commonly employed to improve long-term stability but adds to manufacturing complexity and cost.

6.3 Biological Barriers and Immune Clearance

Following systemic administration, nanoparticles are rapidly opsonized by serum proteins and cleared by the mononuclear phagocyte system (MPS), particularly in the liver and spleen.[45] PEGylation reduces opsonization but may induce anti-PEG antibodies with repeated dosing (the ABC phenomenon). Penetration through biological barriers such as the tumor stroma, blood-brain barrier, and mucus layers remains challenging.[46]

6.4 Toxicity and Safety Concerns

The unique properties of nanoparticles that make them valuable for drug delivery—small size, high reactivity, and ability to penetrate biological barriers—also raise concerns about potential toxicity.[47] Nanoparticles can generate reactive oxygen species (ROS), induce inflammation, disrupt mitochondrial function, and interact with cellular components in unpredictable ways. Cytotoxicity, genotoxicity, immunotoxicity, and neurotoxicity have been reported for various nanoparticle types in vitro and in vivo.[48]

6.5 High Development Cost

The development and clinical translation of nanomedicine is expensive, requiring specialized equipment for synthesis, characterization, and quality control, as well as extensive preclinical and clinical testing.[49] The complex regulatory requirements for nanomedicines add further to the development cost and timeline.

6.6 Regulatory Uncertainties

The regulatory landscape for nanomedicines is still evolving. There is lack of standardized characterization methods, clear definitions, and harmonized global guidelines for nanomedicine approval, which creates uncertainty for developers and slows clinical translation.[50]

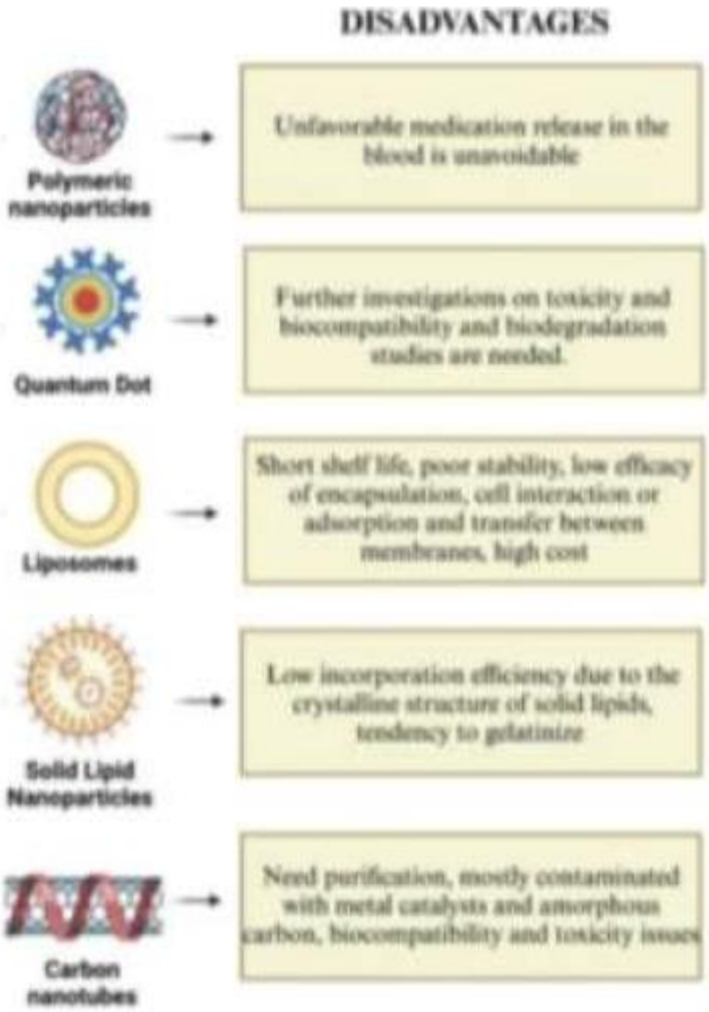


Fig. 03: Limitation of Nanotechnology

7. TYPES OF NANOCARRIERS

Nanocarriers are nanoscale colloidal systems designed to encapsulate, protect, and deliver therapeutic agents to specific sites in the body. They can be broadly classified as lipid-based, polymer-based inorganic-based, and carbon-based nanocarriers.[51] Table I summarizes the major types of nanocarriers, their size ranges, key features, and representative examples.

Table 1: Classification and Characteristics of Major Nanocarriers.

Nanocarrier Type	Size Range	Key Features	Examples
Liposomes	50–500 nm	Phospholipid bilayer; encapsulates hydrophilic and hydrophobic drugs	Doxil®, Ambisome®
Niosomes	100–500 nm	Non-ionic surfactant vesicles; stable alternative to liposomes	Span 60-based niosomes
SLN (Solid Lipid Nanoparticles)	50–1000 nm	Solid lipid matrix; high drug loading and stability	Compritol-based SLN
NLC (Nanostructured Lipid	100–500 nm	Solid and liquid lipid blend; reduces drug	Glyceryl behenate

Carriers)		expulsion	NLC
Polymeric NPs	10–1000 nm	Biodegradable; controlled release via PLGA, PLA	PLGA nanoparticles
Dendrimers	2–10 nm	Highly branched; precise drug conjugation	PAMAM dendrimers
Micelles	10–100 nm	Self-assembling amphiphilic block copolymers	PEG-PCL micelles
Nanoemulsions	20–200 nm	Oil-in-water or water-in-oil; thermodynamically stable	Propofol nanoemulsion
Carbon Nanotubes	0.5–50 nm dia	High surface area; functionalized for drug conjugation	SWCNT, MWCNT
Metallic NPs	1–100 nm	Gold, silver, iron oxide; imaging and photothermal therapy	AuNPs, Fe3O4 NPs

7.1 Liposomes

Liposomes are spherical vesicles composed of one or more concentric phospholipid bilayers surrounding an aqueous core.[52] They are the most clinically advanced nanocarrier system. The phospholipid bilayer mimics biological membrane structure, conferring excellent biocompatibility and biodegradability. Liposomes can encapsulate hydrophilic drugs in the aqueous core and hydrophobic drugs within the lipid bilayer, enabling versatile drug loading.[53]

Liposomes are classified as uniflagellar (small SUV: 20–100 nm; large LUV: 100–500 nm) or multilamellar vesicles (MLV: >500 nm). Sterically stabilized (stealth) liposomes are surface-coated with polyethylene glycol (PEG) to reduce opsonization and extend circulation half-life from minutes to over 24 hours.[54] Immunoliposomes bear surface-conjugated antibodies for active targeting. The first FDA-approved nanomedicine, Doxil® (PEGylated liposomal doxorubicin, 1995), demonstrated a 4-fold reduction in cardiotoxicity compared to free doxorubicin due to reduced cardiac tissue exposure.[55]

7.2 Niosomes

Niosomes are non-ionic surfactant-based vesicles structurally analogous to liposomes. They consist of non-ionic surfactants (Span 60, Brij, Tween) and cholesterol, forming bilayer structures that can encapsulate both hydrophilic and hydrophobic drugs.[56] Niosomes offer several advantages over liposomes including greater chemical stability due to the absence of oxidizable phospholipids, lower cost of non-ionic surfactants, and ease of preparation and storage.[57] Niosomes are particularly valuable for topical and transdermal drug delivery, enhancing skin permeation of drugs like cyclofenil, tretinoin, and oestradiol. Pronaoses—dry, free-flowing granules that hydrate to form noisome—offer improved stability and convenience of storage and transportation.[58]

7.3 Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles (SLNs), developed in the early 1990s, consist of a solid lipid matrix (glyceryl behenate, Compritol 888 ATO, beeswax, cetyl palmitate) stabilized by surfactant(s) in aqueous dispersion.[59] The solid lipid matrix provides structural rigidity, protecting encapsulated drugs from chemical degradation and providing sustained drug release through matrix erosion. SLNs are produced by hot or cold high-pressure homogenization (HPH) or microemulsion techniques. Key advantages include biodegradability, avoidance of organic solvents in preparation, suitability for lipophilic drug delivery, and potential for large-scale production.[60]

SLNs exhibit high drug loading efficiency for lipophilic drugs (log P > 3) and can be administered via multiple routes including parenteral, oral, pulmonary, and topical routes. However, SLNs have limitations including drug expulsion during polymorphic transitions of the lipid, low loading capacity for hydrophilic drugs, and relatively high polydispersity.[61]

7.4 Nanostructured Lipid Carriers (NLC)

Nanostructured Lipid Carriers (NLCs), developed as second-generation lipid nanoparticles, incorporate a blend of solid and liquid lipids (oils) to create an imperfect lipid crystal matrix with greater accommodation space for drug molecules.[62] The inclusion of liquid lipid creates physical disorder in the crystal structure, reducing drug expulsion and improving loading capacity 5–50 times compared to SLNs. NLCs can be formulated in three models: Type I (imperfect model), Type II (amorphous model), and Type III (multiple model).[63] NLCs offer superior drug loading, reduced drug leakage, during storage, improved physical stability, and enhanced skin penetration, making them particularly attractive for dermatological and cosmetic applications.[64]

7.5 Polymeric Nanoparticles

Polymeric nanoparticles are solid, colloidal systems (10–1000 nm) prepared from natural polymers (chitosan, alginate, gelatin, albumin) or synthetic polymers (PLGA, PLA, PCL, PMMA).[65] They exist as nanocapsules (drug in a polymeric shell) or nanospheres (drug dispersed in a polymeric matrix). Biodegradable and biocompatible PLGA (poly lactic-co-glycolic acid) nanoparticles are the most extensively studied due to their FDA-approved safety profile, predictable degradation kinetics, and ability to provide controlled drug release over days to months through polymer hydrolysis.[66]

Surface modification of polymeric nanoparticles with PEG extends circulation half-life, while conjugation with targeting ligands (folate, transferrin, RGD peptides, antibodies) achieves active targeting to tumor cells, the brain, and other pathological tissues. PLGA nanoparticles have been successfully developed for delivery of anticancer drugs (doxorubicin, paclitaxel, cisplatin), anti-TB drugs, vaccines, and gene therapy agents.[67]

7.6 Dendrimers

Dendrimers are highly symmetric, tree-like branched macromolecules with a precisely defined size, shape, and molecular weight. They consist of a central core, repetitive branching units (generations), and multiple terminal functional groups.[68] The most extensively studied dendrimer is PAMAM (polyamidation dendrimer), which has been evaluated for drug delivery, gene transfection, and imaging applications.

Dendrimers can incorporate drugs through electrostatic interactions, hydrophobic interactions, or covalent conjugation. Generation 4 (G4) and G5 PAMAM dendrimers have interior cavities capable of encapsulating hydrophobic drug molecules (host-guest chemistry) as well as surface groups for drug conjugation and targeting ligand attachment.[69]

Dendrimers offer unique advantages including monodisperse size distribution, multivalency (multiple drug molecules and targeting ligands per carrier), precise structural control, and high drug loading through dendrimer interior cavities. However cytotoxicity—particularly for cationic dendrimers—and complex synthesis procedures remain challenges.[70]

7.7 Polymeric Micelles

Polymeric micelles are self-assembling nanostructures formed by the spontaneous organization of amphiphilic block copolymers in aqueous media above the critical micelle concentration (CMC).[71] They consist of a hydrophobic core that solubilizes poorly water-soluble drugs and a hydrophilic corona (typically PEG) that ensures aqueous dispersibility, steric stabilization, and reduced non-specific protein adsorption.

Polymeric micelles typically have a diameter of 10–100 nm with a narrow size distribution and CMC values in the micromolar range (much lower than surfactant micelles), making them more stable *in vivo*.[72] Block copolymers commonly used include PEG-PLGA, PEG-PLA, PEG-PCL, and PEG-PS. Genexol-PM (paclitaxel-loaded PEG-PLGA micelles) has received regulatory approval in South Korea and is in Phase III clinical trials in the USA for breast and pancreatic cancer treatment.[73]

7.8 Nanoemulsions

Nanoemulsions are thermodynamically or kinetically stable emulsions with droplet diameters ranging from 20 to 200 nm. They consist of oil and water phases stabilized by surfactants (Cremophor EL, Tween 80, Labrasol) and co-surfactants.[74] Unlike macroemulsions, nanoemulsions possess greater transparency (optically clear), smaller droplet size, and higher physical stability against sedimentation or creaming.

Nanoemulsions can be oil-in-water (o/w) for parenteral or oral delivery of lipophilic drugs, or water-in-oil (w/o) for topical applications.[75] They have been used for delivery of propofol (parenteral anesthesia), cyclosporine A (topical ocular delivery), and various antifungals (topical formulations). Self-nanoemulsifying drug delivery systems (SNEDDS) are anhydrous lipid-surfactant mixtures that spontaneously emulsify upon contact with gastrointestinal fluids, dramatically improving oral bioavailability of BCS Class II drugs.[76]

7.9 Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical structures of rolled graphene sheets with extraordinary mechanical, electrical, and thermal properties.[77] Single-walled carbon nanotubes (SWCNTs) have a diameter of 0.4–2.5 nm, while multi-walled carbon Multi-walled carbon nanotubes (MWCNTs) have a diameter of 2–100 nm. The exceptionally high surface area and aspect ratio of CNTs allow loading of large amounts of drugs on their surfaces or in their hollow interiors through non-covalent (π-π stacking, hydrophobic interactions) or covalent interactions.[78] CNTs can penetrate cell membranes via endocytosis or nanopenetration, enabling intracellular drug delivery. Surface functionalization with carboxylic acid groups, PEG, antibodies, and targeting ligands improves biocompatibility, dispersibility, and active targeting.[79]

CNTs have been explored for delivery of anticancer drugs (doxorubicin, paclitaxel), gene therapy agents, and photosensitizers for photodynamic therapy. However, concerns about potential toxicity (similar to asbestos fibers) due to their fibrous morphology, biopersistence, and potential to penetrate cell nuclei and cause DNA damage must be carefully addressed.[80]

7.10 Metallic Nanoparticles

Metallic nanoparticles include gold nanoparticles (AuNPs), silver nanoparticles (AgNPs), iron oxide nanoparticles (IONPs, Fe_3O_4), titanium dioxide nanoparticles, and zinc oxide nanoparticles.[81] Gold nanoparticles possess unique size-tunable optical properties (surface plasmon resonance), high surface area for drug conjugation, and excellent biocompatibility, making them promising platforms for photothermal therapy, photodynamic therapy, and drug delivery.[82]

Gold nanorods and nanoshells efficiently absorb near-infrared (NIR) light and convert it to heat, enabling photothermal ablation of tumors. Iron oxide nanoparticles (IONPs) are superparamagnetic, enabling MRI contrast imaging, magnetic hyperthermia, and magnetically guided drug delivery.[83] Silver nanoparticles possess broad-spectrum antimicrobial activity and are explored for wound healing and anti-infective applications.

Surface functionalization of metallic nanoparticles with thiol-containing ligands, PEG, and targeting moieties is easily achieved through well-established gold-thiol chemistry.[84]

8. METHODS OF PREPARATION OF NANOPARTICLES

Nanoparticle preparation methods are broadly classified into two fundamental approaches: the top-down approach (physical methods) and the bottom-up approach (chemical/physicochemical methods).[85] The choice of method depends on the nanocarrier type, desired particle properties, drug characteristics, and intended route of administration.

8.1 Top-Down Approach

The top-down approach involves the breakdown of bulk materials into nanoscale particles through mechanical or physical processes. This approach does not require chemical synthesis and is generally scalable for industrial production. However, it may result in broader particle size distributions and surface defects.[86]

8.1.1 High-Pressure Homogenization (HPH)

High-pressure homogenization (HPH) is the most widely used top-down method for preparation of SLNs, NLCs, and nanoemulsions. In HPH, the pre-emulsion is forced through a narrow gap under pressures of 100–2000 bar, causing intense cavitation forces, shear, and turbulence that disrupt particle size to the nanometer range [87]. Two variants exist: hot HPH (drug and lipid above melting point) and cold HPH (suitable for heat-sensitive drugs, lipid below melting point). HPH is readily scalable to pilot and industrial scale using commercially available homogenizers (Avestin Emulsiflex, APV Gaulin).

8.1.2 Media Milling (Nanomilling)

Media milling or pearl milling employs small balls (0.2–3 mm pearl balls) of grinding media in a high-speed milling vessel to reduce micron-sized drug crystals to nanosuspensions with particle sizes of 100–500 nm. The Nanocrystal® technology (Élan Drug Technologies) uses this approach and has been successfully scaled up for several commercial products including Rapamune® (sirolimus) and Emend® (aprepitant).[88]

8.1.3 Sonication and Microfluidization

Probe sonication and bath sonication apply ultrasonic energy to disrupt particle aggregates and reduce particle size. Microfluidization uses high-pressure interaction chambers to achieve nanoemulsification through simultaneous impingement of two fluid streams.[89]

8.2 Bottom-Up Approach

The bottom-up approach involves the assembly of nanostructures from atomic, molecular, or macromolecular building blocks through controlled physicochemical processes. This approach enables precise control over particle size, morphology, and surface properties, though scalability can be challenging.[90]

8.2.1 Solvent Injection / Nanoprecipitation

The nanoprecipitation method (Fessi method) involves dissolving the polymer and drug in an organic solvent (acetone, ethanol) and injecting it into an aqueous non-solvent phase under magnetic stirring. The rapid diffusion of the organic solvent causes precipitation of polymer-drug nanoparticles of 100–300 nm. This simple, reproducible, and solvent-friendly method is widely used for PLGA nanoparticles.[91]

8.2.2 Emulsification-Solvent Evaporation

In this method, the drug and polymer are dissolved in an organic solvent, emulsified into an aqueous phase with a surfactant by sonication or homogenization, and the organic solvent is subsequently evaporated under reduced pressure to form nanoparticles. Single-emulsion (o/w) is used for hydrophobic drugs; double-emulsion (w/o/w) is used for hydrophilic drugs and peptides.[92]

8.2.3 Thin-Film Hydration (Liposome Preparation)

This is the classical method for liposome preparation. Phospholipids are dissolved in an organic solvent (chloroform or methanol), the solvent is evaporated under vacuum to form a dry thin lipid film, and the film is hydrated with an aqueous buffer under agitation above the phase transition temperature of the lipid.[93] The resulting multilamellar vesicles (MLVs) are extruded through polycarbonate membranes (100–400 nm pore size) using a Lipex extruder to produce unilamellar liposomes of defined size.

Drug encapsulation is achieved either during the hydration step (passive loading) or after liposome formation using pH gradient or ammonium sulfate gradient active loading methods.

8.2.4 Self-Assembly

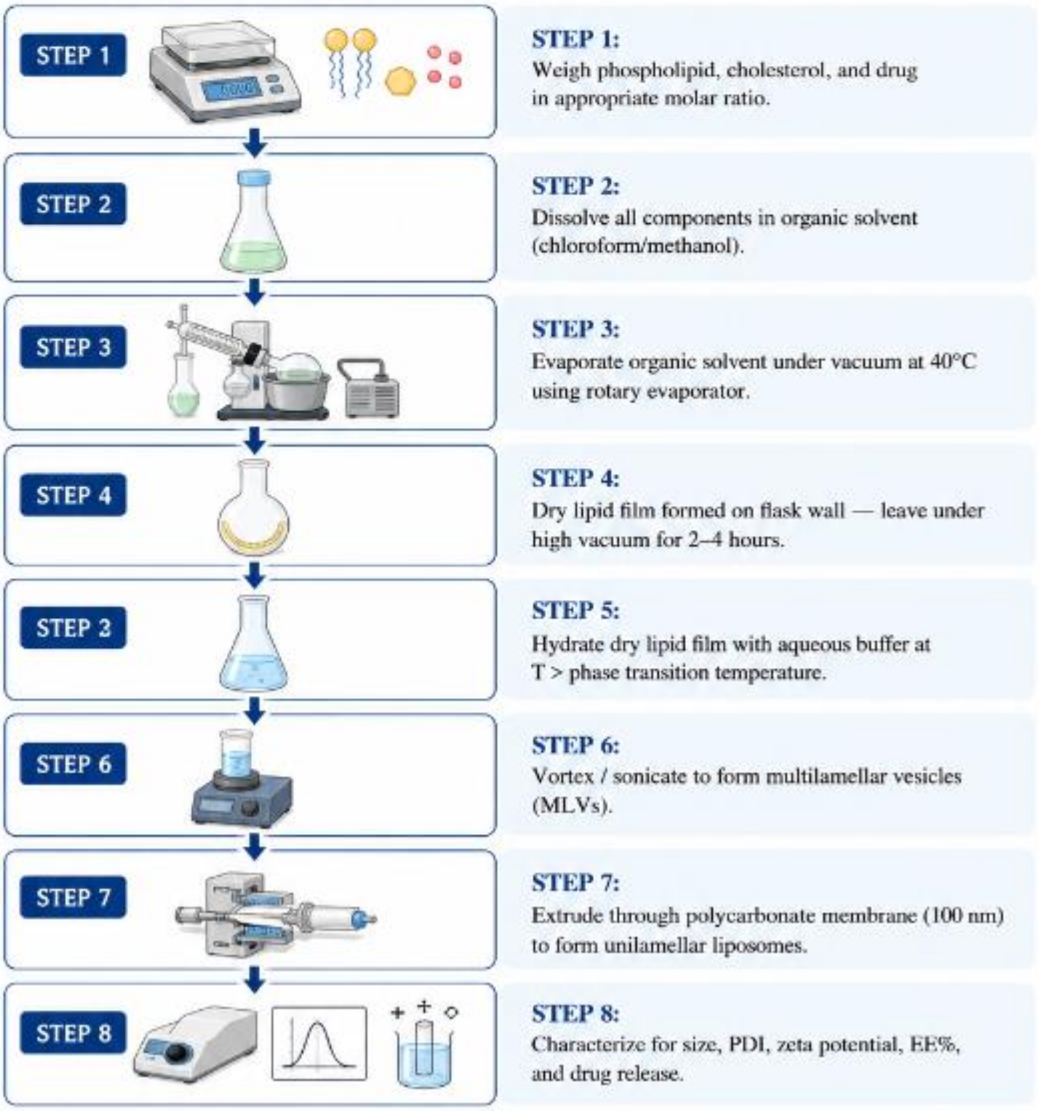
Block copolymer micelles and dendrimers self-assemble from their building blocks in aqueous media through hydrophobic interactions, electrostatic interactions, and hydrogen bonding. The critical micelle concentration (CMC) and critical aggregation concentration (CAC) are thermodynamic parameters governing the stability of self-assembled nanostructures.[94]

8.2.5 Ionic Gelation and Coacervation

Chitosan nanoparticles are prepared by ionic gelation with tripolyphosphate (TPP), which cross-links the positively charged chitosan chains to form spontaneous nanoparticles of 200–400 nm size. Gelatin nanoparticles are prepared by coacervation—the desolvation of the polymer by controlled addition of a non-solvent (acetone) followed by chemical cross-linking with glutaraldehyde.[95]

Table 2: Comparison of Top-Down and Bottom-Up Approaches for Nanoparticle Preparation

Parameter	**Top-Down Approach**	**Bottom-Up Approach**
Principle	Breakdown of bulk material	Assembly from atomic/molecular units
Methods	Milling, High-pressure homogenization	Self-assembly, Chemical synthesis
Size Control	Less precise	Highly precise
Cost	High energy consumption	Lower energy use
Surface Defects	More surface defects	Minimal defects
Scalability	Good for large batches	Challenging for scale-up
Examples	Nanosuspensions by pearl milling	Liposomes, dendrimers synthesis



STEP 1: Weigh phospholipid, cholesterol, and drug in appropriate molar ratio.

STEP 2: Dissolve all components in organic solvent (chloroform/methanol).

STEP 3: Evaporate organic solvent under vacuum at 40°C using rotary evaporator.

STEP 4: Dry lipid film formed on flask wall — leave under high vacuum for 2–4 hours.

STEP 5: Hydrate dry lipid film with aqueous buffer at T > phase transition temperature.

STEP 6: Vortex / sonicate to form multilamellar vesicles (MLVs).

STEP 7: Extrude through polycarbonate membrane (100 nm) to form unilamellar liposomes.

STEP 8: Characterize for size, PDI, zeta potential, EE%, and drug release.

Figure 1: Flowchart – Preparation of Liposomes by Thin-Film Hydration Method.

FUTURE PERSPECTIVES

The future of nanotechnology in drug delivery is extraordinarily promising, driven by convergence with advanced biology, artificial intelligence, precision medicine, and advanced manufacturing technologies.[151] Several key directions will shape the next decade of nanomedicine development.

Personalized or precision nanomedicine—tailoring nanoparticle formulations based on a patient's genetic profile, tumor microenvironment, and disease stage—is expected to become a clinical reality. Patient-specific targeting ligands based on genomic profiling, combined with patient-derived tumor organoid models for predicting nanoparticle performance, will enable individualized nanomedicine design.[152]

The integration of theragnostic nanoparticles—combining therapeutic and diagnostic functions in a single nano platform will enable real-time monitoring of treatment response and dose adjustment. Iron oxide nanoparticles loaded with therapeutic agents provide simultaneous MRI-guided therapy. Gold nano shells enable optical coherence tomography imaging and photothermal therapy.[153]

Overcoming the EPR variability in clinical patients—a significant limitation for passive targeting strategies—will be addressed through strategies including vascular normalization with anti-angiogenic agents, photodynamic priming of tumor vasculature, and use of ultrasound/microbubbles to transiently increase vascular permeability.[154]

The development of oral biologics using nanoparticle carriers—enabling oral delivery of insulin, GLP-1 agonists, antibodies, and nucleic acids—remains a major unmet clinical need. Mucus-penetrating nanoparticles (MPP) coated with PEG can traverse the intestinal mucus layer, reaching the epithelium for absorption of large biomolecules.[155]

Advanced manufacturing technologies including microfluidics, continuous flow synthesis, and 3D bioprinting will enable precise, scalable, and reproducible production of nanoparticles with exceptional batch-to-batch consistency, addressing the major manufacturing challenges that currently limit clinical translation.[156]

Nanotechnology for treating infectious diseases—including antibiotic-loaded nanoparticles for drug-resistant bacterial infections (MRSA, MDR-TB), nanomedicine for HIV/AIDS, and antifungal nanoformulations—is a rapidly growing area driven by the global antimicrobial resistance crisis.[157]

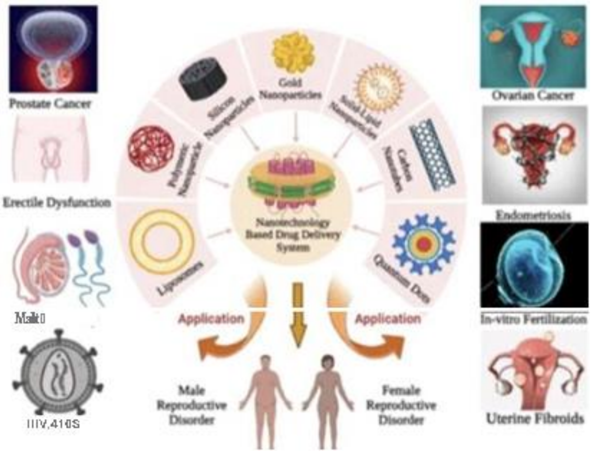


Fig. 04: Future Perspective of Nanotechnology.

CONCLUSION

Nanotechnology has undeniably transformed the landscape of drug delivery, offering elegant solutions to many of the fundamental challenges that have long limited the therapeutic potential of pharmacologically active agents. By engineering drug carriers at the nanoscale, pharmaceutical scientists have achieved remarkable improvements in drug solubility, bioavailability, stability, pharmacokinetics, targeted delivery, and controlled release that were not possible with conventional formulation approaches.

The diverse array of nanocarrier platforms—including liposomes, niosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, dendrimers, micelles, nanoemulsions, carbon nanotubes, and metallic nanoparticles—offers versatile options for the delivery of a wide spectrum of therapeutic agents including hydrophilic and hydrophobic small molecules, peptides, proteins, nucleic acids, and theranostic agents by virtually every route of administration.

The clinical successes of Doxil®, Abraxane®, Onpattro®, and the COVID-19 mRNA-LNP vaccines stand as definitive proof-of-concept for the clinical utility of nanotechnology in drug delivery and have provided the scientific community and industry with validated regulatory pathways and manufacturing frameworks for future nanomedicine development.

However, significant challenges remain in the areas of manufacturing scalability, long-term stability, biocompatibility and toxicity assessment, immune interactions, and the establishment of harmonized global regulatory frameworks. The EPR effect, while a powerful rationale for passive tumor targeting, is increasingly recognized to be heterogeneous across tumor types and patient populations, necessitating complementary active targeting strategies and improved vascular access approaches.

The future of nanomedicine lies in the convergence of nanotechnology with artificial intelligence, precision medicine, CRISPR gene editing, biomimicry, and advanced manufacturing to develop intelligent, personalized, and clinically translatable nanotherapeutic platforms. The continued collaboration between academic researchers, clinicians, industry partners, and regulatory agencies will be essential to realize the full therapeutic potential of nanotechnology and bring its benefits to patients across the globe.

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