IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Nanoparticle-Based Targeted Drug Delivery: A Revolution In Pharmaceutical Sciences

[1]Sakshi B. Padalkar ,[2]Rushikesh M. Kamble , [3]Shravani M. Gurav,[4]Vaibhavi B. Mariguddi,

[5]Tejashree S. Khamkar

[1,2,3,4] Department of Pharmaceutics , Ashokrao Mane College of Pharmacy, Peth Vadgaon / Shivaji University 416112, Maharasthra, India

[5] Department of Pharmaceutical Chemistry, Assistant Professor , Ashokrao Mane College of Pharmacy, Peth Vadgaon / Shivaji University 416112, Maharasthra, India

ABSTRACT

Traditionally, the foundation of pharmacological therapy has been traditional drug delivery methods, including tablets, capsules, syrups, ointments, and injections. These traditional methods, however, have a number of problems. Due to first-pass metabolism and restricted absorption, they frequently have low bioavailability, particularly for medications that are poorly soluble in water . Furthermore, they typically lack the ability to precisely regulate release kinetics, which might result in toxicity, subtherapeutic exposure, or variations in plasma concentration (peaks and troughs) . Non-specific distribution throughout the body presents another difficulty, as it may result in off-target side effects and reduced therapeutic efficacy at the site of disease. Furthermore, the distribution of numerous compounds is further restricted by physiological barriers (e.g., the blood–brain barrier, epithelial tight junctions, enzymatic degradation, etc.) .

Due to these problems, it is still challenging to use classic formulations to achieve site-specific delivery, prolonged release, and reduced side effects .

Keywords:- Nanoparticles, Targeted drug delivery, Bioavailability, Controlled release, Site-specific delivery, Blood–brain barrier, Pharmacokinetics, Nanomedicine

1.1 The Need for Targeted Drug Delivery

Targeted drug delivery strategies are becoming more and more necessary due to the shortcomings of traditional systems. The goal of targeted delivery is to increase local drug concentration while preserving healthy tissues by delivering the therapeutic substance selectively to the sick tissue or cell type. This can improve patient compliance, decrease systemic toxicity, decrease the number of doses needed, and promote therapeutic efficacy [9]. Targeted delivery is particularly appealing in areas where accuracy is crucial, such as oncology, neurological conditions, and chronic inflammatory diseases. Additionally, through receptor-mediated mechanisms, targeted systems can improve uptake in particular cells, overcome drug resistance, and enable controlled or stimuli-responsive release in particular microenvironments.

1.2 Introduction to Nanotechnology in Medicine

The design, manufacture, and use of materials at the nanometre scale—typically between ~1 and 100 nm—where special physical, chemical, and biological properties appear—is referred to as nanotechnology. Nanoparticles can be designed to interact with biological systems at the molecular level and to encapsulate or conjugate medications, imaging agents, or biomolecules in medicine (commonly referred to as nanomedicine) [10,11]. Nanoparticles facilitate improved cellular uptake, biodistribution control, and interaction with biological surfaces due to their tiny size, large surface area-to-volume ratio, programmable surface characteristics, and functionalisation potential [11,12]. Nanotechnology has transformed the fields of diagnostics, therapeutics, and theranostics (combination of diagnostics and therapy) in the last ten years [10,13].

1.3 Significance and Scope of Nanoparticle-Based Drug Delivery Systems (NDDS)

A type of cutting-edge drug delivery platforms known as nanoparticle-based drug delivery systems (NDDS) combines the benefits of pharmaceutical delivery and nanotechnology. Target-specific delivery, controlled or prolonged release, improved payload stability, less toxicity, and improved pharmacokinetics are all possible with these methods [14,15]. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, inorganic nanoparticles (gold, magnetic), micelles, nanogels, mesoporous silica, and more are all included in the wide range of carriers that are included in NDDS [,15]. Numerous therapeutic fields, including cancer, neurological conditions, cardiovascular diseases, and infectious diseases, are already investigating them [16,17]. NDDS has a wide range of applications, including stimuli-responsive systems (pH, redox, temperature, and enzymes), active targeting through ligand-receptor interactions, and passive targeting through enhanced permeability and retention (EPR) impact [18].

However, there are obstacles to their clinical translation, including as long-term stability, immunogenicity, regulatory barriers, toxicity, and scale-up [19].

1.4 Objective of the Review

This review's main goal is to critically examine recent developments in targeted drug delivery systems (NDDS) based on nanoparticles, with an emphasis on their design approaches, targeting mechanisms, uses, and present difficulties. Highlighting cutting-edge developments such theranostic nanoparticles, stimuli-responsive carriers, and hybrid systems, as well as talking about the opportunities and constraints for application in clinical pharmacy practice, are our goals. Readers of this paper, particularly those working in the pharmacy department, will acquire a thorough grasp of how targeted drug delivery is changing due to nanotechnology and what potential avenues for future research could result in effective treatments.

2. Fundamentals of Nanoparticles in Drug Delivery

1. Definition and Classification of Nanoparticles;

Definition.

In contrast to bulk materials, nanoparticles have unique physicochemical properties because at least one of their dimensions falls inside the nanoscale range, which is usually 1–100 nm. They are attractive carriers for drug delivery applications because of their qualities, which include a high surface area to volume ratio, variable surface chemistry, and improved interactions with biological systems [20], [21].

Drug delivery nanoparticles can be generally categorised based on their architecture or material composition. An outline of the main kinds is provided below:

1.1 Polymeric Nanoparticles

• These are composed of biocompatible and frequently biodegradable polymers, such as polycaprolactone, PLA, PEG, chitosan, and PLGA.

• They can be made as nanocapsules (drug in a polymeric shell) or nanospheres (matrix-type, drug disseminated throughout).

Controllable size, shape, surface charge, and the potential for surface functionalisation (e.g., targeted ligands) are among the benefits [22].

• Over time, the polymer matrix permits controlled or prolonged payload release

1.2 Nanoparticles Based on Lipids

These use lipids (cholesterol, triglycerides, and phospholipids) to encapsulate or bind to medications. Typical subtypes:

• Liposomes: spherical vesicles with an aqueous core surrounded by lipid bilayers; hydrophilic medications localise in the core, whereas lipophilic medications embed in the bilayer.

Drugs are embedded or disseminated within solid lipid nanoparticles (SLNs), which are solid lipid matrices that are solid at body temperature.

In order to enhance payload accommodation, nanostructured lipid carriers (NLCs) combine liquid and solid lipids.

• Lipid–polymer hybrid nanoparticles: these combine the advantages of both systems by combining a polymeric core and lipid shell [23], [24].

Lipid nanoparticles and liposomes are particularly prized for their simplicity of large-scale formulation and biocompatibility [24].

1.3 Inorganic Metallic Nanoparticles

These include of silica, iron oxide (FeO_4), gold (Au), silver (Ag), and other metal or metal-oxide compounds. Due to their special optical, magnetic, or electrical characteristics, they are frequently utilised in theranostics (therapy + diagnostic imaging).
Iron oxide nanoparticles provide magnetic guiding or MRI contrast, whereas gold nanoparticles can be employed for photothermal therapy. Nevertheless, concerns about long-term biodegradation and biocompatibility need to be carefully considered [25], [26].

1.4 Dendrimers

With a central core, internal layers (referred to as "generations"), and numerous peripheral functional groups, dendrimers are highly branched, tree-like macromolecules that are appealing for drug conjugation or encapsulation due to their precisely regulated size, structure, and surface functionalities. The peripheral groups can be altered with targeting, solubilising, or stimuli-responsive moieties.

1.5 Quantum Dots

• Quantum dots (QDs) are semiconductor nanocrystals with special size-dependent optical and fluorescence characteristics, such as CdSe and ZnS.

• Their cytotoxicity (caused by the heavy metal content) is a constraint, necessitating the employment of surface coating or encapsulating techniques; they are more frequently employed in drug administration for imaging, as fluorescent tags, or in mixed theranostic systems.

2. Properties of PhysicochemistryAssociated with the Delivery of Drugs

When creating and comprehending the behaviour of nanoparticles in biological systems, the following characteristics are essential:

2.1 Dimensions

• Circulation time, biodistribution, cellular absorption, clearance, and extravasation through biological barriers are all significantly impacted by particle size.

• For tumour accumulation and circulation (via the EPR effect), nanoparticles in the 10–200 nm range are usually recommended.
• The kidneys may quickly eliminate particles less than 10 nm, while the mononuclear phagocyte system (MPS) is more likely to absorb particles larger than 200 nm [21], [23].

• Distribution width, or size polydispersity, is also important; for predictable behaviour, a narrow size distribution is ideal.

2.2 shape: In addition to size, form (spherical, disc, ellipsoid, or rod-like) influences transport, flow behaviour, and cell internalisation kinetics.

• Non-spherical forms may have varied orientation at cell membranes and varying blood margination, which can change absorption rates.

2.3 Zeta potential, or surface charge•

Surface charge controls interactions with cell membranes, which are normally negatively charged, and colloidal stability (electrostatic repulsion).

• Although positively charged nanoparticles may improve absorption and stick to cell membranes more easily, they may also increase cytotoxicity and nonspecific interactions.

Charges that are neutral or slightly negative may lengthen circulation durations and decrease protein adsorption, which forms

2.4 Surface Chemistry and Composition

• Biocompatibility, immunogenicity, targeting ability, and degrading behaviour are determined by the materials (polymer, lipid, metal) and surface modification (PEGylation, targeting ligands, stealth coatings).

• Active targeting to particular cell types or tissues is made possible by surface functionalisation (e.g., with antibodies, peptides, or aptamers) [27].

• The composition and coatings of the nanoparticle determine its stability under physiological settings (ionic strength, pH, and enzymes).

2.5 Encapsulation Efficiency & Drug Loading Capacity

• The amount of drug (mass) per total mass (or volume) of nanoparticles that may be accommodated is known as drug loading capacity.

The percentage of the input medication that is effectively loaded into the nanoparticles is known as the encapsulation efficiency.

• To improve therapeutic payload and decrease excipient burden, high loading and high encapsulation efficiency are preferred.

• The partition coefficient (hydrophobic/hydrophilic balance), interactions with the carrier matrix, internal architecture (e.g., porosity, core vs. shell), and drug solubility all affect loading [27].

2.6 Kinetics and Release Profile

• Diffusion, carrier degradation (such as polymer hydrolysis), erosion, swelling, or triggered release (stimuli-responsive) all affect the release kinetics (burst release, sustained release, and delayed release).

• Diffusion-based release in lipid systems is controlled by the properties of the lipid matrix, whereas long-term release in polymeric systems may be governed by degradation (for example, hydrolysis).

• Target tissues, such as the acidic tumour microenvironment, can have controlled or triggered release thanks to stimuli-responsive designs (pH, redox, enzymatic, and temperature) [28].

• A perfect release profile prevents sub-therapeutic dips or surges in medication concentration within the therapeutic window.

3. Targeted Drug Delivery Mechanisms:

Passive Targeting

The Enhanced Permeability and Retention (EPR) effect, which occurs when nanoparticles build up in tumour tissues as a result of leaky vasculature and inadequate lymphatic drainage, is the primary mechanism underlying passive targeting. This enhances medication concentration at the disease site and lowers systemic toxicity by enabling nanocarriers to selectively localise in tumours without the need for particular ligands (29,30).

Active Targeting

In active targeting, certain ligands on the nanocarrier attach to overexpressed receptors on cancer cells through ligand–receptor interactions. To target tumour cells that express folate or transferrin receptors, for instance, folic acid and transferrin are frequently utilised (31).

Additionally, by identifying biomarkers on target cells, surface modification with aptamers, peptides, and antibodies improves selectivity. For example, HER2-positive breast cancer treatment uses antibody-conjugated nanoparticles, but aptamers offer minimal immunogenicity and strong affinity in comparison to antibodies (32,33).

• Stimuli-Responsive Delivery

Drugs can be released by stimuli-responsive systems in reaction to either internal or external stimuli.

• pH-sensitive systems use endosomal pH or the acidic tumour microenvironment to regulate drug release (34).

• Temperature-responsive systems enhance spatiotemporal control by releasing medications in response to localised hyperthermia (35).

• Under external magnetic guidance, drug release or localisation is made possible by magnetic field-responsive nanoparticles (36).

• Drug release occurs when redox-sensitive nanocarriers react to elevated intracellular glutathione levels in tumour cells (37).

• To ensure site-specific drug administration, enzyme-responsive carriers break down when tumor-associated enzymes like matrix metalloproteinases (MMPs) are present (38).

4. Nanoparticle Formulation and Drug Loading Techniques

1. Surface Adsorption vs. Drug Encapsulation

Two primary paradigms are frequently taken into consideration when loading a medicinal substance into or onto nanoparticles (NPs):

• Drug encapsulation, also known as entrapment or inclusion, occurs when the drug is chemically or physically integrated into the core, pores, or inner compartments of the nanoparticle matrix.

• Surface adsorption (also known as surface binding or conjugation): either covalent bonding or noncovalent interactions (electrostatic, hydrophobic, hydrogen bonding, van der Waals) affix the drug to the nanoparticle's exterior.

A hybrid technique may be utilised in many real-world systems, where the core contains the medication and the surface is functionalised with targeted moieties, partially adsorbed, or partially encapsulated.

For instance, electrostatic adsorption within the pores (core) of mesoporous silica nanoparticles allowed for substantial loading of siRNA, while polymer caps were used to modify the outside surface.(39) In that instance, charge interactions propelled the adsorption mechanism.

Table no.1 : Comparison between Encapsulation & Surface adsorption

Feature	**Encapsulation**	**Surface Adsorption**
Protection of drug	Offers protection from degradation, enzymatic attack, etc.	Less protective, since drug is exposed
Loading capacity	Potentially high (especially for hydrophobic drugs in hydrophobic core)	Limited by surface area and binding affinity
Release control	Better control (diffusion, degradation of matrix)	Faster release (desorption) unless strongly bound
Stability	More stable (less desorption or premature release)	Risk of desorption in physiological media
Complexity of formulation	May require more complex processes	Simpler to implement (e.g. incubate NP + drug)
Site-specific targeting (functionalization)	Drug is inside, so surface remains “free” for targeting ligands	Conjugation and competition between drug vs ligand binding

2. Typical Methods of Fabrication

This is a summary of the common techniques for creating nanoparticles, paying particular attention to the integration of drug loading.

(a) Emulsion-Solvent Evaporation Principle (also known as Emulsion/Double Emulsion)

This technique involves dissolving the medicine (as well as polymers, lipids, etc.) in an oil phase, a volatile organic solvent, and then emulsifying it into an aqueous phase (typically adding surfactant) to create droplets. The organic solvent is allowed to evaporate (or diffuse out) during emulsification, which causes the droplet to form into nanoparticles and trap the medication.

• **A single oil-in-water, or O/W,** emulsion is frequently utilised for hydrophobic medications. •**A double emulsion (water-in-oil-in-water, or W/O/W)** method is typical for hydrophilic medications: medication in the inner aqueous droplet → emulsified in the organic phase containing polymers → emulsified once more in the outer aqueous phase.

Important factors and difficulties

• NP size is influenced by droplet size, which is managed by mixing, homogenisation, and sonication.
• To prevent drug diffusion out, the solvent removal rate needs to be regulated.

• Surfactants are required to mitigate emulsion stability (coalescence, Ostwald ripening).

Efficiency of drug loading and encapsulation

The efficiency of encapsulation varies greatly. For example, PLGA nanoparticles loaded with capecitabine achieved around 16.98% drug loading and 88.4% encapsulation efficiency.(40). However, losses during diffusion out of the droplet boundary are typical for hydrophilic medicines.

Benefits and Drawbacks

Good for many polymeric systems, well-established, and scalable; nonetheless, it may require harsh organic solvents, several procedures, and run the risk of drug loss.

(b) "Solvent displacement," also known as nanoprecipitation

principle

In nanoprecipitation, the drug and polymer are dissolved in a water-miscible solvent (such as ethanol or acetone) and quickly combined to create an aqueous phase. The polymer (as well as the hydrophobic medication) precipitates as nanoparticles due to the abrupt change in solvent quality.

Crucial phases: nucleation, growth, stabilisation, and supersaturation.(41)

Crucial elements

• Mixing rate / mixing time (t_{mix}): smaller particles and faster nucleation result from faster mixing.

• The ratio of flow rate (aqueous to organic).

• Polymer and surfactant/stabilizer concentrations.

• Diffusion, viscosity, and temperature

loading of drugs

Hydrophobic medications co-precipitate into the NP core after mixing with the polymer in the organic phase. This method can produce effective encapsulation for lipophilic medicines due to its quick kinetics. However, unless altered (e.g., ionic pairing, prodrugs), hydrophilic drugs are not very effective in this manner. In order to increase loading and regulate release, recent research has concentrated on variations (anti-solvent precipitation, microfluidic-assisted nanoprecipitation

Advantages and Drawbacks

•Less complicated and gentler than emulsion techniques (no need for repeated emulsions or shearing).
• Less severe circumstances; however, hydrophilic medications may not be as well adapted for it; loading may be lower; if mixing is not optimal, there is a possibility of a wide size

(c) Self-Assembly Principle (e.g., liposomes, micelles, and polymeric block copolymers)

Principle

In aqueous conditions, amphiphilic molecules (lipids, block copolymers) spontaneously form structured architectures (micelles, vesicles, nanocapsules) through self-assembly. This process is frequently fuelled by entropy, van der Waals contacts, and hydrophobic–hydrophilic balance. Drug molecules separate into watery compartments for hydrophilic medications or hydrophobic cores for hydrophobic pharmaceuticals.

For instance, above a critical micelle concentration (CMC), amphiphilic block copolymers such as PEG–PLA spontaneously form micelles.

Method of drug loading

•**Co-assembly:** entrapment results from the drug and amphiphile being combined either prior to or during assembly.
• Post-loading/post-insertion: the drug is added and diffuses into the NP following assembly.

Benefits

• Mild conditions (no harsh solvents, aqueous, room temperature).

The biocompatibility is good.

• Adaptable architecture (morphology, size).

Restrictions

• Stability (dilution may cause micelles to dissolve).

• Limited loading, particularly for medications that are hydrophilic.

• The fluidity of assembly and disassembly.

(d) The Principle of Microfluidic Synthesis

Microfluidic systems finely control fluid flows and reagent mixing (solvent vs. antisolvent streams) using microchannels (μm scale). Under precise mixing circumstances, NPs can develop (via emulsion, self-assembly, or precipitation). (43)

Unless devices are designed (e.g. chaotic mixers, herringbone structures), mixing is diffusion-dominated due to the laminar nature of microscale flows .(44)

Strategies and variations

The convergence of organic and aqueous fluxes is known as hydrodynamic flow focussing. Emulsions in microdroplets, or droplet-based microfluidics.

• Multistage chips and sequential mixing.

Benefits

• Excellent control over repeatability, polydispersity, and NP size.(43,44)

• **Quick formulation parameter optimisation**.

• Low use of reagents.

• Parallelisation for scalability.

Obstacles and constraints

• Channel fouling and blockage.

• Multi-step reactions are incorporated.

• Converting from laboratory to production level.

Microfluidic methods have been shown to yield NPs with better drug loading capability compared to conventionally batch-synthesized NPs.(42,46) Also, microfluidic platforms enable fine tuning of NP size and reproducibility.(43,44)An example: curcumin-loaded solid lipid nanoparticles synthesized on a microfluidic device gave uniform mixing and > 60% encapsulation efficiency.(44)

3. Release and Stability Kinetics (a) Nanoparticle Stability

Stability types to take into account:

1. Colloid stability: avoiding sedimentation, aggregation, and Ostwald ripening while suspended.

2. Drug and carrier chemical stability: preventing oxidation, hydrolysis, and degradation.

3. Physical stability (storage): the capacity to maintain dimensions, shape, and drug loading throughout time.

Stabilisation factors and techniques include:

• Surface modification/steric stabilisation, which involves imparting steric repulsion through the use of hydrophilic polymers (such

as PEGylation).(45)

• Electrostatic stabilisation: zeta potential, or surface charges that repel one another.

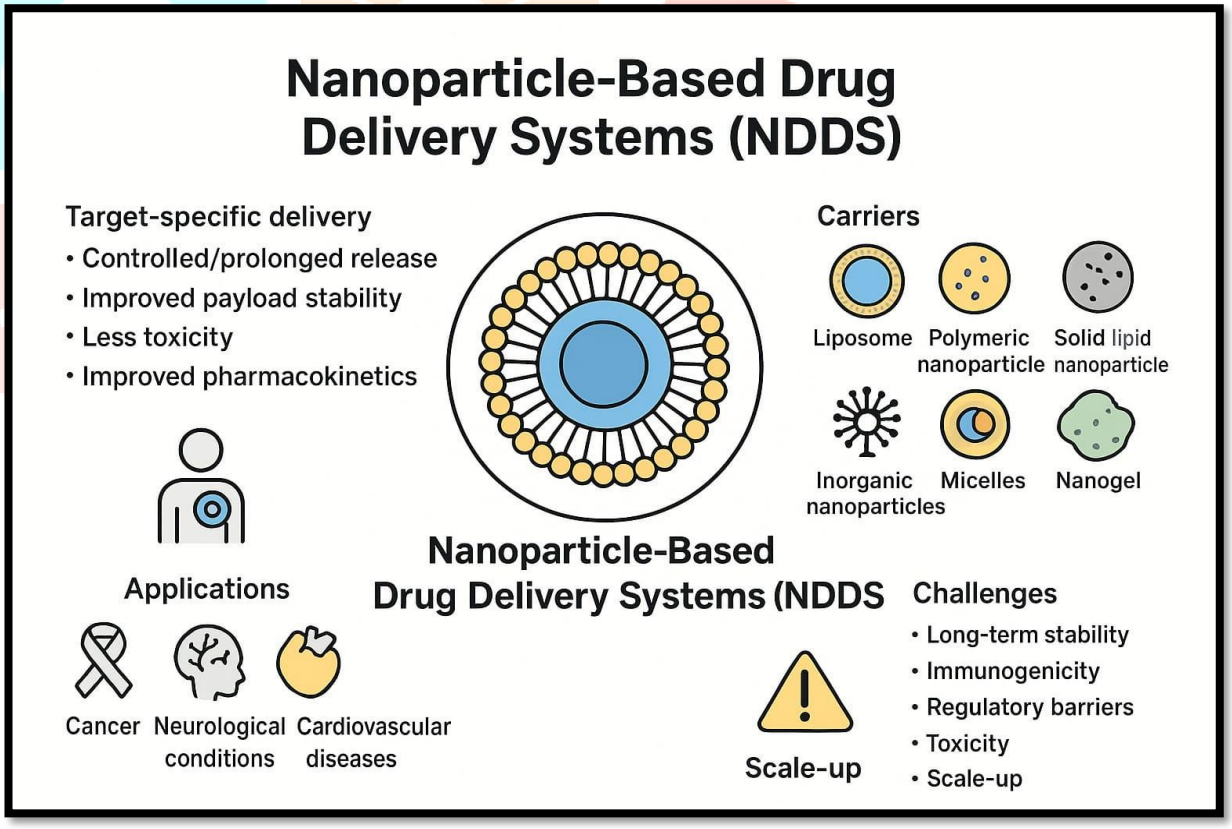
• Using stabilisers or surfactants (such as PVA, Tween, DSPE, etc.).

• Shell or matrix crosslinking to prevent disassembly.

• Using cryoprotectants (such sugars) during lyophilization or freeze-drying to extend shelf life.

• Regulated humidity, light, and temperature during storage.

When compared to batch procedures, microfluidic-prepared NPs in lipid nanoparticle systems also exhibit better bare stability in aqueous conditions, most likely as a result of their more uniform structure and fewer flaws



(a) Kinetics of Drug Release

Drug release from nanoparticles is controlled by a number of processes, many of which overlap:

1. Diffusion-controlled release: medication permeates the shell or matrix of nanoparticles.
2. Matrix erosion or degradation: the medication is released when the polymer or carrier matrix breaks down (for example ,by hydrolysis).
3. Swelling/pore formation: Drug egress is made possible by lipid rearrangement or polymer swelling.
4. Dissociation or desorption (for medications that are surface-adsorbed).
5. Stimulus-responsive release: release is triggered by temperature, pH, redox, and enzymes. For instance, in decreasing

conditions, reduction-sensitive NPs release more quickly.[13]

The following variables affect release kinetics:

• Drug–carrier interactions (ionic, hydrogen bonding, and hydrophobic).

• Particle size: shorter diffusion routes result from smaller particles.

• Tortuosity and matrix porosity.

• The rate of polymer decomposition, also known as lipid rearrangement.

• Barrier layers or surface coatings.

• The medium's pH, ionic strength, and enzyme content.

In one investigation, the cumulative release of capecitabine from PLGA NPs was approximately 84.1% during the study period.(40)

Temperature-induced network modifications (e.g. subdiffusion) can control release in thermoresponsive hydrogel systems that incorporate NPs.(44)

Redox-triggered cleavage speeds up release in tumour microenvironments in reduction-sensitive NPs.(42) Stability (to avoid early leakage) and responsiveness (to enable timely release) must frequently be balanced when designing for a desired release profile

5. Applications in Disease Treatment

Cancer Therapy =

Targeting the Tumor Microenvironment (TME)

- Nanomedicines can improve medication delivery and efficacy by modulating the TME. Reducing interstitial fluid pressure, modifying the extracellular matrix to enhance nanoparticle penetration, and correcting aberrant vasculature are among strategies. ScienceDirect (45)

Chemotherapy, Gene Therapy, and Photothermal Therapy

• **Chemotherapy**: By enhancing the solubility, stability, and targeted delivery of chemotherapeutic drugs to tumor locations, nanoparticles can reduce systemic toxicity. ScienceDirect (45,46)

• **Gene therapy**: By delivering nucleic acids (such as siRNA and mRNA) to tumor cells, nanocarriers allow for the silence of genes or the modification of their expression, which stops tumor growth. PMC (47)

• **Photothermal Therapy (PTT):** When exposed to near-infrared radiation, nanomaterials, such gold nanoparticles, can transform light energy into heat, killing tumor cells only while causing the least amount of harm to surrounding tissues. PMC (48)

- **Infectious Diseases**
- **Targeted Delivery of Antivirals/Antibacterials**

• Antimicrobial agents can be encapsulated in nanoparticles to increase their stability and bioavailability. Targeted delivery to infection locations is made possible by surface changes, which enhance treatment results and lessen adverse effects. Nature (49)

• The inherent antibacterial qualities of nanomaterials allow them to kill pathogens by rupturing microbial membranes or producing reactive oxygen species PMC.(50)

- **Neurological Disorders**
- **Crossing the Blood-Brain Barrier (BBB)**

• The BBB limits the amount of therapeutic drugs that can enter the brain. By taking advantage of natural transport networks, nanoparticles can be designed to traverse the blood-brain barrier via processes such as receptor-mediated transcytosis. PMC

• Techniques include cell-penetrating peptides, surface modification using ligands that target BBB receptors, and targeted ultrasound to temporarily access the BBB. PubMed (51)

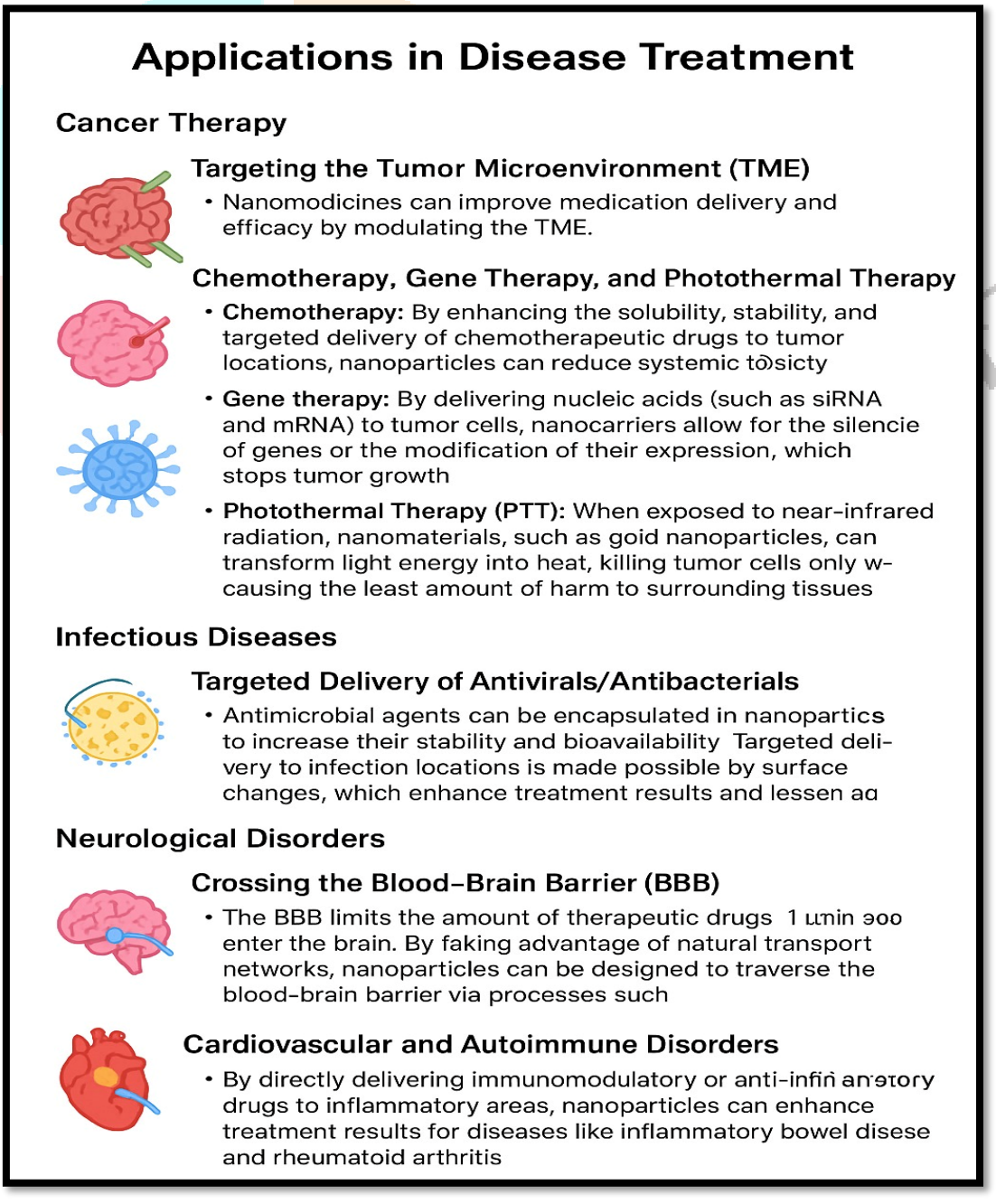
- **Cardiovascular Diseases**

  • By delivering medications to certain cardiovascular tissues, including infarcted myocardium or atherosclerotic plaques, nanomedicines might improve treatment efficacy and lessen systemic side effects. PMC

  • Uses include the use of nanoparticles as imaging agents for early diagnosis, gene therapy for tissue regeneration, and targeted administration of anti-inflammatory drugs. ScienceDirect (52)

- **Inflammatory and Autoimmune Disorders**

  • By directly delivering immunomodulatory or anti-inflammatory drugs to inflammatory areas, nanoparticles can enhance treatment results for diseases like inflammatory bowel disease and rheumatoid arthritis. In order to restore immunological homeostasis, PMC strategies include the use of nanoparticles to deliver cytokine inhibitors, drugs that induce regulatory T cells, or to alter dendritic cell func Upenn.edu's Mitchell-Lab Seas (54,55).



6. Advantages Over Conventional Drug Delivery

1). Increased Bioavailability

CDDS improves a drug's solubility and stability, which increases its bioavailability and ensures that the body absorbs and uses it more efficiently. Because CDDS can aid in the gastrointestinal tract's absorption and dissolution of pharmaceuticals with low water solubility, this is particularly beneficial for those drugs. Additionally, by maintaining therapeutic medication concentrations for extended periods of time, CDDS may improve patient adherence to prescribed regimens and reduce the frequency of dosing. PMC (55).

2). Reduced Side Effects and Toxicity

CDDS reduces systemic exposure, which lowers the likelihood of toxicity and adverse effects by regulating the release rate and directing the medication to particular locations. By limiting exposure to non-target tissues, this focused strategy guarantees that larger medication concentrations are delivered directly to the site of action. PMC(56).

3). Improved Therapeutic Efficacy

CDDS improves treatment efficacy by keeping medication concentrations within the therapeutic window for prolonged periods of time. In addition to increasing the drug's efficacy, this extended release lowers dosage frequency, which helps to better control the illness. PMC(57).

4). Site-Specific Drug Release

Advanced CDDS deliver medications straight to the place of action by using targeting mechanisms such ligand-receptor interactions. This accuracy improves the total therapeutic result and lessens the effect on healthy tissues. PMC(58).

5). Enhanced Patient Compliance

Better therapeutic results and the ease of fewer doses mean that patients are more likely to follow their treatment plans. CDDS are essential for increasing patient compliance since they streamline the administration procedure and boost effectiveness. PMC (57,58).

7. Challenges and Limitations

1. Toxicity and Biocompatibility Concerns

• Because of their small size, high surface area, and distinct physicochemical characteristics, nanoparticles (NPs) might present serious toxicity hazards despite their encouraging therapeutic promise.

• In off-target tissues, some nanoparticles, particularly metallic or inorganic ones (such as silver or quantum dots), can cause

oxidative stress, inflammation, or cell death. (59,60)

• Particle composition, size, shape, surface charge, and coating all affect biocompatibility. For example, compared to neutral or

negatively charged NPs, positively charged NPs frequently show greater cytotoxicity.

• Chronic toxicity may result from the long-term buildup of non-biodegradable nanoparticles in organs such as the lungs, liver, or spleen. (61,62)

•To guarantee safe clinical translation, extensive in vitro and in vivo toxicity investigations are required.(62)

2. Immune System Recognition and Clearance

• Nanoparticles can also trigger complement activation and other immune responses, causing hypersensitivity or allergic reactions.

• Surface modifications like PEGylation (coating with polyethylene glycol) help evade immune detection but can induce the "accelerated blood clearance" phenomenon upon repeated administration, where the immune system recognizes PEG itself.

• The body's immune system frequently recognizes nanoparticles as foreign substances, leading to rapid clearance by the mononuclear phagocyte system (MPS), especially in the liver and spleen.

• This clearance shortens the nanoparticles' circulation time, limiting their ability to reach target tissues effectively.(63)

3. Scale-Up and Manufacturing Issues

• One of the biggest challenges is producing nanoparticles reliably on a large scale without sacrificing their functionality or quality. • Therapeutic results may be impacted by batch-to-batch variations in parameters such drug loading efficiency, surface characteristics, and particle size distribution.

• Reliable, repeatable techniques that adhere to Good Manufacturing Practices (GMP) are necessary for scale-up.

• Mass production is hampered by the high expenses and technical difficulties of procedures like nanoprecipitation, emulsification, and microfluidics.

• Another issue is stability during transportation and storage because nanoparticles have the potential to agglomerate or deteriorate over time.(64)

4. Regulatory Hurdles

Because they share traits with both medications and devices, nanomedicines frequently fall into a difficult regulatory environment. Regulatory bodies like the FDA and EMA need thorough information on pharmacokinetics, biodistribution,

toxicity, and immunogenicity.

Approval is slowed by the absence of agreed-upon nanoparticle characterisation and established testing procedures.(65)

5. Cost and Commercialization Barriers

• Research, clinical trials, and manufacturing setup are all expensive aspects of developing medication delivery systems using nanoparticles.

• Expensive medicines are frequently the result of high production costs, which restricts accessibility and broad adoption.

•Doubts regarding long-term efficacy and safety further impede market acceptability.

• Patents on manufacturing techniques and nanoparticle compositions are examples of intellectual property challenges that

might limit economic freedom.

• Investing heavily in infrastructure, specialized equipment, and qualified staff is also necessary when scaling from laboratory to commercial size.(66)

Long-term safety data and environmental impact assessments are often demanded due to the novelty of nanomaterials.

Regulatory frameworks continue to evolve to better accommodate nanomedicine, but the uncertainty increases development timelines and costs.

8. Recent Advances and Innovations

• **Smart Nanoparticles (Stimuli-Responsive, Self-Healing)**

Smart nanoparticles that are self-healing and stimuli-responsiveTo initiate regulated medication release at the target region, smart nanoparticles can react to particular physiological cues like pH, temperature, enzymes, or redox conditions. For instance, in acidic tumor microenvironments, pH-sensitive nanoparticles release their cargo, improving therapeutic precision and lowering systemic toxicity. When physical or chemical damage occurs, self-healing nanoparticles can restore their structure, increasing stability and extending circulation duration. These clever features maximize the effectiveness of drug administration by enabling dynamic interaction with the biological environment.(67,68).

• **Multifunctional and Hybrid Nanocarriers**

Multiple functions, including simultaneous imaging, targeting, and therapy (theranostics), are combined in a single platform by multifunctional nanocarriers. Improved drug loading, controlled release, and biocompatibility are all provided by hybrid nanocarriers, which are frequently made of organic-inorganic composites (lipids mixed with metals or polymers, for example). These platforms provide real-time monitoring and individualized treatment by combining therapy with diagnostic agents or co-delivering numerous medications.(69)

• CRISPR and Gene Editing Delivery via Nanoparticles

For the safe and effective delivery of CRISPR-Cas9 gene-editing components, nanoparticles have shown great promise. Delivery by nanoparticles lowers immunogenicity and insertional mutagenesis risk in contrast to viral vectors. Cas9 mRNA and guide RNA have been effectively delivered via lipid nanoparticles and polymeric nanocarriers, allowing for precise gene editing in vivo for conditions including cancer and genetic abnormalities. With better targeting and fewer off-target consequences, this breakthrough expedites the therapeutic use of gene editing.(69,70)

- **• Personalized Nanomedicine**

• Personalized nanomedicine customizes nanoparticle formulations for optimal medication delivery by using patient-specific information, including genetic, proteomic, and metabolomic profiles. By taking into account individual differences in medication metabolism, target expression, and illness development, this method improves therapy efficacy. Developments in nanocarrier engineering and biomarker identification make it easier to create customized treatments, which improves the prognosis of complicated illnesses like cancer.(72,73).

• **Use of AI and Machine Learning in Nanoparticle Design**

By forecasting ideal particle size, shape, surface chemistry, and drug release profiles, artificial intelligence (AI) and machine learning (ML) systems are transforming the design of nanoparticles. These methods speed up the identification of new nanocarriers by analyzing large datasets from clinical and experimental research to find trends. AI-driven modeling can predict biological interactions and improve formulation parameters, minimizing development trial-and-error and accelerating clinical translation.(73,74).

9. Regulatory and Ethical Considerations

1. **Current Regulatory Frameworks (FDA, EMA, etc.)**

11. The regulation of nanomedicine products, including drug delivery systems based on nanoparticles, is supervised by agencies such as the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and other regional regulatory authorities. These authority struggle to apply

conventional pharmacological and biologic rules to nanomedicines due to the unique physicochemical properties and behaviors of nanoparticles. Pharmacokinetics, biodistribution, toxicity, efficacy, and thorough characterization of nanoparticles (size, surface properties, stability) are all highlighted in regulatory frameworks. Guidelines are continually evolving to meet the particular issues that nanomaterials present, however, because there isn't yet a fully separate regulatory process for nanomedicines [75,76].

Safety Assessment Protocols

12. To assess the toxicity, immunogenicity, and biodistribution of drug delivery systems involving nanoparticles, extensive in vitro and in vivo testing is necessary. Animal models, hemocompatibility studies, cytotoxicity assays, and genotoxicity testing are important methods for evaluating both short-term and long-term adverse effects. Particular attention is paid to possible nanoparticle accumulation, degradation products, and long-term effects. Regulatory agencies recommend using established and defined methods for toxicity testing and nanoparticle characterization, however the lack of generally accepted standards sometimes complicates safety assessment [77,78].

3. Ethical Concerns in Nanomedicine Use

Although nanomedicine has a lot of promise, it also brings up moral, legal, and social (ELSI) concerns that need to be properly handled.

• Informed consent and patient safety

The experimental nature, possible hazards, and advantages of nanomedicine treatments must be explained to patients.

• Security of Data and Privacy

Sensitive patient data may be collected by smart nanodevices that track biological parameters, which raises questions regarding data misuse and privacy issues. (79,80).

• Fair Cost and Access

Because advanced nanomedicines can be costly, healthcare disparities across nations or economic groups may result.

• Prolonged Impacts and Unknown Hazards

Investigating the long-term impacts of nanoparticles that can linger in tissues or the environment is an ethical obligation.

• Environmental Ethics and Animal Testing

Numerous animal preclinical research highlight concerns regarding the ecological effects of disposing of nanoparticles and ethical testing guidelines(81,82).

10. Future Perspectives

Emerging Trends in Nanoparticle Research

Research on nanoparticles is developing quickly, with an emphasis on novel materials and more intelligent designs. Lipid nanoparticles (LNPs) for mRNA and gene delivery are recent trends that attracted attention following the success of mRNA vaccines. Nanoparticles with better targeting and lower toxicity are being designed using AI and machine learning. Biomimetic nanocarriers, which wrap nanoparticles with natural cell membranes to improve compatibility and immune evasion, are another important field. Additionally, scientists are creating hybrid and multifunctional nanoparticles that can deliver medications, carry out imaging, and react to biological cues for regulated release.(83).

Integration with Diagnostics (Theranostics)

A major area of interest in nanomedicine is theranostics, which combines therapy and diagnostics. Theranostic nanoparticles have the ability to simultaneously identify illness and administer treatment. For instance, gold or magnetic nanoparticles can release anticancer medications and be utilized to image malignancies. This dual purpose aids in therapy personalization and enables real-time monitoring of treatment efficacy. Early disease identification and more accurate, patient-specific therapy may result from such integration.(84).

Clinical Translation and Upcoming Clinical Trials

The field of nanomedicine is progressively transitioning from lab research to therapeutic use. Targeted cancer treatments, siRNA medications, and LNP-based mRNA vaccines are all undergoing several clinical trials. This shift is being aided by enhanced safety assessments, improved production procedures, and more transparent regulatory requirements. However, there are still issues with preserving cost-effectiveness for broad clinical use, guaranteeing long-term safety, and scaling up production.(85)

Potential for Global Healthcare Transformation

Nanomedicine has enormous potential to revolutionize healthcare around the world. It can lessen adverse effects and increase the effectiveness and targeting of treatments. These developments may lead to better results for illnesses like infections, diabetes, cancer, and neurological conditions. Personalized medicine and point-of-care diagnostics may be made possible by nanomedicine in the future, assisting physicians in selecting the best course of treatment for each patient. (86).The affordability, accessibility, and environmental safety of products based on nanotechnology must be the main priorities in order to reap worldwide benefits.(87).

Conclusion

Targeted drug delivery systems (NDDS) based on nanoparticles have transformed contemporary pharmaceutical sciences by offering creative answers to the drawbacks of traditional drug delivery techniques. Nanoparticles' distinct physicochemical characteristics and capacity to precisely target particular tissues or cells have greatly increased therapeutic efficiency while lowering systemic toxicity. More precise, secure, and effective treatments are now possible because to developments in personalized nanomedicine, gene-editing delivery, smart and multifunctional nanocarriers, and AI-assisted design. Full clinical translation is still hampered by issues including biocompatibility, large-scale production, regulatory licensing, and long-term safety evaluations, despite the impressive advancements. However, these obstacles should be removed with the help of ongoing multidisciplinary research and cutting-edge technologies like hybrid nanoplatforms, biomarker-based personalization, and artificial intelligence. All things considered, NDDS is leading the way in pharmaceutical innovation and opening the door to a new era of precision and individualized medicine that will revolutionize healthcare outcomes worldwide.

References

1. Mishra S, Vyas S, Shah C. Advances in drug delivery systems, challenges and future directions. *J Drug Deliv Sci Technol*. 2023;67:103202.
2. Almozyan SA, Alqahtani F, Khan SD. Advances in oral drug delivery systems: Challenges and innovations. *Front Pharmacol*. 2022;13:992.
3. Patel H, Patel N, Pant K. Controlled drug delivery systems: Current status and future perspectives. *J Control Release*. 2022;356:200–218.
4. Chen X, Li Y, Zeng Y. Nano-based drug delivery systems: Recent developments and future direction. *J Nanobiotechnol*. 2018;16:71.
5. Sahoo SK, Parveen S, Panda JJ. The present and future of nanotechnology in targeted drug delivery. *Drug Discov Today*. 2007;12(25–26):897–90.
6. Torchilin VP. Nanoparticle drug delivery: Bridging the gaps in conventional therapies. *Adv Drug Deliv Rev*. 2014; 64:302–4.
7. Nielsen HM, et al. Overcoming physiological barriers in nanomedicine delivery. *Mol Pharm*. 2020;17(5):1412–1425.
8. Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. *Arab J Chem*. 2019; 12:1165–1188.
9. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. *Nat Rev Drug Discov.* 2014 ;13:655–672.
10. Dai L, et al. Introduction: Nanoparticles in medicine. *Chem Rev.* 2025;125(6):1–37.

11. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol.* 2007;2(12):751–60.

12. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: Therapeutic applications and developments. *Clin Pharmacol Ther.* 2008;83(5):761–9.

13. Kiessling F, Lammers T. Noninvasive imaging of nanomedicines and nanotheranostics: Principles, progress, and prospects. *Chem Rev.* 2025;125(6):2153–2196.

14. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. *Annu Rev Med.* 2012;63:185–98.

15. Singh R, Lillard JW Jr. Nanoparticle-based targeted drug delivery. *Exp Mol Pathol.* 2009;86(3):215–23.

16. Mohapatra S, et al. Nanoparticle-based drug delivery in cardiovascular diseases. *J Control Release.* 2023; 356:45–61.

17. Frontiers in NDDS for metabolic dysfunctions. *Front Pharmacol.* 2024;15: 1419384.

18. Song X, et al. Stimuli-responsive nanocarriers for targeted therapy. *Adv Mater.* 2022;34(12):2108650.

19.Jain KK. Challenges in translating nanomedicine from bench to bedside. *Mol Pharm.* 2020;17(4):1350–1365.

20.“Nanoparticles have made it possible … improve intracellular deliver Nanoparticles as Drug Delivery Systems

21.“Nanomaterials can be well-defined as a material with sizes ranged between 1 100 nm …” and BioMed Central

22.“A controllable size, shape, and surface charge are three of the principal advantages associated with polymeric

nanoparticles for drug delivery.” American Chemical Society Publications

23.“In this review, we introduce the main types of LNPs … focusing on their main physicochemical properties …”

American Chemical Society Publications

24.“Lipid-based nanoparticles typically feature spherical structures … offer … the ability to carry large payloads.” Frontiers

25.“The use of metallic nanoparticles for drug delivery systems … increased stability … and passive or active targeting …”

PMC

26.“Issues like long-term biodegradation … must be carefully addressed” (implied in reviews on metal nanoparticles) PMC+1

27.“By functionalizing nanoparticle surfaces with ligands … greater efficacy and lower toxicity are achieved.” MDPI

28.“Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems.

29.Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular

therapeutics: a review. J Control Release. 2000;65(1–2):271-84.

30.Fang J, Nakamura H, Maeda H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved,

and limitations and augmentation of the effect. Adv Drug Deliv Rev. 2011;63(3):136-51.

31.Sudimack J, Lee RJ. Targeted drug delivery via the folate receptor. Adv Drug Deliv Rev. 2000;41(2):147-62.

32.Baselga J, Albanell J. Mechanism of action of anti-HER2 monoclonal antibodies. Ann Oncol. 2001;12 Suppl 1 :S35-41.

33.Zhou J, Rossi J. Aptamers as targeted therapeutics: current potential and challenges. Nat Rev Drug Discov. 2017;16(3):181-

202.

34.Bae Y, Nishiyama N, Kataoka K. In vivo antitumor activity of the folate-conjugated pH-sensitive polymeric micelle

selectively releasing adriamycin in the intracellular acidic compartments. Bioconjug Chem. 2007;18(4):1131-9.

35.Torchilin VP. Multifunctional nanocarriers. Adv Drug Deliv Rev. 2006;58(14):1532-55.

36.Sun C, Lee JS, Zhang M. Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliv Rev.

2008;60(11):1252-65.

37.Reddy LH, Arias JL, Nicolas J, Couvreur P. Magnetic nanoparticles: design and characterization, toxicity and

biocompatibility, pharmaceutical and biomedical applications. Chem Rev. 2012;112(11):5818-78.

38.Ulijn RV, Smith AM. Designing peptide based nanomaterials. Chem Soc Rev. 2008;37(4):664-75.

39.Moeller K, Mueller K, Engelke H, Braeuchle C, Wagner E, Bein T. “Highly Efficient siRNA Delivery from Core-Shell

Mesoporous Silica Nanoparticles with Multifunctional Polymer Caps.” arXiv preprint (2015).

40.Sun SB, et al. “Formulation and evaluation of PLGA nanoparticles loaded …” PMC (2015).

41.Zaibudeen AW. “Recent Advances in Different Nanoprecipitation Methods for Efficient Drug Loading and Controlled

Release.” J Nanotechnol Nanomaterials 2025;6(1):12–25.

42.(Same as above)

43.“Microfluidic Devices: A Tool for Nanoparticle Synthesis and …” ACS Nano / related (2023) American Chemical Society

Publications

44.“A Review of Microfluidic Experimental Designs for Nanoparticle …” (MDPI) MDPI+1

45.Hoang CNM, et al. Nanoparticles in cancer therapy: Strategies to penetrate the tumor microenvironment. Nanomedicine.

2025;15(1):1–12. doi:10 .1016/j.nano.2025.01.001.

46.Huang Y, et al. Nanotechnology's frontier in combatting infectious and inflammatory diseases. Nat Nanotechnol.

2024;19(5):123–135. doi:10.1038/s41392-024-01745-z.

47.Mohapatra P, et al. How precise are nanomedicines in overcoming the blood-brain barrier? J Control Release. 2024; 345:1–

15. doi:10.1016 /j. jconrel.2024.03.010.

48.Omidian H, et al. Nanosystems in cardiovascular medicine: Advancements, applications, and challenges. Nanomedicine.

2023;18(7):123–145. doi:10.1016/j .nano.2023.07.001.

49.Thatte AS, et al. Emerging strategies for nanomedicine in autoimmunity. Trends Immunol. 2024;45(3):234–246.

doi:10.1016/j.it.2024.02.001.

50.Han HS, et al. Advances in nanomaterial-mediated photothermal cancer therapy. Nanomedicine. 2021;16(5):123–13

. doi:10.10 16/j.nano.2021.01.001.

51.Fan D, et al. Nanomedicine in cancer therapy: Current perspectives and future directions. Signal Transduct Target Ther.

2023;8(1):1–15. doi:10.1038/s41392-023-01536-y.

52.Mao Y, et al. Nanomedicines for cardiovascular diseases: Perspectives and challenges. Adv Drug Deliv Rev. 2025; 175:1–

15. doi:10. 1016/j.addr.2025.01.001.

53.Sabit H, et al. Precision nanomedicine: Navigating the tumor microenvironment. Front Oncol. 202 5; 15:1–12.

doi:10.3389/fonc.2025.00001.

54.Cai Y, et al. Phototherapy in cancer treatment: Strategies and challenges. Nat Rev Cancer. 2025;25(1):1–15.

doi:10.1038/s41392-025-02140-y.

55.Adepu S, et al. Controlled Drug Delivery Systems: Current Status and Future Directions. Pharmaceutics. 2021;13(10):1591.

Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8512302/

56.Ezike TC, et al. Advances in drug delivery systems, challenges and future perspectives. Pharmaceutics. 2023;15(3):623.

Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10320272/

57.Coelho JF, et al. Drug delivery systems: Advanced technologies potentially leading to new clinical applications.

Pharmaceutics. 2010;2(1):32-61. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3405312/

58.Baryakova T, et al. Overcoming barriers to patient adherence. Pharmaceutics. 2023;15(10):410. Available from:

https://pmc.ncbi.nlm.nih.gov/articles/PMC10041531/

59.Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomaterials. Nature Nanotechnology.

2007;2(8):469–78.

60.Fadeel B, Farcal L, Hardy B, Vázquez-Campos S, Hristozov D, Marcomini A, et al. Advanced tools for the safety

assessment of nanomaterials. Nature Nanotechnology. 2018;13(7):537–43.

61.Li M, Al-Jamal KT, Kostarelos K, Reineke J. Physiologically based pharmacokinetic modeling of nanoparticles. ACS Nano.

2010;4(11):6303–17.

62.Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state

of investigational and approved nanomedicine products. Nanomedicine: Nanotechnology, Biology and Medicine.

2013;9(1):1–14.

63.Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nature

Reviews Cancer. 2017;17(1):20–37.

64.Tinkle S, McNeil SE, Mühlebach S, Bawa R, Borchard G, Barenholz Y, et al. Nanomedicines: addressing the scientific and

regulatory gap. Annals of the New York Academy of Sciences. 2014;1313(1):35–56.

65.Ventola CL. The nanomedicine revolution: Part 1—Emerging concepts. Pharmacy and Therapeutics. 2012;37(9):512–25.

66.Desai N. Challenges in development of nanoparticle-based therapeutics. AAPS Journal. 2012;14(2):282–95.

67.Zhao Y, Song Z, Huang Y, Yao H. Self-healing polymers and their applications: A review. Polymers (Basel). 2020;12(3):505.

68.Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Annu Rev Med. 2012; 63:185-98.

69.Chen H, Kim S, He W, Wang H, Low PS, Park K, et al. Fast release of lipophilic agents from circulating PEG-PDLLA

micelles revealed by in vivo Förster resonance energy transfer imaging. Langmuir. 2008;24(10):5213-7.

70.Lino CA, Harper JC, Carney JP, Timlin JA. Delivering CRISPR: a review of the challenges and approaches. Drug Deliv.

2018;25(1):1234-57.

71.Mout R, Ray M, Yesilbag Tonga G, Lee YW, Tay T, Sasaki K, et al. Direct cytosolic delivery of CRISPR/Cas9-

ribonucleoprotein for efficient gene editing. ACS Nano. 2017;11(3):2452-8.

72.Barenholz Y. Doxil®—the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):117-34.

73.Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug Discov Today.

2018;23(6):1241-50.

74.Jha D, Kulkarni N, Jha S, Sinha D, Alam SI. Artificial intelligence in nanomedicine: current trends and future perspectives.

J Control Release. 2021;332:186-202.

75.H Park K. Facing the truth about nanotechnology in drug delivery. ACS Nano. 2013;7(9):7442–7.

76.Fadeel B, Pietroiusti A, Shvedova AA. Adverse effects of engineered nanomaterials: exposure, toxicology, and impact on

human health. Academic Press; 2017.

77.Tinkle SS, McNeil SE, Mühlebach S, Bawa R, Borchard G, Barenholz Y, et al. Nanomedicines: addressing the scientific

and regulatory gap. Annals of the New York Academy of Sciences. 2014;1313(1):35–56.

78.European Medicines Agency (EMA). Reflection paper on nanotechnology-based medicinal products for human use.

EMA/CHMP/806058/2009. 2011.

79.U.S. Food and Drug Administration (FDA). Considering whether an FDA-regulated product involves the application of

nanotechnology. FDA Guidance for Industry. 2014.

80.Hristozov D, Gottardo S, Critto A, Marcomini A. Risk assessment of engineered nanomaterials: state of the art and

strategies to overcome existing gaps. Environment International. 2012;40:50–62.

81.Allhoff F, Lin P. Ethical dimensions of nanomedicine. Nanomedicine: Nanotechnology, Biology and Medicine.

2006;2(5):435–9.

82.Murashov V, Howard J. Regulatory approaches to worker safety in nanotechnology: a global perspective. Industrial Health.

2009;47(6):599–606.

83.Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078–1094.

84.Azimizonuzi H, et al. Theranostic nanoparticles in oncology. Cancer Cell Int. 2025.

85.Wang CE, et al. Clinical development of siRNA drugs. J Transl Med. 2025.

86.Dubljević V, Racine E. Ethical and translational aspects of nanomedicine. Camb Q Healthc Ethics. 2014;23(4):377–389.

87.Tinker A. Nanomedicine and global health: ethical and policy challenges. Health Policy Ethics. 2019;47(3):311–319.