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A REVIEW ON NANOPARTICLES IN MEDICINES: A BREAKTHROUGH APPROACH TO TARGETED DRUG DELIVERY

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ABSTRACT

The emergence of nanotechnology has significantly advanced the field of drug delivery, offering innovative solutions to overcome longstanding challenges in traditional pharmacotherapy, such as poor bioavailability, systemic toxicity, and non-specific drug distribution. This review explores the role of nanoparticles as a breakthrough approach in targeted drug delivery systems. Various types of nanoparticles including liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles—are discussed in terms of their design, functionality, and clinical potential. Emphasis is placed on the mechanisms by which nanoparticles enhance drug targeting to specific sites, such as tumours and inflamed tissues, thereby improving therapeutic efficacy while minimizing adverse effects. Additionally, the review addresses current limitations, including biocompatibility, scalability, and regulatory hurdles, and highlights recent advances that pave the way for the successful translation of nanomedicine into clinical practice. Overall, nanoparticles represent a transformative strategy in modern medicine, holding great promise for personalized, efficient, and safer drug delivery.

KEYWORDS: Nanoparticles, Nanocarriers, Targeted delivery, Theragnostic, Applications.

INTRODUCTION

Drug delivery is a critical aspect of pharmaceutical development and clinical therapy. Despite advances in drug discovery, many therapeutic agents fail to achieve optimal efficacy due to challenges in their delivery to the intended site of action.[1] There are some of the key challenges in drug delivery:

1. **Low bioavailability:** Bioavailability refers to the proportion of a drug that enters systemic circulation in an active form after administration. The reasons for low bioavailability of drugs due to several reasons:[1]
   - i. **Poor solubility:** Many drugs are hydrophobic and do not dissolve well in aqueous biological fluids.[1]
   - ii. **Degradation:** Drugs can be degraded by enzymes in the gastrointestinal tract (e.g., proteases, nucleases).[1]
   - iii. **First-pass metabolism:** Drugs taken orally are metabolized by the liver before reaching systemic circulation, reducing active drug levels.[1]
   - iv. **Poor permeability:** Some drugs cannot efficiently cross biological membranes such as the intestinal epithelium or blood-brain barrier.[1]

2. **Systemic Toxicity:** Toxic effects of a drug that occur when it affects tissues or organs outside the target site. The systemic toxicity of drugs occurs due to following reasons:[1]
   - i. **Non-specific distribution:** Drugs often circulate throughout the body, affecting healthy tissues.[1]
   - ii. **High doses of drugs:** Due to low bioavailability or poor targeting, higher doses are needed, increasing the risk of toxicity.[1]
   - iii. **Accumulation:** Drugs with long half-lives or slow clearance can accumulate in organs, especially the liver and kidneys.[1]

3. **Targeting and Specificity**
   - i. **Lack of Targeting:** Many drugs cannot selectively reach or accumulate in diseased tissues (e.g., tumours, infections), leading to reduced efficacy and off- target effects.[1]
   - ii. **Biological barriers:** Barriers like the blood-brain barrier, mucosal layers, and cellular membranes limit drug access to certain tissues.[1]

4. **Drug Stability**
   - i. **Chemical instability:** Some drugs degrade when exposed to light, oxygen, moisture, or varying pH conditions.[1]

ii. **Biological instability:** Enzymatic degradation can render drugs inactive before they reach their target.[1]

5. **Patient Compliance**

i. **Frequent dosing:** Drugs with short half-lives require multiple doses per day, which can lead to poor adherence.[1]

ii. **Side effects:** Unpleasant or dangerous side effects can discourage patients from continuing treatment.[1]

6. **Controlled and Sustained Release:** Ensuring that drugs are released at a controlled rate over a period of time to maintain therapeutic levels is a major challenge, especially in chronic diseases.[1]

7. **Formulation and Delivery Route Limitations**

i. **Oral delivery:** Convenient but not suitable for all drugs, especially peptides and proteins.[1]

ii. **Parenteral delivery (e.g., injections):** More invasive and less accepted by patients, especially for chronic treatments.[1]

iii. **Topical, inhalation, and transdermal routes:** Limited by penetration depth and absorption variability.[1]

There are several emerging strategies to overcome the above challenges: such as, nanocarriers (e.g., liposomes, nanoparticles), targeted drug delivery systems (e.g., ligand- receptor targeting), controlled release formulations (e.g., hydrogels, implantable devices), and prodrugs (chemically modified to enhance bioavailability and stability).[2]

Nanotechnology is the science and engineering of materials and devices at the nano meter scale, typically ranging from 1 to 100 nano meters. At this scale, materials exhibit unique physical, chemical, and biological properties that differ significantly from their bulk counterparts. These properties such as increased surface area, enhanced reactivity, and tuneable optical or magnetic behaviour make nanotechnology particularly attractive for applications in medicine, especially in pharmacology.[2]

What are Nanoparticles?

Nanoparticles are extremely small particles with dimensions typically in the range of 1 to 100 nano meters. They can be made from various materials, including polymers, lipids, metals, and ceramics. Nanoparticles have gained significant attention in the field of drug delivery due to their unique properties that make them suitable for targeted and controlled release of therapeutic agents.[2]

The convergence of nanotechnology and pharmacology has given rise to “nanomedicine,” a rapidly evolving interdisciplinary field focused on the application of nanoscale materials and devices for the diagnosis, treatment, and prevention of diseases. In pharmacology, nanotechnology is revolutionizing drug development and delivery by addressing some of the most persistent challenges in traditional drug therapy, such as: poor bioavailability, systemic toxicity, non-specific drug distribution, uncontrolled drug release, barrier penetration (e.g., blood-brain barrier).[2]

Key Nanotechnology Platforms in Drug Delivery[3]

1. **Liposomes:** Phospholipid bilayer vesicles that can encapsulate both hydrophilic and hydrophobic drugs. Used in FDA-approved drugs like Doxil® (liposomal doxorubicin) for cancer treatment.
2. **Polymeric Nanoparticles**: Biodegradable particles made from polymers like PLGA. Enable controlled and sustained release of drugs.
3. **Solid Lipid Nanoparticles (SLNs)**: Combine the advantages of liposomes and polymeric nanoparticles with improved stability.
4. **Dendrimers**: Highly branched, tree-like macromolecules with multiple functional end groups for drug loading and targeting.
5. **Nanoemulsions:** Oil-in-water or water-in-oil emulsions that improve the solubility of poorly water-soluble drugs.
6. **Inorganic Nanoparticles:** Gold nanoparticles, iron oxide nanoparticles, and quantum dots are used for drug delivery, imaging, and theragnostic.

Advantages of Nanoparticles in Drug Delivery[4]

- **Targeted Delivery:** Nanoparticles can be designed to target specific cells or tissues, allowing for the drug to be delivered directly to the site of action, reducing side effects. Nanocarriers can be engineered to accumulate in specific tissues (e.g., tumours) via passive (EPR effect) or active targeting mechanisms.
- **Controlled Release:** Nanoparticles can be designed to release drugs in a controlled manner by maintaining therapeutic levels over time, and also providing sustained therapeutic effects and minimizing the need for frequent dosing.
- **Enhanced Solubility:** Poor solubility of certain drugs can be improved by encapsulating them within nanoparticles, thus enhancing bioavailability hydrophobic drugs.
- **Protection of Drugs:** Nanoparticles can protect drugs from degradation in the body, improving their stability.
- **Reduced Side Effects**: By delivering drugs specifically to diseased cells, healthy tissues are spared, minimizing systemic toxicity.
- **Multifunctionality**: Nanocarriers can be designed to combine therapeutic and diagnostic functions (termed as “theragnostic”).
- **Overcoming Biological Barriers**: (e.g., Blood Brain Barrier, cell membranes).
- Enhanced patient compliance.

Importance of Targeting Drugs to Specific Sites (e.g., Tumors, Inflamed Tissues):[4] One of the most critical goals in modern pharmacology and drug delivery is the precise targeting of drugs to specific tissues or cells, such as tumours or inflamed areas. This targeted approach addresses many limitations of conventional drug therapy, where drugs are distributed systemically and affect both diseased and healthy tissues.

1. **Enhancing Therapeutic Efficacy**[4]
- **Localized Concentration:** Targeting increases drug accumulation at the disease site, ensuring higher local concentrations where the drug is most needed.
- **Overcoming Resistance:** For example, in cancer therapy, targeted delivery can bypass some resistance mechanisms by directly delivering cytotoxic agents into resistant tumor cells.

2. **Reducing Systemic Toxicity and Side Effects**[4]
- **Minimizing Off-Target Effects:** Many potent drugs (e.g., chemotherapy agents) cause severe side effects when they interact with healthy tissues.
- **Improved Tolerability:** By confining drug action to the disease site, patients experience fewer adverse reactions, which can improve compliance and overall outcomes.

3. **Overcoming Biological Barriers**[4]
- **Tumor Microenvironment:** Solid tumours have unique physiological features (e.g., leaky vasculature, acidic pH) that can be exploited using targeted drug delivery systems such as nanoparticles.
- **Inflamed Tissues:** Sites of inflammation often exhibit enhanced permeability and retention (EPR), allowing for passive targeting of nanocarriers.
- **Blood-Brain Barrier (BBB):** Site-specific delivery systems can be designed to cross the BBB, making treatment of neurological disorders more feasible.

4. **Allowing for Lower Doses**[4]
- **Higher Local Efficacy:** With precise targeting, smaller doses may achieve therapeutic effects, which reduces drug load and minimizes systemic exposure.
- **Reduced Drug Wastage:** More of the administered drug reaches its intended target rather than being metabolized or excreted without therapeutic benefit.

5. **Enabling Personalized and Precision Medicine**[4]
- **Biomarker-Driven Targeting:** Drugs can be attached to ligands (e.g., antibodies, peptides) that recognize specific markers on tumor cells or inflamed tissues.
- **Adaptive Therapy:** Drug delivery systems can be designed to respond to stimuli in the target environment (e.g., pH, enzymes, temperature) for controlled release.

6. **Applications in Disease-Specific Contexts**[4]
- **Cancer:** Tumor-targeting drugs reduce the need for high-dose chemotherapy and mitigate toxic effects like immunosuppression, hair loss, and nausea.
- **Autoimmune Diseases:** Targeting inflamed joints in rheumatoid arthritis or intestinal tissues in inflammatory bowel disease (IBD) can avoid systemic immunosuppression.
- **Infectious Diseases:** Targeting infected tissues helps contain infections and avoid harm to normal flora or immune tissues.

Types of Nanoparticles for Drug Delivery[5]

1. **Lipid-based Nanoparticles:** Liposomes and lipid nanoparticles are composed of lipid bilayers and can encapsulate hydrophilic and lipophilic drugs.
2. **Solid Lipid Nanoparticles**: It is used for improved drug stability.
3. **Polymeric Nanoparticles:** These are made from biocompatible polymers and can be tailored for specific drug release kinetics, targeting, and controlled drug release.
4. **Metal Nanoparticles:** Gold, silver, and other metal nanoparticles have unique properties and can be functionalized for drug delivery and imaging such as, Gold/silver nanoparticles for theragnostic applications.
5. **Dendrimers:** Highly branched polymers that can carry drugs on their surface or within their structure such as, Quantum dots and carbon nanotubes.
6. **Mesoporous Silica Nanoparticles:** These have porous structures that can host drug molecules within their pores such as nanocomposites.

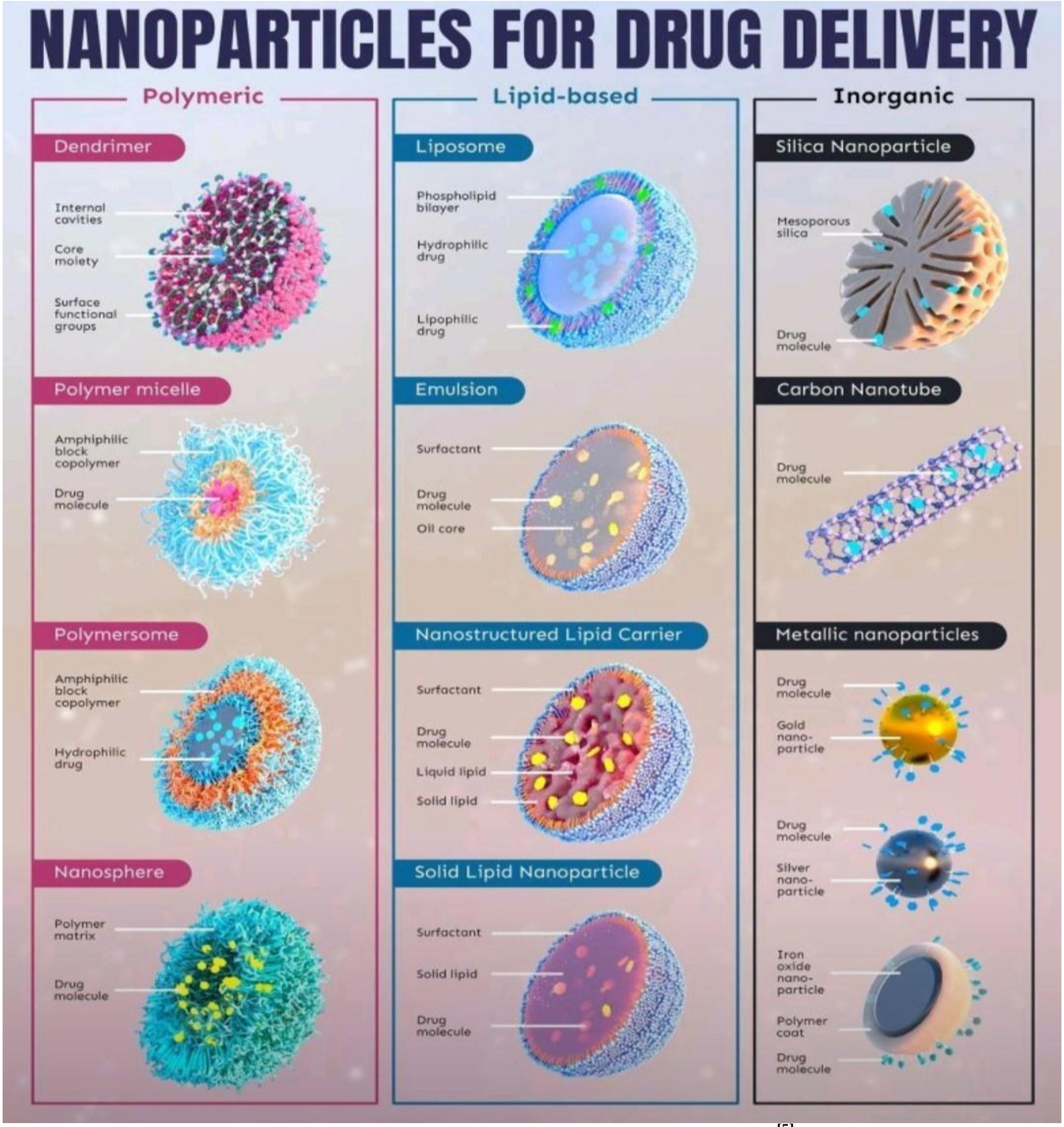

Figure 1: Types of Nanoparticles for Drug Delivery.[5]

Ideal Characteristics of Nanoparticles[5]

- **Biocompatibility:** Nanoparticles must be biocompatible to avoid adverse reactions in the body.
- **Size and Shape:** The size and shape of nanoparticles can influence their biodistribution and cellular uptake.
- **Stability:** Nanoparticles should remain stable during storage and circulation in the body.
- **Controlled Release:** Achieving precise control over drug release kinetics can be challenging.
- **Regulatory Approval:** Nanoparticles for drug delivery require rigorous safety and efficacy testing for regulatory approval.

Mechanisms of Targeted Drug Delivery Using Nanoparticles[6]

a. Passive Targeting

- Enhanced permeability and retention (EPR) effect.
- Tumor microenvironment exploitation.

b. Active Targeting

- Ligand-receptor interactions.
- Surface functionalization with antibodies, peptides, or aptamers.

c. Stimuli-Responsive Delivery

- pH, temperature, enzyme-sensitive nanoparticles.

Applications in Medicine[6]

- **Cancer therapy** – e.g., paclitaxel-loaded nanoparticles.

- **Infectious diseases** – antimicrobial-loaded NPs.
- **Cardiovascular diseases** – targeted thrombolytic delivery.
- **Neurological disorders** – crossing the blood-brain barrier.
- **Gene therapy and vaccines** – nucleic acid delivery using lipid nanoparticles (e.g., mRNA COVID-19 vaccines).

Challenges and Limitations[7]

- Biocompatibility and toxicity concerns.
- Large-scale manufacturing and reproducibility.
- Regulatory hurdles and high cost.
- Clearance and biodistribution unpredictability.

APPLICATIONS & FUTURE PERSPECTIVES[8]

The field of nanomedicine is rapidly evolving, and several promising directions are shaping its trajectory. Future advancements are expected to go beyond current capabilities, incorporating cutting-edge technologies and interdisciplinary insights. The following key areas highlight transformative trends in the future of nanoparticle-based drug delivery:

1. **Personalized Nanomedicine:** Personalized nanomedicine involves designing nanoparticle-based therapies tailored to an individual's genetic, molecular, and pathological profile. By integrating patient-specific biomarkers with targeted delivery systems, treatments can be customized to achieve maximum therapeutic effect with minimal side effects:

- **Biomarker-driven targeting:** Use of genomic, proteomic, and metabolomic data to identify disease-specific targets for nanoparticle conjugation.
- **Customizable nanocarriers:** Modular nanoparticle platforms that can be rapidly adapted to different patient profiles or disease subtypes.
- **Companion diagnostics:** Integration of nanoparticles with imaging agents to monitor drug distribution and treatment efficacy in real time.

This approach enhances treatment precision, improves patient outcomes, and minimizes trial-and-error drug regimens, ultimately contributing to the broader goal of precision medicine.

2. **Smart Nanoparticles (AI-Integrated, Feedback-Responsive):** Smart nanoparticles are advanced nanocarriers capable of responding to specific stimuli (e.g., pH, enzymes, temperature) or external cues (e.g., magnetic fields, light) to trigger drug release at the right time and place. Future iterations are expected to integrate artificial intelligence (AI) and biosensors for real-time decision-making and autonomous therapeutic responses:

- **Stimuli-responsive systems:** Nanoparticles that release drugs only in response to tumor- specific conditions or inflammatory signals.
- **AI-guided design and optimization:** Use of machine learning algorithms to predict optimal nanoparticle configurations based on patient data.
- **Closed-loop systems:** Feedback-based nanoparticles capable of detecting disease progression markers and adjusting drug release accordingly.

Smart nanoparticles reduce the need for external intervention, increase delivery precision, and offer dynamic treatment strategies in complex diseases like cancer, autoimmune disorders, and metabolic conditions.

3. **Nanorobotics for Precision Therapy:** Nanorobots are tiny, programmable machines at the nanoscale that can navigate through the human body, diagnose conditions, and deliver therapies at the cellular or even subcellular level. Though still in early stages, their potential in revolutionizing precision therapy is enormous.

- **Navigation and control:** Development of nanorobots capable of directed movement via external magnetic fields or autonomous propulsion.
- **On-board diagnostics and delivery:** Integration of sensors and therapeutic payloads to diagnose and treat conditions in situ.
- **Cell-specific interaction:** Nanorobots designed to recognize and interact with specific cell types, such as cancer stem cells or infected macrophages.

Nanorobotics may enable ultra-precise, minimally invasive interventions such as unclogging arteries, destroying tumours cell-by-cell, or delivering gene therapies directly into the nucleus ushering in a new era of micro-invasive medicine.

4. **Greater Interdisciplinary Collaboration:** The future of nanomedicine relies heavily on cross-disciplinary collaboration among fields such as materials science, pharmacology, data science, biomedical engineering, and clinical medicine.

- Collaborative innovation platforms: Integration of research hubs and consortia that bring together diverse experts to co-develop next-generation nano-therapies.
- Unified regulatory frameworks: Engagement of regulatory scientists to develop flexible guidelines that accommodate the complexity of nanoparticle systems.
- Translational pipelines: Strengthening partnerships between academia, biotech, and healthcare sectors to streamline bench-to-bedside transitions.

Interdisciplinary synergy accelerates innovation, ensures clinical relevance, and supports the development of safer, more effective, and scalable nanomedicine solutions.

GENERAL METHODS FOR THE PREPARATION OF NANOPARTICLES[9,10,11]

The preparation of nanoparticles involves various physical, chemical, and biological approaches, each tailored to achieve specific particle sizes, surface properties, and drug encapsulation efficiencies. These methods can be broadly classified into two categories:

1. **Top-Down Methods:** These techniques involve breaking down bulk materials into nanosized particles using physical or mechanical processes.

a. Milling (Mechanical Attrition)

- **Principle:** Uses high-energy ball mills to reduce particle size.
- **Applications:** Suitable for inorganic nanoparticles or crystalline drug formulations.
- **Advantages:** Scalable; simple process.
- **Limitations:** Poor control over particle size distribution and surface properties.

b. High-Pressure Homogenization

- **Principle:** Forces a suspension through a narrow gap at high pressure, leading to particle disruption.
- **Applications:** Commonly used for lipid-based nanoparticles (e.g., solid lipid nanoparticles).
- **Advantages:** Produces uniform particles; scalable.
- **Limitations:** Heat generation can degrade thermolabile drugs.

2. **Bottom-Up Methods:** These approaches build nanoparticles from molecular or atomic units through chemical or biological synthesis.

a. Solvent Evaporation Method

- **Principle:** A drug-polymer solution is emulsified into an aqueous phase; the organic solvent is then evaporated, forming nanoparticles.
- **Applications:** Polymeric nanoparticles (e.g., PLGA).
- **Advantages:** Good encapsulation efficiency; applicable to hydrophobic drugs.
- **Limitations:** Requires organic solvents; residual solvent toxicity is a concern.

b. Nanoprecipitation (Solvent Displacement)

- **Principle:** A solution of the drug and polymer in a water-miscible organic solvent is added to an aqueous phase, leading to spontaneous nanoparticle formation.
- **Advantages:** Simple and fast; good for hydrophobic drugs.
- **Limitations:** Limited to low-viscosity systems; low yield in some cases.

c. Emulsification-Solvent Diffusion

- **Principle:** Involves forming an oil-in-water emulsion followed by solvent diffusion, leading to nanoparticle formation.
- **Applications:** Used for biodegradable polymer nanoparticles.
- **Advantages:** Avoids high shear forces; suitable for sensitive molecules.
- **Limitations:** Emulsion stability is critical; multistep process.

d. Ionic Gelation (Polyelectrolyte Complexation)

- **Principle:** Oppositely charged polymers (e.g., chitosan and tripolyphosphate) are mixed to form nanoparticles through electrostatic interaction.
- **Applications:** Ideal for protein or nucleic acid delivery.
- **Advantages:** Mild conditions; suitable for hydrophilic drugs.
- **Limitations:** Particle stability can be an issue; pH-sensitive.

e. Supercritical Fluid Technology

- **Principle:** Supercritical fluids (e.g., CO_2) are used to precipitate solutes into nanoparticles.
- **Advantages:** Solvent-free or low solvent; environmentally friendly.
- **Limitations:** Requires specialized equipment and high pressure.

3. **Emerging and Hybrid Methods**

- **Microfluidics:** Enables precise control of nanoparticle size and uniformity using small- scale flow channels.
- **Spray Drying:** Converts a liquid feed into dry nanoparticles by rapid evaporation.
- **Green Synthesis:** Uses biological agents (e.g., plant extracts, microbes) for eco-friendly nanoparticle synthesis.

GENERAL EVALUATION PARAMETERS OF NANOPARTICLES[12,13]

Evaluating nanoparticles is essential to ensure their safety, efficacy, stability, and suitability for biomedical applications, particularly in drug delivery. These evaluation parameters can be broadly categorized into physicochemical, biological, and functional assessments.

1. Physicochemical Characterization

a. Particle Size and Size Distribution

- **Techniques:** Dynamic Light Scattering (DLS), Nanoparticle Tracking Analysis (NTA), Electron Microscopy (SEM/TEM).
- **Importance:** Influences drug release, cellular uptake, biodistribution, and stability.

b. Zeta Potential

- **Technique:** Electrophoretic Light Scattering.
- **Importance:** Indicates surface charge, predicting stability and interaction with biological membranes. Typically, values > ±30 mV suggest good stability.

c. Morphology and Surface Topography

- **Techniques:** Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM).
- **Importance:** Provides insight into particle shape (spherical, rod, irregular), surface smoothness, and potential aggregation.

d. Drug Loading and Encapsulation Efficiency

- **Techniques:** UV-Vis Spectrophotometry, HPLC.
- **Importance:** Determines the amount of drug incorporated into nanoparticles and the effectiveness of the delivery system.

e. Surface Area and Porosity

- **Technique:** BET (Brunauer–Emmett–Teller) analysis.
- **Importance:** Affects drug adsorption capacity and release kinetics.

f. Crystallinity and Physical State

- **Techniques:** X-Ray Diffraction (XRD), Differential Scanning Calorimetry (DSC).
- **Importance:** Identifies the physical state of the drug (amorphous or crystalline) within nanoparticles, influencing stability and dissolution.

g. Chemical Composition and Functional Groups

- **Techniques:** Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), Raman Spectroscopy.
- **Importance:** Confirms the presence of functional groups, chemical bonding, and possible drug–carrier interactions.

2. In-vitro Biological Evaluation

a. Drug Release Profile

- **Technique:** Dialysis method, Franz diffusion cell.
- **Importance:** Assesses release kinetics (e.g., burst release, sustained release) under physiological conditions.

b. Cytotoxicity

- **Techniques:** MTT assay, LDH assay, Trypan Blue exclusion.
- **Importance:** Evaluates the biocompatibility of nanoparticles with normal and diseased cells.

c. Cellular Uptake

- **Techniques:** Confocal microscopy, Flow cytometry.
- **Importance:** Measures how effectively nanoparticles enter target cells.

d. Hemocompatibility

- **Techniques:** Haemolysis test, platelet aggregation assay.
- **Importance:** Ensures that nanoparticles do not damage blood cells or trigger clotting when administered intravenously.

3. In-vivo Evaluation

a. Biodistribution

- **Technique:** Imaging (MRI, PET, SPECT), Fluorescent or Radiolabelling.
- **Importance:** Tracks nanoparticle accumulation in target and non-target organs/tissues.

b. Pharmacokinetics (ADME)

- **Parameters:** Absorption, Distribution, Metabolism, Excretion.
- **Importance:** Determines the systemic behaviour and therapeutic window of the drug-loaded nanoparticles.

c. Toxicological Studies

- **Assays:** Organ histopathology, liver and kidney function tests.
- **Importance:** Evaluates short- and long-term safety in animal models.

4. Stability Studies

a. Physical and Chemical Stability

1. **Conditions:** Storage under varied temperature, humidity, and light.
2. **Importance:** Determines shelf-life, aggregation tendencies, and changes in drug loading or release profiles.

b. Sterility and Endotoxin Testing:

- **Techniques:** Limulus Amoebocyte Lysate (LAL) test.
- **Importance:** Ensures safety for injectable or implantable formulations.

CONCLUSION

Nanoparticles have emerged as a revolutionary platform in the field of medicine, offering transformative potential in the targeted delivery of therapeutic agents. By addressing key limitations of conventional drug delivery such as poor bioavailability, systemic toxicity, and non-specific distribution nanoparticle-based systems provide a more efficient, precise, and patient-friendly approach to treatment. This review highlights the diverse types of nanoparticles and their mechanisms for targeting diseased tissues, particularly tumours and inflamed regions. Advances in nanoparticle engineering have led to enhanced drug stability, controlled release profiles, and improved therapeutic outcomes. Furthermore, ongoing innovations such as smart nanoparticles, AI integration, and nanorobotics point toward a future where therapies can be personalized and dynamically responsive to the body's needs. Despite the immense promise, challenges such as large-scale production, long-term safety, and regulatory approval remain. Addressing these hurdles through interdisciplinary collaboration and continued research is essential for translating nanomedicine from bench to bedside. Hence, nanoparticles represent a groundbreaking advancement in modern therapeutics paving the way for safer, more effective, and targeted treatments that are reshaping the future of personalized medicine.

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