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NANOPARTICLE MEDIATED DRUG DELIVERY SYSTEMS FOR CANCER TREATMENT

Chapter 2: Fundamentals of Nanotechnology and Nanoparticles

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Abstract

Nanotechnology has fundamentally transformed biomedical science and cancer therapeutics by enabling rational design and fabrication of materials at the nanometre scale. Nanoparticles, characterised by tunable size, high surface-area-to-volume ratio, and surface functionalisability, represent the cornerstone of modern nanomedicine. This chapter provides a comprehensive introduction to nanotechnology and nanoparticles as the foundational framework for understanding nanoparticle-based drug delivery systems in oncology. Beginning with historical milestones and defining principles of nanotechnology, the discussion progresses to a detailed examination of nanoparticle characteristics, including size, surface charge, morphology, and colloidal stability, and their relevance to drug loading, pharmacokinetics, and tumour targeting. A taxonomic classification of nanoparticle systems encompassing lipid-based, polymeric, inorganic, carbon-based, and hybrid platforms is presented, with emphasis on their structural attributes and cancer drug delivery applications. Synthesis methodologies, including bottom-up and top-down approaches, are critically reviewed with attention to scalability, reproducibility, and pharmaceutical relevance. The enhanced permeability and retention (EPR) effect, active targeting strategies, and stimuli-responsive release mechanisms are analysed in the context of improving tumour selectivity and therapeutic indices. The chapter also addresses current translational challenges, including regulatory hurdles and *in vivo* biological barriers, and charts future directions for intelligent nanoparticle design. This foundational chapter establishes the conceptual and scientific vocabulary necessary for subsequent chapters addressing specific nanoparticle platforms in cancer therapy.





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Keywords: Nanotechnology; Nanoparticles; Drug Delivery; EPR Effect; Targeted Delivery

1. Introduction

Cancer remains one of the foremost global health challenges, accounting for approximately 10 million deaths worldwide in 2020 and projected to impose an even greater burden in coming decades as population's age and lifestyle-associated risk factors persist (1). The shortcomings of conventional chemotherapy, characterised by dose-limiting toxicities, poor tumour selectivity, multi-drug resistance, and subtherapeutic drug concentrations at tumour sites, have sustained the search for more effective and less harmful therapeutic strategies (2,3). Among the innovations to emerge from this effort, nanotechnology-based drug delivery has generated extraordinary scientific momentum, offering the prospect of delivering therapeutic agents with unprecedented precision to malignant cells while sparing healthy tissue (4,5).

Nanotechnology encompasses the science, engineering, and application of materials and devices whose smallest functional components exist at the nanoscale, broadly defined as 1 to 1000 nanometres (nm), where quantum mechanical and surface physicochemical phenomena govern behaviour in ways fundamentally distinct from bulk materials (6). The convergence of nanotechnology with pharmacology, molecular biology, and materials science has given rise to nanomedicine, a discipline focused on the exploitation of nanoscale phenomena for the diagnosis, prevention, and treatment of disease (7).

Nanoparticles (NPs) constitute the primary tools of nanomedicine, serving as carriers that can encapsulate diverse drug payloads, protect them from premature degradation, extend circulatory half-life, and enable controlled release at sites of therapeutic need (8,9). The significance of nanoparticle-based drug delivery in oncology derives from several converging biological and physicochemical realities. Solid tumours exhibit abnormal vasculature characterised by leaky endothelium and impaired lymphatic drainage, collectively producing the enhanced permeability and retention (EPR) effect through which macromolecular and particulate carriers preferentially accumulate in tumour tissue (10). Nanoparticles exploiting this phenomenon can passively concentrate in tumours at levels far exceeding those achievable by free small-molecule drugs. Furthermore, surface chemistry of nanoparticles can be engineered to display targeting ligands (antibodies, peptides, aptamers) that actively recruit nanoparticles to receptors overexpressed on tumour cells, improving selectivity further (11,12). Encapsulation of hydrophobic drugs within nanoparticles dramatically improves aqueous dispersibility, a persistent limitation of many oncology agents. Stimuli-responsive nanoparticles capable of releasing payloads in response to tumour microenvironmental triggers (low pH, elevated glutathione, or enzyme activity) represent a further dimension of smart therapeutic design (13).





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Despite considerable progress, translation of nanoparticle drug delivery from bench to bedside remains challenging. Biological barriers including the protein corona phenomenon, mononuclear phagocyte system (MPS) clearance, interstitial transport limitations, and cellular internalisation constraints attenuate the theoretical advantages of nanoparticle targeting in clinical settings (14). A rigorous understanding of the fundamental principles governing nanoparticle design, characterisation, and biological behaviour is accordingly essential for researchers seeking to advance the field. This chapter provides that foundational understanding, serving as the scientific bedrock upon which subsequent chapters elaborate specific nanoparticle systems and their cancer therapy applications (15).

2. Historical Perspective and Milestones in Nanotechnology

The intellectual genesis of nanotechnology is conventionally attributed to the celebrated 1959 lecture by physicist Richard P. Feynman, "There's Plenty of Room at the Bottom," delivered at the California Institute of Technology. In it, Feynman articulated the theoretical possibility of manipulating matter at the atomic and molecular scale and speculated on the remarkable physical properties that might emerge at such dimensions (16). Although Feynman did not use the term 'nanotechnology,' his prescient vision established a conceptual framework that would inspire generations of researchers across physics, chemistry, biology, and engineering.

The term 'nanotechnology' itself was first coined by Norio Taniguchi in 1974 to describe precision machining at the nanometre scale. (17) K. Eric Drexler subsequently expanded the concept in his 1986 work *Engines of Creation*, envisioning molecular machines capable of manufacturing complex structures atom by atom, which stimulated intense public and scientific debate about the ultimate possibilities and risks of atomic-scale fabrication (18).

The biomedical application of nanotechnology gained decisive momentum with two landmark developments. First, Bangham and colleagues described phospholipid vesicles (liposomes) in 1965, providing the first colloidal carrier system with demonstrated capacity to encapsulate aqueous and lipid-soluble molecules (19). Second, Birrenbach and Speiser reported the first polymeric nanoparticles in 1976, demonstrating that polymer chemistry could yield drug-carrying colloidal systems with tunable degradation profiles (20). The clinical translation milestone arrived in 1995 with FDA approval of Doxil (liposomal doxorubicin), marking the first nanomedicine to receive regulatory clearance and demonstrating that nanoparticle encapsulation could reduce the cardiotoxicity of anthracycline chemotherapy while maintaining antitumour efficacy (21).

Subsequent decades witnessed an accelerating proliferation of nanomaterial types and biomedical applications. The discovery of carbon nanotubes by Iijima in 1991 introduced a





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class of nanomaterials with extraordinary mechanical and electronic properties (22). The synthesis of quantum dots opened avenues in optical imaging and theranostics (23). Gold nanoparticles in biomedical applications exploited unique plasmonic properties for imaging and photothermal therapy (24). More recently, lipid nanoparticles as mRNA delivery vehicles, dramatically validated in the COVID-19 vaccines of 2020–2021, confirmed lipid-based nanoparticle technology at an unprecedented global scale of production (25). As of 2024, more than 60 nanomedicine products have received regulatory approval globally, with hundreds of additional formulations in clinical trials, reflecting the maturation of the field from conceptual innovation to therapeutic reality (26). Key milestones across this history are summarised in Table 2.1.

Table 2.1: Key Historical Milestones in Nanotechnology and Nanomedicine Development

Year	Milestone	Significance	Ref.
1959	Feynman's 'There's Plenty of Room at the Bottom' lecture	Conceptual foundation of nanotechnology	(16)
1965	Liposome description (Bangham)	First colloidal drug carrier system	(19)
1974	Taniguchi coins 'nanotechnology'	Formal nomenclature established	(17)
1976	Birrenbach & Speiser: polymeric nanoparticles	First polymer-based drug carriers	(20)
1986	Drexler: Engines of Creation	Molecular machine concept popularised	(18)
1991	Iijima: carbon nanotube discovery	New nanomaterial class for biomedical use	(22)
1994	EPR effect characterised	Mechanistic basis for passive tumour targeting	(10)
1995	FDA approves Doxil (liposomal doxorubicin)	First clinically approved nanomedicine	(21)
2004	First gold NP cancer therapy clinical trials	Inorganic NPs enter clinical translation	(67)
2010s	Stimuli-responsive/smart NPs developed	Active drug release control achieved	(107)
2020–21	Lipid NP mRNA COVID-19 vaccines approved	Global-scale validation of lipid NP technology	(25)
2024	>60 approved nanomedicines globally	Field maturation; expanding clinical pipeline	(26)

3. Defining Principles of Nanotechnology

3.1 Nanoscale and Scale-Dependent Properties





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Nanotechnology is formally defined by the National Nanotechnology Initiative (NNI) as the understanding and control of matter at dimensions between approximately 1 and 100 nm, where unique phenomena enable novel applications (27). While this definition emphasises the 1–100 nm range, the biomedical and pharmaceutical sciences routinely extend practical consideration to particles up to 1000 nm, recognising that particles in this broader range exhibit properties distinctly different from bulk materials and remain within the nanomedicine domain (6, 28).

The remarkable properties of nanoscale materials derive from two interconnected phenomena: quantum confinement effects and an extraordinary surface-area-to-volume ratio. As particle dimensions decrease below approximately 10 nm, the continuous energy bands of bulk materials are replaced by discrete quantum energy levels, producing size-dependent optical, electronic, and magnetic properties, effects exploited in quantum dot fluorescence and superparamagnetic iron oxide nanoparticle (SPION) MRI contrast (29). The surface-area-to-volume relationship dictates that for a sphere of diameter d , the ratio equals $6/d$; thus a 10 nm sphere exposes 600 times more surface area per unit volume than a 6 μm sphere, dramatically amplifying surface reactivity, drug adsorption capacity, and interaction with biological molecules (30).

3.2 Quantum Effects and Size-Dependent Phenomena

Quantum confinement occurs when the dimensions of a material become comparable to or smaller than the de Broglie wavelength of electrons, confining their motion and quantising their energy states. This phenomenon underlies the tuneable fluorescence of semiconductor quantum dots (QDs): by altering QD diameter from 2 to 8 nm, emission wavelength can be shifted across the entire visible spectrum from blue to red without altering chemical composition (31). Similarly, gold nanoparticles display a localised surface plasmon resonance (LSPR) that shifts with particle size and shape, enabling plasmonic photothermal therapy and surface-enhanced Raman scattering (SERS) sensing applications relevant to cancer diagnostics (32).

Superparamagnetism emerges in iron oxide nanoparticles when their diameter falls below approximately 20 nm, at which point each particle constitutes a single magnetic domain whose magnetic moment randomises in the absence of an applied field, producing zero net magnetisation. This property is essential for preventing particle aggregation in biological fluids while retaining high magnetic responsiveness for MRI contrast enhancement and magnetically guided drug delivery (33).

3.3 Nanomedicine: Convergence of Nanotechnology and Medicine

Nanomedicine, as formally defined by the European Science Foundation, is the application of nanotechnology for the prevention, diagnosis, and treatment of disease, encompassing drug





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delivery, molecular imaging, diagnostics, and regenerative medicine (7). Within oncology, nanomedicine pursues three principal objectives: (i) improving the therapeutic index of cytotoxic agents by preferential delivery to tumour tissue; (ii) enabling multimodal ‘theranostic’ approaches that combine therapeutic and diagnostic functions within a single nanoparticle platform; and (iii) overcoming drug resistance mechanisms by intracellular delivery of nucleic acid therapeutics (including siRNA and mRNA) that modulate resistance pathways (34,35).

4. Physicochemical Characteristics of Nanoparticles

4.1 Particle Size and Size Distribution

Particle size is the cornerstone physicochemical characterisation metric of any nanoparticle formulation, dictating biodistribution, circulation half-life, cellular uptake, and elimination pathway. Nanoparticles in the 10–100 nm range circulate longest in the bloodstream; particles below 8 nm are rapidly cleared by renal filtration, while particles above 200 nm are efficiently sequestered by the mononuclear phagocyte system (MPS), particularly in the liver and spleen (36). For tumour targeting via the EPR effect, nanoparticles in the 20–200 nm range demonstrate optimal passive accumulation, as they are sufficiently small to extravasate through the fenestrations of tumour vasculature (typically 200–800 nm) while escaping renal clearance (10,37).

Polydispersity index (PDI) quantifies the breadth of the size distribution, with values below 0.2 considered acceptable for pharmaceutical formulations. Dynamic light scattering (DLS) provides the standard laboratory measurement of hydrodynamic diameter and PDI, while nanoparticle tracking analysis (NTA) offers number-based size distributions particularly valuable for heterogeneous populations (38). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) provide direct visualisation of particle morphology, complementing ensemble DLS measurements. Asymmetric flow field-flow fractionation (AF4) coupled to multi-angle light scattering (MALS) enables high-resolution size fractionation and characterisation of complex nanoparticle populations (39).

4.2 Surface Charge and Zeta Potential

The electrical charge at the nanoparticle surface, quantified by the zeta potential (ζ -potential), critically influences colloidal stability, protein adsorption, cellular uptake, and *in vivo* fate. Dispersions with zeta potential values above ± 30 mV are typically electrostatically stable, as particles repel one another and thus resist aggregation. Neutral particles ($\zeta \approx 0$ mV) may aggregate readily unless stabilised by steric mechanisms such as polyethylene glycol (PEG) coating (40).





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Cationic nanoparticles interact avidly with the negatively charged cell membrane phospholipids and anionic proteoglycans of the extracellular matrix, promoting cellular uptake by electrostatic attraction, a property exploited in gene delivery. However, cationic surfaces also promote non-specific protein adsorption and erythrocyte aggregation, limiting systemic circulation (41). Anionic nanoparticles generally exhibit longer circulation times but less efficient non-targeted cellular uptake. PEGylation, the covalent attachment of PEG chains, reduces protein adsorption (opsonisation), MPS recognition, and immune clearance regardless of surface charge, extending blood circulation from minutes to many hours (42).

4.3 Surface Chemistry and Functionalisation

The surface of a nanoparticle constitutes the primary interface with the biological environment and represents the principal locus of pharmaceutical engineering. Surface functionalisation, the covalent or non-covalent attachment of functional molecules, enables active targeting, controlled drug release, reduced immunogenicity, and enhanced intracellular trafficking (43). Common surface modification strategies include amide coupling (NHS/EDC chemistry), thiol-maleimide conjugation, click chemistry (azide-alkyne cycloaddition), and polyelectrolyte layer-by-layer deposition (44). The choice of linker chemistry influences the stability of surface conjugates and, in the case of stimuli-responsive linkers such as hydrazones and disulfides, enables triggered release of attached drug molecules in tumour microenvironmental conditions (45).

4.4 Drug Loading, Encapsulation Efficiency, and Release Kinetics

Drug loading capacity (DLC) and encapsulation efficiency (EE) are critical formulation parameters that determine the therapeutic payload per nanoparticle and the proportion of drug successfully incorporated during preparation. DLC is typically expressed as drug mass per total nanoparticle mass (w/w%), while EE represents the fraction of total drug incorporated versus total drug used in preparation (46). Drug-polymer compatibility, hydrophobic/hydrophilic balance, and preparation conditions govern both parameters.

Drug release from nanoparticles follows diverse kinetic models (zero-order, first-order, Higuchi matrix diffusion, and Korsmeyer-Peppas), depending on the mechanism of drug incorporation and the structural properties of the carrier matrix (47). Ideally, oncological nanoparticle formulations exhibit a biphasic release profile: a controlled initial release to establish therapeutic plasma concentrations followed by sustained release to maintain efficacy above the minimum effective concentration while remaining below toxic thresholds (48).





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4.5 Morphology and Architecture

Nanoparticle shape profoundly influences biodistribution, cellular uptake, and vascular margination. Spherical particles are the most widely studied, but non-spherical geometries (discs, rods, worms, and cage structures) confer distinct biological behaviours. Filamentous worm-like micelles exhibit reduced phagocytic uptake and extended blood circulation compared to spheres of equivalent hydrodynamic diameter (49). High-aspect-ratio nanorods demonstrate enhanced vascular margination and wall adhesion in flow chamber models relevant to endothelial targeting (50). Hollow Nanocapsules architectures enable higher drug loading than solid nanocores of equivalent size. The emerging field of DNA origami-based nanostructures demonstrates that programmable, precisely defined three-dimensional nanoscale architectures can be constructed from nucleic acids, enabling nanometre-level control of drug presentation geometry (51). These physicochemical characteristics and their pharmaceutical implications are summarised in Table 4.1.

Table 4.1: Key Physicochemical Characteristics of Nanoparticles and Their Pharmaceutical Implications

Parameter	Typical Range	Measurement Technique	Pharmaceutical Implication	Ref.
Hydrodynamic size	10–1000 nm	DLS, NTA, TEM	Biodistribution, EPR targeting, renal clearance	(36,37)
PDI (polydispersity)	<0.2 (ideal)	DLS	Formulation uniformity and batch reproducibility	(38)
Zeta potential	±30 mV (stable)	Laser Doppler electrophoresis	Colloidal stability, cellular uptake, MPS clearance	(40)
Surface chemistry	Variable	XPS, FTIR, NMR	Targeting ligand attachment, stealth properties	(43,44)
Drug loading (%)	5–40% w/w	UV-Vis, HPLC	Therapeutic dose per administered dose	(46)
Encapsulation efficiency	>70% (ideal)	UV-Vis, HPLC	Manufacturing efficiency and cost-effectiveness	(46)
Drug release half-life	Hours to days	Dialysis, Franz cell	Therapeutic duration and dosing frequency	(47,48)
Morphology	Sphere, rod, disc, worm	TEM, SEM, AFM	Cellular uptake, vascular margination, phagocytosis	(49,50)

5. Classification of Nanoparticles for Drug Delivery

Nanoparticle drug delivery systems can be classified into five principal categories based on core composition and structural features: lipid-based, polymeric, inorganic, carbon-based, and hybrid nanoparticles (Figure 1). Each class offers specific advantages, limitations, and roles within cancer therapy, as summarised in Table 5.1 and detailed in the sections that follow.





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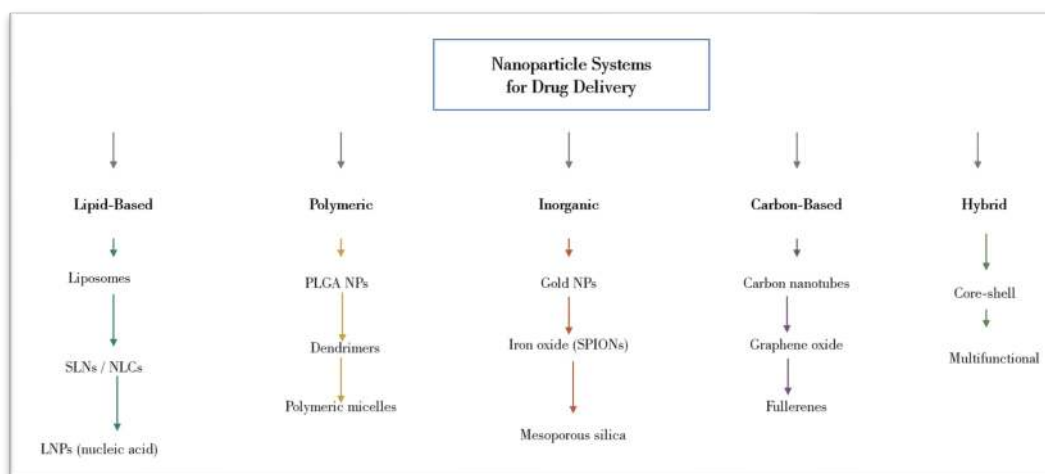


Fig.1 Taxonomic classification of nanoparticle platforms used in cancer drug delivery, grouped by core composition: lipid-based, polymeric, inorganic, carbon-based, and hybrid/composite systems.

5.1 Lipid-Based Nanoparticles

5.1.1 Liposomes

Liposomes are spherical vesicular nanostructures composed of one or more concentric phospholipid bilayers enclosing an aqueous core. Their amphiphilic architecture simultaneously accommodates hydrophilic drugs within the aqueous core and lipophilic drugs within the bilayer, providing extraordinary versatility in drug encapsulation (Figure 2) (52). Liposomes represent the most clinically advanced nanoparticle platform, with multiple FDA-approved products including Doxil (doxorubicin), DaunoXome (daunorubicin), Marqibo (vincristine), and Vyxeos (cytarabine/daunorubicin), collectively demonstrating improved safety profiles relative to free drug formulations (53). Contemporary liposome engineering incorporates PEGylation for stealth properties, pH-sensitive lipid compositions for endosomal escape, and surface-displayed antibody fragments or peptides for active tumour targeting (54).

5.1.2 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

SLNs consist of a solid lipid matrix stabilised by surfactants. Their solid-state matrix provides greater chemical stability than the fluid membranes of liposomes, reduces premature drug leakage, and allows sustained drug release (55). NLCs incorporate a blend of solid and liquid lipids, creating crystal imperfections in the lipid matrix that accommodate drug molecules more efficiently and reduce drug expulsion upon storage, a recognised limitation of SLNs (56). Both platforms are composed of physiologically tolerated lipids and have been evaluated extensively in preclinical cancer therapy studies.





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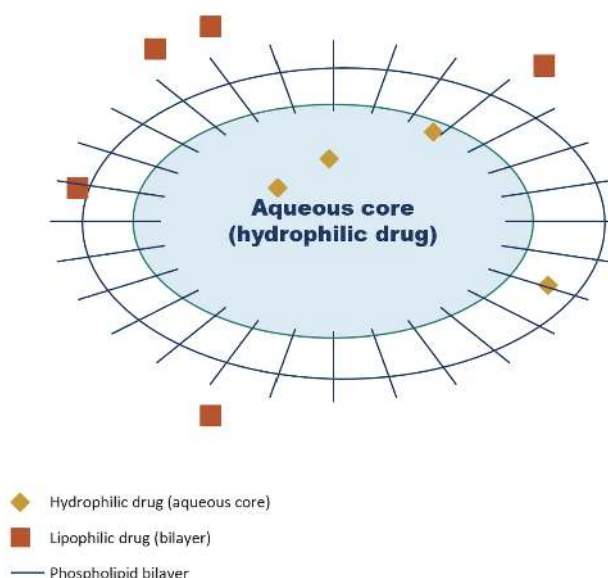


Fig.2 Schematic cross-section of a liposomal nanocarrier, illustrating the phospholipid bilayer and the distinct loading sites available for hydrophilic and lipophilic drug payloads

5.1.3 Lipid Nanoparticles (LNPs) for Nucleic Acid Delivery

The emergence of gene silencing (siRNA) and gene expression (mRNA) therapeutics in oncology has positioned ionisable lipid nanoparticles as a pre-eminent delivery platform for nucleic acids. Ionisable lipids are protonated at low endosomal pH ($pK_a \sim 6.0\text{--}6.5$), enabling electrostatic complexation with anionic nucleic acids during formulation and endosomal escape through membrane disruption, while remaining neutral at physiological pH to minimise systemic toxicity (57). The clinical success of mRNA COVID-19 vaccines and ongoing trials of siRNA-LNP formulations targeting oncogenes such as KRAS, PLK1, and EG5 have established LNPs as the leading nucleic acid delivery platform entering oncology clinical practice (58).

5.2 Polymeric Nanoparticles

5.2.1 PLGA and Biodegradable Polymeric Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is the most extensively studied synthetic biodegradable polymer in nanomedicine, benefiting from FDA and EMA approval for use in parenteral drug products and a well-characterised hydrolytic degradation profile yielding lactic acid and glycolic acid, endogenous metabolites eliminated via the citric acid cycle (59). PLGA nanoparticles encapsulate both hydrophobic and hydrophilic drugs, provide sustained release over days to weeks, protect labile molecules such as proteins and oligonucleotides from enzymatic degradation, and can be surface-modified with targeting ligands. The PLGA





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copolymer ratio, molecular weight, and end-group chemistry are tuneable parameters governing degradation rate and drug release kinetics (60).

5.2.2 Dendrimers

Dendrimers are hyperbranched, tree-like macromolecules synthesised through iterative addition of branching units from a central core, producing successive generations with precisely defined molecular architecture, narrow polydispersity, and multivalent surface functionalisation capacity (61). Each generation (G0, G1, G2...) doubles the number of surface groups, enabling high-density display of targeting ligands, imaging agents, or drug molecules. Polyamidoamine (PAMAM) dendrimers, the most studied class, have been extensively explored as carriers for anticancer drugs including cisplatin, methotrexate, and doxorubicin, and as transfection agents for nucleic acid delivery (62). Surface amine groups of PAMAM dendrimers confer cationic charge and membrane-disrupting toxicity at higher generations ($\geq G5$), necessitating surface modification for biocompatibility (63).

5.2.3 Polymeric Micelles

Polymeric micelles self-assemble from amphiphilic block copolymers at concentrations above their critical micelle concentration (CMC), forming core-shell nanostructures with a hydrophobic core for drug encapsulation and a hydrophilic shell for colloidal stabilisation (64). Their small size (10–100 nm), low CMC relative to surfactant micelles, and tunable core chemistry make them attractive carriers for hydrophobic anticancer drugs. Genexol-PM (paclitaxel-PEG-PLA micelle) has received approval in South Korea and is in advanced clinical trials in the United States, representing one of the most clinically advanced polymeric nanoparticle formulations (65).

5.3 Inorganic Nanoparticles

5.3.1 Gold Nanoparticles (AuNPs)

Gold nanoparticles possess a compelling combination of properties for cancer nanomedicine: biocompatibility, straightforward surface chemistry via Au-thiol bonds enabling conjugation of drugs, antibodies, and PEG, and size/shape-tuneable LSPR enabling photothermal cancer therapy and photo acoustic imaging (66). Gold Nano shells and nanorods exhibit strong near-infrared absorption (700–900 nm, the biological window of optical transparency), enabling deep-tissue photothermal tumour ablation. CYT-6091, a PEGylated colloidal gold-TNF conjugate, has completed Phase I clinical trials in advanced solid tumours, demonstrating preferential tumour accumulation (67).

5.3.2 Iron Oxide Nanoparticles (IONPs/SPIONs)





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Superparamagnetic iron oxide nanoparticles (SPIONs) serve as MRI contrast agents (T2-weighted darkening) and exhibit multifunctionality, combining MRI contrast, magnetic hyperthermia potential, and drug loading via surface conjugation, which has stimulated extensive investigation as theranostic platforms (68). NanoTherm, an aminosilane-coated SPION suspension, is approved in the European Union for MRI-guided magnetic hyperthermia treatment of glioblastoma multiforme following intratumoral injection, representing the first iron oxide-based cancer therapy approval (69).

5.3.3 Mesoporous Silica Nanoparticles (MSNPs)

Mesoporous silica nanoparticles feature a honeycomb-like porous internal structure (pore diameter 2–50 nm) providing extraordinary drug loading capacity, with surface areas of 600–1200 m²/g and pore volumes of 0.5–2.0 cm³/g, which can accommodate small-molecule drugs, proteins, siRNA, and imaging agents (70). Surface silanols enable versatile chemical functionalisation, and nanovalve gating systems, responsive to pH, light, or redox conditions, can be engineered to prevent premature drug release until tumour microenvironment triggers gate opening (71). Their rigid inorganic framework provides excellent colloidal stability, though biocompatibility and biodegradability represent ongoing development priorities relative to organic nanoparticle platforms (72).

5.4 Carbon-Based Nanomaterials

Carbon nanotubes (CNTs), cylindrical graphene sheet allotropes available as single-walled (SWCNTs) or multi-walled (MWCNTs) structures, exhibit exceptional mechanical strength, electrical conductivity, high aspect ratios, and large surface areas that facilitate drug loading through non-covalent π - π stacking, hydrophobic, and electrostatic interactions (73). Functionalised CNTs traverse cell membranes through passive diffusion or endocytosis with high efficiency, making them attractive intracellular delivery vehicles. Graphene and graphene oxide (GO) nanoplateforms have emerged as highly versatile two-dimensional carbon nanomaterials for co-delivery of drug and gene cargo, photothermal therapy, and bio sensing (74). Clinical translation of carbon-based carriers remains at an earlier stage than lipid and polymer systems, constrained by purification challenges, *in vivo* persistence, and potential pulmonary toxicity concerns (75).

5.5 Hybrid and Composite Nanoparticles

Hybrid nanoparticles integrate two or more material components (lipid-polymer, lipid-inorganic, or polymer-inorganic) to synergistically combine the advantageous properties of constituent materials. Lipid-polymer hybrid nanoparticles, consisting of a PLGA polymeric core coated with a lipid shell, simultaneously exploit the high encapsulation efficiency and sustained release of the polymer core and the biocompatibility, surface functionalisation





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capacity, and biomimetic properties of the lipid shell (76). Cell membrane-coated nanoparticles, polymer or inorganic nanoparticle cores cloaked with native erythrocyte, platelet, or cancer cell membranes, achieve immune evasion and homotypic tumour targeting through biological membrane mimicry (77). Exosome-mimetic nanoparticles, fabricated from extracellular vesicle components, leverage natural cellular communication pathways for high-efficiency drug delivery with minimal immunogenicity, representing a frontier of bioinspired nanoparticle design (78).

Table 5.1: Classification of Nanoparticle Drug Delivery Systems for Cancer Therapy

NP Category	Type	Composition	Size Range	Key Cancer Application	Ref.
Lipid-based	Liposomes	Phospholipid bilayer	50–200 nm	Doxorubicin, cisplatin delivery (Doxil, Lipoplatin)	(52,53)
Lipid-based	SLN/NLC	Solid/liquid lipid matrix	50–400 nm	Paclitaxel, curcumin oral/IV delivery	(55,56)
Lipid-based	LNP	Ionisable lipid + helper lipids	60–150 nm	siRNA/mRNA oncogene silencing	(57,58)
Polymeric	PLGA NPs	Poly(lactide-co-glycolide)	100–500 nm	Sustained-release chemotherapy	(59,60)
Polymeric	Dendrimers	PAMAM, PPI	1–10 nm	Drug conjugates; gene delivery	(61,62)
Polymeric	Micelles	PEG-PLA, PEG-PCL	10–100 nm	Hydrophobic drug solubilisation	(64,65)
Inorganic	Gold NPs	Au core, thiol SAM	5–150 nm	Photothermal therapy; CT imaging	(66,67)
Inorganic	SPIONs	Fe ₃ O ₄ /Fe ₂ O ₃ core	5–50 nm	MRI contrast; magnetic hyperthermia	(68,69)
Inorganic	Mesoporous silica	SiO ₂ porous framework	50–300 nm	High drug loading; stimuli-release	(70,71)
Carbon-based	CNTs	SWCNT/MWCNT	1–100 nm diameter	Intracellular drug/gene delivery	(73)
Carbon-based	Graphene oxide	2D oxidised graphene	20–500 nm	Photothermal + drug co-delivery	(74)
Hybrid	Lipid-polymer	PLGA core + lipid shell	100–300 nm	Biomimetic; combined properties	(76,77)





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6. Synthesis Approaches for Nanoparticles

Nanoparticle synthesis strategies are broadly categorised into two paradigms: bottom-up approaches, which build nanostructures from molecular or atomic precursors; and top-down approaches, which reduce bulk materials to nanoscale dimensions through physical or mechanical processes (Figure 3). Representative methods within each category, along with their scalability and key limitations, are compared in Table 6.1.

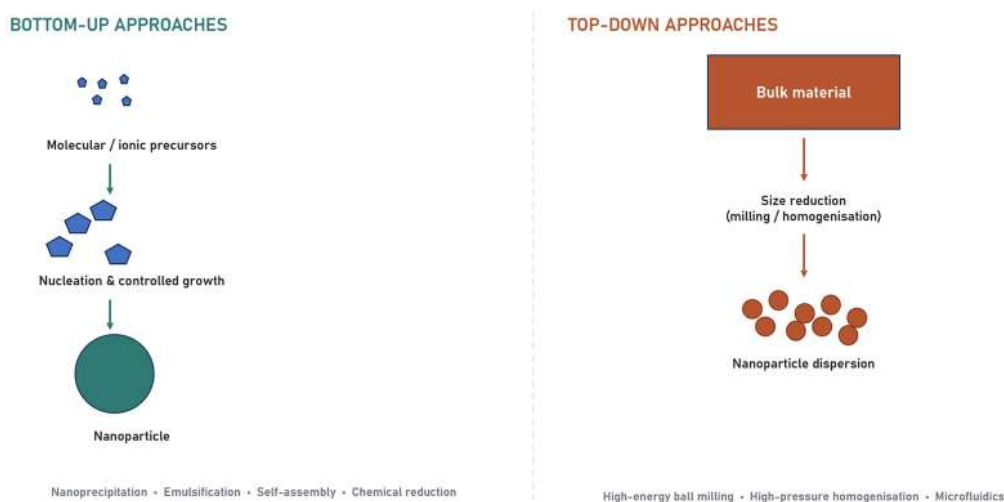


Fig.3 Comparison of bottom-up (molecular assembly) and top-down (bulk size-reduction) strategies for pharmaceutical nanoparticle synthesis

6.1 Bottom-Up Approaches

6.1.1 Nano precipitation (Solvent Displacement Method)

Nano precipitation, introduced by Fessi and colleagues in 1989, is the most widely employed method for PLGA and polymer-based nanoparticle fabrication in pharmaceutical research (79). The polymer and drug are dissolved in a water-miscible organic solvent (acetone, acetonitrile, DMSO), which is then injected into an aqueous continuous phase under agitation. Rapid interdiffusion of solvents creates local supersaturation, driving polymer chain collapse and nanoparticle nucleation and growth. Key formulation variables include polymer concentration, organic-to-aqueous phase ratio, solvent injection rate, and the presence and type of stabiliser (80). The method is readily scalable using microfluidic platforms that provide precise mixing geometry control, yielding nanoparticles of exceptional size uniformity ($PDI < 0.1$) (81).

6.1.2 Emulsification Methods

Emulsification-solvent evaporation methods generate nanoparticles through formation and subsequent solvent removal from oil-in-water (o/w) emulsions for hydrophobic drug





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encapsulation, or water-in-oil-in-water (w/o/w) double emulsions for hydrophilic drug encapsulation. High-energy emulsification provides the mechanical energy to overcome Laplace pressure and produce nanodroplets, which harden into nanoparticles upon solvent evaporation (82). High-pressure homogenisation, operating at pressures of 200–1500 bar through narrow gaps generating intense shear and cavitation forces, is particularly amenable to industrial-scale production of SLNs and NLCs (83).

6.1.3 Self-Assembly

Self-assembly exploits the thermodynamic driving forces of hydrophobic/hydrophilic interactions, electrostatic interactions, van der Waals forces, and hydrogen bonding to spontaneously organise amphiphilic molecules into well-defined nanostructures including liposomes, micelles, and vesicles (84). Polyelectrolyte complex (PEC) nanoparticles for nucleic acid delivery self-assemble through electrostatic interaction between cationic polymers such as chitosan or Polyethyleneimine and anionic nucleic acid cargo, with the N/P ratio (ratio of polymer amine to nucleic acid phosphate groups) being the critical formulation determinant of particle size and transfection efficiency (85).

6.1.4 Chemical Reduction and Colloidal Synthesis

Inorganic nanoparticles are typically synthesised by chemical reduction of metal salt precursors in the presence of stabilising agents. The citrate reduction synthesis of gold nanoparticles (Turkevich method) reduces chloroauric acid with trisodium citrate, producing spherical AuNPs of 10–20 nm diameters with a narrow size distribution, where particle size is controlled by the gold-to-citrate molar ratio (86). The seed-mediated growth approach produces gold nanorods of defined aspect ratio in the presence of cetyltrimethylammonium bromide (CTAB) and silver nitrate, with Ag^+ concentration governing nanorod aspect ratio and therefore LSPR wavelength (87). Co-precipitation synthesis of iron oxide nanoparticles involves controlled addition of $\text{Fe}^{2+}/\text{Fe}^{3+}$ salts to alkaline solution under inert atmosphere (88).

6.2 Top-Down Approaches

6.2.1 Milling and High-Energy Ball Milling

Media milling (Nano milling) reduces bulk crystalline drug particles to nanosuspensions using milling media in a high-energy mill. The resulting drug nanosuspensions, typically in the 200–500 nm range, exhibit dramatically improved dissolution rates through increased surface area, enabling formulation of practically insoluble drugs with improved oral bioavailability (89). Process variables such as media size, milling rate, drug and stabiliser concentrations, milling time, and temperature need to be fine-tuned in order to achieve the desired particle size without significant amorphisation or degradation (90).





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6.2.2 High-Pressure Homogenisation

Piston-gap homogenisers force coarse drug suspensions through a narrow homogenisation gap at high pressure (500–1500 bar), generating extreme shear forces, cavitation, and turbulence that comminute particles to the nanoscale. Multiple homogenisation cycles reduce particle size progressively (91). The technique is readily scalable to pharmaceutical manufacturing scale, requires no organic solvents, and has been applied to produce SLNs, nanosuspensions, and drug Nanocrystals (92).

6.2.3 Microfluidics and Nanofluidics

Microfluidic platforms offer precise control of mixing hydrodynamics through engineered microchannel geometries, enabling continuous-flow nanoparticle synthesis with exceptional size uniformity and batch-to-batch reproducibility unachievable by bulk mixing methods (93). NxGen microfluidic cartridges have been adopted for GMP-compliant LNP synthesis in the mRNA vaccine and gene therapy space, enabling rapid scale-up from microlitres to litres per minute by device numbering (94). The ability to rapidly screen formulation variables using nanolitre-volume reaction compartments accelerates formulation development and reduces material costs (95).

Table 6.1: Comparative Overview of Nanoparticle Synthesis Methods

Method	NP Type Produced	Scalability	Key Limitation	Ref.
Nanoprecipitation	Polymeric NPs, LNPs	High (microfluidics)	Organic solvent residue removal	(79,80)
Emulsification-solvent evaporation	Polymeric NPs, SLNs	Moderate to high	Broad PDI; surfactant removal	(82,83)
Self-assembly (film hydration)	Liposomes, micelles	Moderate (extrusion bottleneck)	Batch variability; large size range	(84,85)
Chemical reduction	AuNPs, IONPs, QDs	Moderate	Ligand exchange; surface purification	(86,87)
Co-precipitation	Iron oxide NPs	High	Broad size distribution	(88)
Media milling	Drug nanosuspensions	High (industrial)	Contamination from milling media	(89,90)
High-pressure homogenisation	SLNs, nanosuspensions	Very high (industrial)	Temperature-sensitive drugs excluded	(91,92)
Microfluidics	LNPs, polymeric NPs	High (numbering up)	High capital cost; channel fouling	(93,94)





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7. Tumour Targeting Strategies

7.1 Passive Targeting and the EPR Effect

The enhanced permeability and retention (EPR) effect, first articulated by Matsumura and Maeda in 1986, describes the tendency of macromolecules and nanoparticles to preferentially accumulate in tumour tissue relative to normal tissue (10). The mechanistic basis of the EPR effect resides in the abnormal tumour vasculature generated by dysregulated angiogenesis: tumour blood vessels are heterogeneous, tortuous, fenestrated with large interendothelial gaps (200–800 nm), and deficient in pericyte coverage, collectively permitting extravasation of macromolecular and colloidal species that would be excluded by the tight junctions of healthy endothelium (96). Simultaneously, tumours lack functional lymphatic drainage, impairing clearance of extravasated macromolecules and enabling prolonged retention (Figure 4) (97).

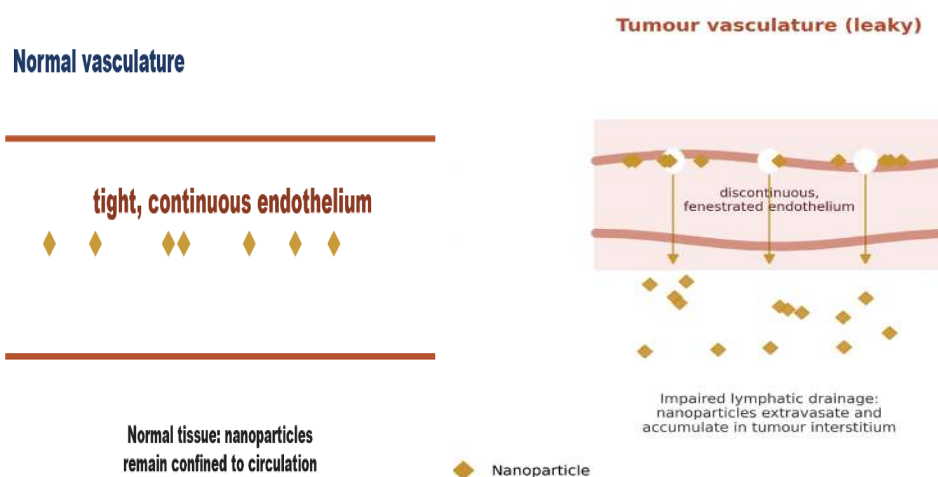


Fig.4 The enhanced permeability and retention (EPR) effect: leaky tumour vasculature and impaired lymphatic drainage allow nanoparticles to passively accumulate within tumour tissue.

While the EPR effect has been extensively validated in preclinical rodent tumour models, its magnitude and consistency in human tumours is markedly more variable, influenced by tumour type, vascularisation, interstitial fluid pressure, and patient-specific factors (98). Meta-analyses of published clinical nanoparticle biodistribution data suggest that, on average, only 0.7% of an administered nanoparticle dose accumulates in solid tumours, highlighting the limitations of passive targeting alone and emphasising the necessity of complementary active targeting strategies (99). Strategies to enhance EPR exploitation include co-administration of vascular modulating agents, tumour priming with low-dose metronomic chemotherapy to reduce interstitial pressure, and the use of albumin-binding NP designs that exploit endogenous transcytosis pathways (100).





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7.2 Active Targeting Strategies

Active targeting involves the surface functionalisation of nanoparticles with ligands that bind selectively to receptors overexpressed on cancer cells or tumour-associated endothelial cells, enhancing selectivity beyond passive EPR accumulation through receptor-mediated endocytosis (Figure 5) (11). Active targeting improves intracellular drug delivery after tumour accumulation rather than increasing total tumour uptake per se, as the EPR effect remains the prerequisite for nanoparticle extravasation from circulation into the tumour interstitium (101).

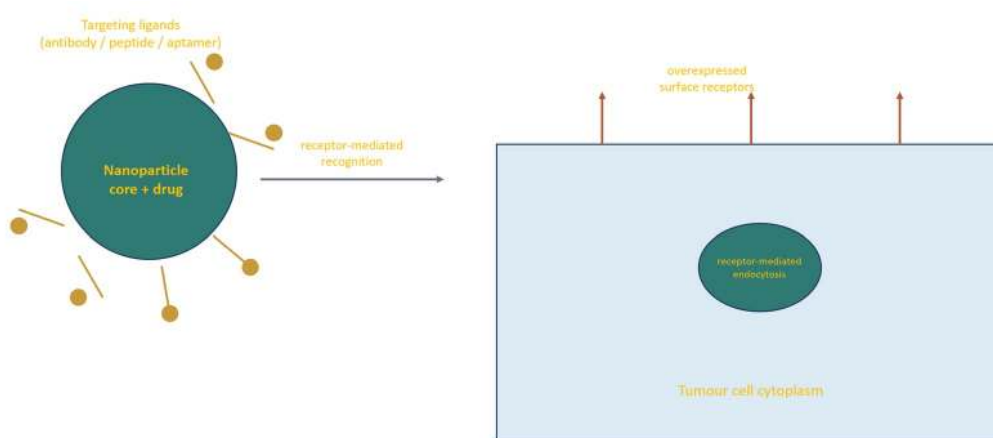


Fig.5 Active targeting through surface-conjugated ligands (antibodies, peptides, or aptamers) that bind receptors overexpressed on tumour cells, promoting receptor-mediated endocytosis of the nanocarriers

7.2.1 Antibody and Antibody Fragment Targeting

Whole monoclonal antibodies (mAbs) or antibody fragments (Fab', scFv, nanobodies) conjugated to nanoparticle surfaces enable targeting to tumour-associated antigens including HER2 (breast cancer), EGFR (lung, colorectal cancer), CD20 (B-cell lymphoma), and folate receptor (ovarian cancer) (12). Trastuzumab-conjugated liposomes demonstrated superior tumour cell killing in HER2-overexpressing breast cancer xenografts compared to untargeted liposomes. MM-302, a HER2-targeted liposomal doxorubicin, advanced to Phase II clinical trials (102).

7.2.2 Folate Receptor Targeting

The folate receptor alpha (FR- α) is overexpressed in numerous malignancies, including ovarian (90%), lung, breast, and cervical cancers, while exhibiting restricted expression in normal tissues, providing a selective tumour target. (103) Folate-conjugated nanoparticles exploit the high affinity of folic acid for FR- α ($K_d \sim 0.1$ nM) to drive receptor-mediated endocytosis. Folic acid is a small, stable, non-immunogenic targeting ligand that survives nanoparticle processing





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conditions, making it one of the most widely explored active targeting moieties in preclinical nanoparticle oncology (104).

7.2.3 Aptamer Targeting

Aptamers, single-stranded DNA or RNA oligonucleotides selected by Systematic Evolution of Ligands by Exponential enrichment (SELEX) to bind defined molecular targets with high affinity, offer a fully synthetic alternative to antibodies for nanoparticle surface functionalization (105). A10 aptamer-conjugated PLGA-PEG nanoparticles targeting prostate-specific membrane antigen (PSMA) demonstrated significantly enhanced uptake in LNCaP prostate cancer cells and improved anti-tumour efficacy of docetaxel in xenograft models. BIND-014, a PSMA-targeted docetaxel PLGA-PEG nanoparticle, completed Phase I/II clinical trials in metastatic castration-resistant prostate cancer and non-small cell lung cancer (106).

7.3 Stimuli-Responsive Drug Release

Stimuli-responsive nanoparticles are engineered to withhold their drug payload during systemic circulation and release it in response to specific triggers characteristic of the tumour microenvironment (TME) or applied externally, enabling spatial and temporal control of drug delivery (Figure 6) (107). The TME is characterised by a distinctly acidic pH (6.4–6.8 in the interstitium; 4.5–5.5 in lysosomes), elevated glutathione concentrations (2–10 mM, 100–1000-fold above plasma levels), overexpressed matrix metalloproteinases (MMPs), elevated reactive oxygen species, and hypoxia, each representing a potential endogenous trigger for responsive release (108).

pH-sensitive nanoparticles incorporating acid-cleavable hydrazone or acetal linkers, or pH-titratable ionisable lipids, swell and disintegrate in acidic endosomes, releasing drug cargo intracellularly following receptor-mediated uptake. Redox-responsive nanoparticles crosslinked by disulfide bonds undergo rapid decrosslinking in the reducing intracellular environment of elevated glutathione, triggering payload release after cellular uptake (109). Externally applied stimuli (near-infrared light, alternating magnetic fields, and high-intensity focused ultrasound) enable remote activation of photothermal, magnetic hyperthermia, and sonodynamic therapy from nanoparticle platforms incorporating photo absorbers, magnetic cores, or sonosensitisers (110).





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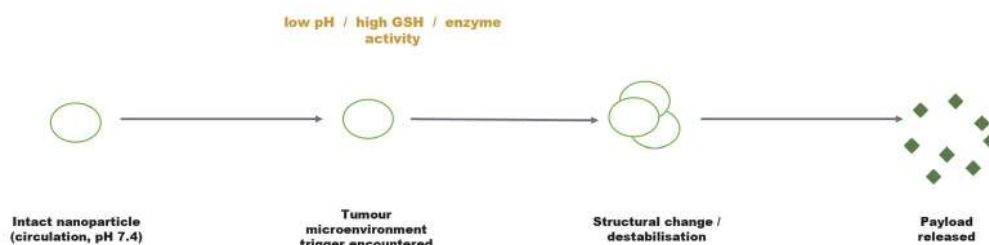


Fig.6 Stimuli-responsive nanoparticle drug release: microenvironmental cues within the tumour (acidic pH, elevated glutathione, or enzymatic activity) trigger structural destabilisation and payload release.

8. Biological Barriers to Nanoparticle Drug Delivery

Following intravenous administration, nanoparticles must negotiate a sequence of biological barriers, spanning protein corona formation, mononuclear phagocyte system clearance, and interstitial and cellular-level resistance within the tumour, before an effective dose reaches malignant cells (Figure 7).

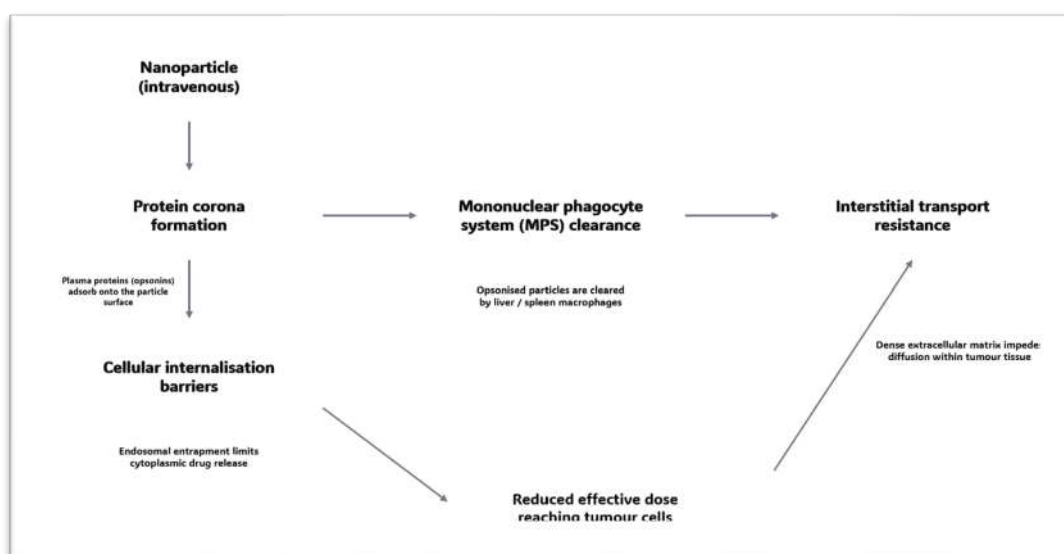


Fig.7 Sequential biological barriers encountered by nanoparticle drug carriers following intravenous administration, from protein corona formation and MPS clearance to interstitial and cellular-level resistance

8.1 Protein Corona Formation

Immediately upon entry into the bloodstream, nanoparticles are enveloped by a layer of adsorbed plasma proteins, the protein corona that fundamentally redefines the biological identity of the nanoparticle surface (111). The corona comprises a dense ‘hard corona’ of high-





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affinity proteins (albumin, fibrinogen, immunoglobulins, apolipoproteins, complement proteins) irreversibly bound to the surface and a loosely adsorbed ‘soft corona’ of dynamically exchanging proteins (112). The protein corona masks surface targeting ligands, reduces uptake by intended cell populations, activates complement-mediated clearance, and promotes phagocytic recognition by macrophages of the MPS through display of opsonins (113). Strategies to mitigate protein corona formation include PEGylation, zwitterionic coatings, cell membrane camouflage, and pre-coating with specific proteins that confer stealth or targeting properties (114).

8.2 Mononuclear Phagocyte System Clearance

The mononuclear phagocyte system (MPS), comprising circulating monocytes and tissue-resident macrophages in the liver (Kupffer cells), spleen, lymph nodes, and bone marrow, surveys the bloodstream for particulate foreign material and efficiently engulfs opsonised nanoparticles through phagocytosis (115). MPS clearance is the primary pharmacokinetic determinant of nanoparticle blood circulation half-life. Uncoated, positively charged, or opsonised nanoparticles are typically cleared within minutes to hours, while PEGylated, neutral, or biomimetically coated NPs can circulate for hours to days (116). Accelerated blood clearance (ABC) phenomenon, whereby repeated administration of PEGylated nanoparticles induces anti-PEG IgM responses that accelerate clearance of subsequent doses, represents a clinically relevant concern for patients receiving repeated nanomedicine cycles (117).

8.3 Tumour Microenvironment and Interstitial Barriers

Even nanoparticles that successfully extravasate into the tumour interstitium face formidable barriers to reaching cancer cells throughout the tumour mass. Elevated interstitial fluid pressure (IFP) in solid tumours, arising from leaky vasculature, impaired lymphatic drainage, and dense extracellular matrix (ECM), opposes convective transport and confines nanoparticle distribution to perivascular regions (118). The dense collagen and hyaluronic acid-rich ECM provides a steric and adhesive barrier to nanoparticle diffusion, particularly limiting penetration of particles above 60–100 nm. Strategies to overcome tumour stromal barriers include enzyme-mediated ECM degradation (hyaluronidase, collagenase), tumour-penetrating peptides (iRGD), and ultra-small nanoparticles (<20 nm) designed for deeper diffusion (119).

9. Characterisation Techniques for Pharmaceutical Nanoparticles

Comprehensive physicochemical characterisation is essential for quality control, batch reproducibility, and mechanistic understanding of nanoparticle formulations. Regulatory guidelines from the FDA, EMA, and ICH mandate characterisation of size, charge, morphology, drug loading, release kinetics, and stability for nanoparticle investigational new





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drug (IND) applications. (120) The principal techniques used for each property are summarised in Table 9.1.

Table 9.1: Characterisation Techniques for Pharmaceutical Nanoparticles

Property	Primary Technique(s)	Information Provided	Regulatory Relevance	Ref.
Hydrodynamic size, PDI	DLS; NTA	Mean size, size distribution	Critical quality attribute (CQA)	(38,39)
Morphology, core size	TEM, SEM, AFM, cryo-TEM	Shape, surface texture, internal structure	Confirm expected architecture	(39)
Zeta potential	Laser Doppler electrophoresis	Surface charge, colloidal stability	Stability prediction CQA	(40)
Drug loading / EE	HPLC, UV-Vis spectrophotometry	Drug content per NP mass	Dosing accuracy CQA	(46)
Drug release	Dialysis bag, Franz cell, flow-through	Release rate, mechanism	<i>In vitro</i> dissolution specification	(47)
Surface chemistry	FTIR, XPS, NMR, Raman	Functional groups, conjugation proof	Targeting ligand verification	(43,44)
Molecular weight	GPC/SEC, SLS, MALDI	Polymer MW; corona proteins	Raw material specification	(60)
Stability (physical)	DLS, NTA over time	Aggregation propensity	Shelf-life specification	(38)
Sterility / endotoxin	LAL assay, membrane filtration	Bacterial endotoxin, sterility	Parenteral safety CQA	(120)
<i>In vitro</i> cytotoxicity	MTT, LDH, annexin V assays	Cell viability, apoptosis	Early safety screening	(14)

10. Regulatory and Translational Considerations

The translation of nanoparticle formulations from laboratory innovation to clinically available medicine is governed by an evolving regulatory framework that imposes rigorous safety, quality, and efficacy requirements. In the United States, the FDA's Nanotechnology Task Force has published guidance documents addressing the safety assessment of nanotechnology products, emphasising that the unique properties of nanoscale materials may necessitate novel testing paradigms beyond those established for conventional pharmaceuticals (121). The European Medicines Agency (EMA) has developed reflection papers on nanotechnology-based





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medicinal products and established the Joint CHMP/CAT Expert Group on nanomedicines to coordinate scientific advice (122).

Critical regulatory considerations for nanoparticle drug products include: (i) demonstration of physicochemical equivalence between clinical-scale and development-scale batches ('nanosimilarity'); (ii) comprehensive characterisation of the drug release mechanism and its sensitivity to physiological variables such as pH, ionic strength, and proteins; (iii) *in vitro/in vivo* correlation (IVIVC) development to enable dissolution specification setting; (iv) immunotoxicological assessment addressing complement activation, cytokine induction, and cell-mediated immune responses; and (v) genotoxicity and carcinogenicity testing of novel nanomaterials (123). The approval of generic nanomedicines ('nanosimilars') presents particular challenges, as minor differences in nanoparticle physical chemistry may produce clinically meaningful differences in biodistribution and safety profiles not detectable by traditional drug equivalence testing (124).

Manufacturing scalability represents a critical bottleneck for nanoparticle clinical translation. Process parameters that govern nanoparticle characteristics at laboratory scale change non-linearly upon scale-up, necessitating systematic process development using Quality by Design (QbD) principles and design of experiments (DoE) methodologies to define the design space within which critical quality attributes (CQAs) remain within specification (125). Continuous manufacturing technologies, including microfluidics, in-line flow chemistry, and continuous spray drying, offer inherent scale-up advantages by maintaining consistent process parameters independent of production volume (126).

11. Future Directions and Emerging Frontiers

The nanotechnology drug delivery field is poised at the frontier of several transformative innovations. Artificial intelligence (AI) and machine learning are increasingly applied to nanoparticle formulation development, enabling high-dimensional optimisation of complex multi-variable formulation and process spaces beyond the reach of conventional experimental design (127). Neural network models trained on nanoparticle property-activity datasets predict encapsulation efficiency, particle size, and *in vitro/in vivo* drug release from formulation input variables, enabling virtual screening of formulation candidates before physical synthesis (128). High-throughput nanoparticle synthesis using automated robotic platforms coupled to in-line analytical characterisation generates large training datasets to fuel such machine learning models (129).

Personalised nanomedicine represents a paradigm shift from population-level nanoparticle design toward patient-specific formulations. Patient tumour biopsies can be used to identify





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specific receptor overexpression profiles, enabling selection or tailoring of targeting ligands for individualised nanoparticle regimens. (130) CAR-T cell therapy combined with nanoparticle drug delivery, whereby CAR-T cells are loaded with cytotoxic nanoparticles before adoptive transfer, enabling cell-guided nanoparticle delivery to tumour sites, represents a pioneering convergence of cellular immunotherapy and nanomedicine (131).

CRISPR-Cas9 genome editing delivered by nanoparticles offers transformative potential in oncology, enabling disruption of oncogenes, restoration of tumour suppressor function, and modulation of the tumour immune microenvironment at the genomic level. (132) Lipid nanoparticles have demonstrated efficacy in hepatic delivery of CRISPR components *in vivo*, and ongoing development of organ-selective LNP formulations aims to expand *in vivo* genome editing to extrahepatic cancer targets (133). Nanoparticle-enabled co-delivery of immunostimulatory agents with chemotherapy or checkpoint inhibitors to the tumour microenvironment may orchestrate a localised immune response, converting immunologically ‘cold’ tumours to ‘hot’ ones amenable to systemic immunotherapy (134).

12. Conclusions

Nanotechnology and nanoparticles have fundamentally transformed the landscape of cancer pharmacotherapy, providing tools of unprecedented sophistication for engineering drug delivery systems with tailored pharmacokinetics, improved tumour targeting, and controlled release capabilities. This chapter has systematically developed the scientific framework underlying nanoparticle-based drug delivery, progressing from the fundamental physics of nanoscale phenomena through nanoparticle physicochemical characterisation, compositional classification, and synthesis methodologies to the biological mechanisms of tumour targeting and the formidable barriers that constrain translational success (1-5).

The field has matured well beyond its early proof-of-concept phase, with more than 60 nanomedicine products approved globally and an expanding clinical pipeline spanning liposomes, polymeric nanoparticles, inorganic NPs, and lipid nanoparticles. Each approved product has generated invaluable clinical insights into the safety, pharmacokinetics, and patient-relevant outcomes of nanoparticle drug delivery, iteratively refining design principles and regulatory expectations. (26,121) The integration of active targeting, stimuli-responsive release, and biomimetic surface engineering into next-generation nanoparticle designs promises to address the limitations of passive EPR-based delivery that have constrained first-generation nanomedicines (107,119).





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References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2021 May;71(3):209-49.
2. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nano-enabled medical applications*. 2020 Nov 23:61-91.
3. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nature reviews cancer*. 2002 Jan 1;2(1):48-58.
4. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. *Nature reviews cancer*. 2017 Jan;17(1):20-37.
5. Morris SA, Gaheen S, Lijowski M, Heiskanen M, Klemm J. Experiences in supporting the structured collection of cancer nanotechnology data using caNanoLab. *Beilstein Journal of Nanotechnology*. 2015 Jul 21;6(1):1580-93.
6. Wassay A. Future of nanotechnology in South Asia: Indo-Pak military deployment. *Defence Studies*. 2025 Aug 14:1-7.
7. Esf E. Nanomedicine: An ESF-European Medical Research Councils (EMRC) Forward Look Report. Strasbourg cedex, France. 2005.
8. Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS nano*. 2009 Jan 27;3(1):16-20.
9. Ahire SM, Pawar PS, Shewale VV, Jadhav SP, Mahajan SK. Magnetic Particles for Targeted Drug Delivery and Biomedical Applications.
10. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer research*. 1986 Dec 1;46(12_Part_1):6387-92.
11. Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. *Adv Drug Deliv Rev*. 2011;63(3):131-5. doi:10.1016/j.addr.2010.03.011
12. Byrne JD, Betancourt T, Brannon-Peppas L. Active targeting schemes for nanoparticle systems in cancer therapeutics. *Advanced drug delivery reviews*. 2008 Dec 14;60(15):1615-26.
13. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. *Nature materials*. 2013 Nov;12(11):991-1003.





WISELEAF SCIENTIFIC VENTURES

14. Poon W, Kingston BR, Ouyang B, Ngo W, Chan WC. A framework for designing delivery systems. *Nature nanotechnology*. 2020 Oct;15(10):819-29.
15. Doane TL, Burda C. The unique role of nanoparticles in nanomedicine: imaging, drug delivery and therapy. *Chemical Society Reviews*. 2012;41(7):2885-911.
16. Feynman R. There's plenty of room at the bottom. In *Feynman and computation 2018* Mar 8 (pp. 63-76). CRC Press.
17. Taniguchi N. On the basic concept of 'nano-technology'. In *Proc. Intl. Conf. Prod. Eng. Tokyo, Part II, 1974* 1974. Japan Society of Precision Engineering.
18. Drexler E. Engines of creation: The coming era of nanotechnology. Anchor; 1987 Sep 16.
19. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. *Journal of molecular biology*. 1965 Aug 1;13(1):238-47.
20. Birrenbach G, Speiser PP. Polymerized micelles and their use as adjuvants in immunology. *Journal of pharmaceutical sciences*. 1976 Dec 1;65(12):1763-6.
21. Barenholz YC. Doxil®—The first FDA-approved nano-drug: Lessons learned. *Journal of controlled release*. 2012 Jun 10;160(2):117-34.
22. Iijima S. Helical microtubules of graphitic carbon. *nature*. 1991 Nov 7;354(6348):56-8.
23. Bruchez Jr M, Moronne M, Gin P, Weiss S, Alivisatos AP. Semiconductor nanocrystals as fluorescent biological labels. *science*. 1998 Sep 25;281(5385):2013-6.
24. Ghosh P, Han G, De M, Kim CK, Rotello VM. Gold nanoparticles in delivery applications. *Advanced drug delivery reviews*. 2008 Aug 17;60(11):1307-15.
25. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. *Nature reviews Drug discovery*. 2018 Apr;17(4):261-79.
26. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. *Bioengineering & translational medicine*. 2019 Sep;4(3):e10143.
27. Roco MC. The long view of nanotechnology development: the National Nanotechnology Initiative at 10 years. *Journal of nanoparticle research*. 2011 Feb;13(2):427-45.





WISELEAF SCIENTIFIC VENTURES

28. McNeil SE. Unique benefits of nanotechnology to drug delivery and diagnostics. In: Characterization of nanoparticles intended for drug delivery 2010 Oct 19 (pp. 3-8). Totowa, NJ: Humana Press.
29. Alivisatos AP. Semiconductor clusters, nanocrystals, and quantum dots. *science*. 1996 Feb 16;271(5251):933-7.
30. Oberdorster G, Oberdorster E, Oberdorster J. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environmental health perspectives*. 2005 Jul 1;113(7):823-39.
31. Sharma P, Kumar Mehra N, Jain K, Jain NK. Biomedical applications of carbon nanotubes: a critical review. *Current drug delivery*. 2016 Sep 1;13(6):796-817.
32. Jain PK, Huang X, El-Sayed IH, El-Sayed MA. Noble metals on the nanoscale: optical and photothermal properties and some applications in imaging, sensing, biology, and medicine. *Accounts of chemical research*. 2008 Dec 16;41(12):1578-86.
33. Laurent S, Forge D, Port M, Roch A, Robic C, Vander Elst L, Muller RN. Magnetic iron oxide nanoparticles: synthesis, stabilization, vectorization, physicochemical characterizations, and biological applications. *Chemical reviews*. 2008 Jun 11;108(6):2064-110.
34. Lammers T, Aime S, Hennink WE, Storm G, Kiessling F. Theranostic nanomedicine. *Accounts of chemical research*. 2011 Oct 18;44(10):1029-38.
35. Whitehead KA, Langer R, Anderson DG. Knocking down barriers: advances in siRNA delivery. *Nature reviews Drug discovery*. 2009 Feb;8(2):129-38.
36. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature biotechnology*. 2015 Sep;33(9):941-51.
37. Danhier F. To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine?. *Journal of Controlled Release*. 2016 Dec 28;244:108-21.
38. Bhattacharjee S. DLS and zeta potential—what they are and what they are not?. *Journal of controlled release*. 2016 Aug 10;235:337-51.
39. Bootz, A., Vogel, V., Schubert, D. and Kreuter, J., 2004. Comparison of scanning electron microscopy, dynamic light scattering and analytical ultracentrifugation for the sizing of poly (butyl cyanoacrylate) nanoparticles. *European journal of pharmaceuticals and biopharmaceutics*, 57(2), pp.369-375.





WISELEAF SCIENTIFIC VENTURES

40. Honary S, Zahir F. Effect of zeta potential on the properties of nano-drug delivery systems-a review (Part 1).
41. Goodman CM, McCusker CD, Yilmaz T, Rotello VM. Toxicity of gold nanoparticles functionalized with cationic and anionic side chains. *Bioconjugate chemistry*. 2004 Jul 21;15(4):897-900.
42. Jokerst JV, Lobovkina T, Zare RN, Gambhir SS. Nanoparticle PEGylation for imaging and therapy. *Nanomedicine*. 2011 Jun 1;6(4):715-28.
43. Rosenholm JM, Sahlgren C, Lindén M. Towards multifunctional, targeted drug delivery systems using mesoporous silica nanoparticles—opportunities & challenges. *Nanoscale*. 2010;2(10):1870-83.
44. Hermanson GT. *Bioconjugate techniques*. Academic press; 2013 Jul 25.
45. Cheng R, Meng F, Deng C, Klok HA, Zhong Z. Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery. *Biomaterials*. 2013 May 1;34(14):3647-57.
46. Yallapu MM, Jaggi M, Chauhan SC. Design and engineering of nanogels for cancer treatment. *Drug discovery today*. 2011 May 1;16(9-10):457-63.
47. Siepmann J, Siepmann F. Modeling of diffusion controlled drug delivery. *Journal of controlled release*. 2012 Jul 20;161(2):351-62.
48. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nature reviews Drug discovery*. 2014 Nov;13(11):813-27.
49. Geng YA, Dalhaimer P, Cai S, Tsai R, Tewari M, Minko T, Discher DE. Shape effects of filaments versus spherical particles in flow and drug delivery. *Nature nanotechnology*. 2007 Apr;2(4):249-55.
50. Decuzzi P, Godin B, Tanaka T, Lee SY, Chiappini C, Liu X, Ferrari MJ. Size and shape effects in the biodistribution of intravascularly injected particles. *Journal of Controlled Release*. 2010 Feb 15;141(3):320-7.
51. Li S, Jiang Q, Liu S, Zhang Y, Tian Y, Song C, Wang J, Zou Y, Anderson GJ, Han JY, Chang Y. A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo. *Nature biotechnology*. 2018 Mar;36(3):258-64.
52. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nature reviews Drug discovery*. 2005 Feb 1;4(2):145-60.





WISELEAF SCIENTIFIC VENTURES

53. Bulbake U, Doppalapudi S, Kommineni N, Khan W. Liposomal formulations in clinical use: an updated review. *Pharmaceutics*. 2017 Mar 27;9(2):12.
54. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Advanced drug delivery reviews*. 2013 Jan 1;65(1):36-48.
55. Muller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery—a review of the state of the art. *European journal of pharmaceutics and biopharmaceutics*. 2000 Jul 3;50(1):161-77.
56. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *International journal of pharmaceutics*. 2009 Jan 21;366(1-2):170-84.
57. Kulkarni JA, Witzigmann D, Thomson SB, Chen S, Leavitt BR, Cullis PR, Van Der Meel R. The current landscape of nucleic acid therapeutics. *Nature nanotechnology*. 2021 Jun;16(6):630-43.
58. Hou X, Zaks T, Langer R, Dong Y. Lipid nanoparticles for mRNA delivery. *Nature Reviews Materials*. 2021 Dec;6(12):1078-94.
59. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Prétat V. PLGA-based nanoparticles: an overview of biomedical applications. *Journal of controlled release*. 2012 Jul 20;161(2):505-22.
60. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers*. 2011 Sep;3(3):1377-97.
61. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: starburst-dendritic macromolecules. *Polymer journal*. 1985 Jan;17(1):117-32.
62. Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. *Progress in Polymer Science*. 2014 Feb 1;39(2):268-307.
63. Noriega-Luna B, Godínez LA, Rodríguez FJ, Rodríguez A, Zaldívar-Lelo de Larrea G, Sosa-Ferreyra CF, Mercado-Curiel RF, Manríquez J, Bustos E. Applications of dendrimers in drug delivery agents, diagnosis, therapy, and detection. *Journal of Nanomaterials*. 2014;2014(1):507273.
64. Shewale VV, Chavan DB, Ahire SM, Pawar PS, Jadhav SP. Introduction to nose-to-brain drug delivery: Need and scope. *Nose-to-Brain Drug Delivery: Advances in Intranasal Nanocarriers for CNS Disorders*. 2026;4:1.





WISELEAF SCIENTIFIC VENTURES

65. Oerlemans C, Bult W, Bos M, Storm G, Nijsen JF, Hennink WE. Polymeric micelles in anticancer therapy: targeting, imaging and triggered release. *Pharmaceutical research*. 2010 Dec;27(12):2569-89.
66. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. *Chemical Society Reviews*. 2012;41(7):2740-79.
67. Libutti SK, Paciotti GF, Byrnes AA, Alexander Jr HR, Gannon WE, Walker M, Seidel GD, Yuldasheva N, Tamarkin L. Phase I and pharmacokinetic studies of CYT-6091, a novel PEGylated colloidal gold-rhTNF nanomedicine. *Clinical cancer research*. 2010 Dec 15;16(24):6139-49.
68. Wahajuddin N, Arora S. Superparamagnetic iron oxide nanoparticles: magnetic nanoplateforms as drug carriers. *International journal of nanomedicine*. 2012 Jul 6:3445-71.
69. Maier-Hauff K, Ulrich F, Nestler D, Niehoff H, Wust P, Thiesen B, Orawa H, Budach V, Jordan A. Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. *Journal of neuro-oncology*. 2011 Jun;103(2):317-24.
70. Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery. *Advanced materials*. 2012 Mar 22;24(12):1504-34.
71. Vallet-Regí M, Balas F, Arcos D. Mesoporous materials for drug delivery. *Angewandte Chemie International Edition*. 2007 Oct 8;46(40):7548-58.
72. Croissant JG, Fatieiev Y, Khashab NM. Degradability and clearance of silicon, organosilica, silsesquioxane, silica mixed oxide, and mesoporous silica nanoparticles. *Advanced materials*. 2017 Mar;29(9):1604634.
73. Pawar PS, Ahire SM, Shewale VV, Jadhav S, Mahajan SK. Nanotechnology in herbal medicines: a review. *J Hosp Pharmacy*. 2025;20(1 Suppl 3):1-9.
74. Sanchez VC, Jachak A, Hurt RH, Kane AB. Biological interactions of graphene-family nanomaterials: an interdisciplinary review. *Chemical research in toxicology*. 2012 Jan 13;25(1):15-34.
75. Prato M, Kostarelos K, Bianco A. Functionalized carbon nanotubes in drug design and discovery. *Accounts of chemical research*. 2008 Jan 15;41(1):60-8.
76. Zhang L, Chan JM, Gu FX, Rhee JW, Wang AZ, Radovic-Moreno AF, Alexis F, Langer R, Farokhzad OC. Self-assembled lipid– polymer hybrid nanoparticles: a robust drug delivery platform. *ACS nano*. 2008 Aug 26;2(8):1696-702.





WISELEAF SCIENTIFIC VENTURES

77. Hu CM, Zhang L, Aryal S, Cheung C, Fang RH, Zhang L. Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. *Proceedings of the National Academy of Sciences*. 2011 Jul 5;108(27):10980-5.
78. Sercombe L, Veerati T, Moheimani F, Wu SY, Sood AK, Hua S. Advances and challenges of liposome assisted drug delivery. *Frontiers in pharmacology*. 2015 Dec 1;6:286.
79. Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. *Int J Pharm*. 1989;55(1):R1-4. doi:10.1016/0378-5173(89)90281-0
80. Rao JP, Geckeler KE. Polymer nanoparticles: Preparation techniques and size-control parameters. *Progress in polymer science*. 2011 Jul 1;36(7):887-913.
81. Davoodi P, Lee LY, Xu Q, Sunil V, Sun Y, Soh S, Wang CH. Drug delivery systems for programmed and on-demand release. *Advanced drug delivery reviews*. 2018 Jul 1;132:104-38.
82. Bilati U, Allémann E, Doelker E. Development of a nanoprecipitation method intended for the entrapment of hydrophilic drugs into nanoparticles. *European Journal of Pharmaceutical Sciences*. 2005 Jan 1;24(1):67-75.
83. Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: rationale for development and what we can expect for the future. *Advanced drug delivery reviews*. 2001 Mar 23;47(1):3-19.
84. Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *Journal of pharmaceutical sciences*. 2014 Jan 1;103(1):29-52.
85. Mintzer MA, Simanek EE. Nonviral vectors for gene delivery. *Chemical reviews*. 2009 Feb 11;109(2):259-302.
86. Turkevich J, Stevenson PC, Hillier J. A study of the nucleation and growth processes in the synthesis of colloidal gold. *Discussions of the faraday society*. 1951;11:55-75.
87. Ahire SM, Jadhav SP, Sonawane VN, Shewale VV, Pawar PS, Chavan DB, Mahaparale SP, Mahajan SK. A Comprehensive Review on Formulation and Evaluation of Herbal Niosomes containing *Phaseolus vulgaris* and *zingiber officinale* for the Treatment of Diabetes Mellitus. *Int j adv multidisc res stud*. 2024;4(6).





WISELEAF SCIENTIFIC VENTURES

- 88.Unsoy G, Yalcin S, Khodadust R, Gunduz G, Gunduz U. Synthesis optimization and characterization of chitosan-coated iron oxide nanoparticles produced for biomedical applications. *Journal of Nanoparticle Research*. 2012 Nov;14(11):964.
- 89.Baek JS, Cho CW. Surface modification of solid lipid nanoparticles for oral delivery of curcumin: Improvement of bioavailability through enhanced cellular uptake, and lymphatic uptake. *European Journal of Pharmaceutics and Biopharmaceutics*. 2017 Aug 1;117:132-40.
- 90.Peltonen L, Hirvonen J. Pharmaceutical nanocrystals by nanomilling: critical process parameters, particle fracturing and stabilization methods. *Journal of pharmacy and pharmacology*. 2010 Nov;62(11):1569-79.
- 91.Muller RH, Keck CM. Challenges and solutions for the delivery of biotech drugs—a review of drug nanocrystal technology and lipid nanoparticles. *Journal of biotechnology*. 2004 Sep 30;113(1-3):151-70.
- 92.Shegokar R, Müller RH. Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. *International journal of pharmaceutics*. 2010 Oct 31;399(1-2):129-39.
- 93.Karnik R, Gu F, Basto P, Cannizzaro C, Dean L, Kyei-Manu W, et al. Microfluidic platform for controlled synthesis of polymeric nanoparticles. *Nano Lett*. 2008;8(9):2906-12. doi:10.1021/nl801736q
- 94.Shepherd SJ, Issadore D, Mitchell MJ. Microfluidic formulation of nanoparticles for biomedical applications. *Biomaterials*. 2021 Jul 1;274:120826.
- 95.Lim JM, Swami A, Gilson LM, Chopra S, Choi S, Wu J, Langer R, Karnik R, Farokhzad OC. Ultra-high throughput synthesis of nanoparticles with homogeneous size distribution using a coaxial turbulent jet mixer. *ACS nano*. 2014 Jun 24;8(6):6056-65.
- 96.Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *Journal of controlled release*. 2000 Mar 1;65(1-2):271-84.
97. Ahire SM, Pawar PS, Sonawane VN, Jadhav SP. Personalized Medicine and Pharmacogenomics: Impact of Genetic variation on Drug Response and Individualized Therapy-A Review. *Asian Journal of Pharmacy and Technology*. 2026 Jan 27;16(1):91-8.
- 98.Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. *Journal of controlled release*. 2012 Jul 20;161(2):175-87.





WISELEAF SCIENTIFIC VENTURES

99. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WC. Analysis of nanoparticle delivery to tumours. *Nature reviews materials*. 2016 Apr 26;1(5):16014.
100. Nakamura Y, Mochida A, Choyke PL, Kobayashi H. Nanodrug delivery: is the enhanced permeability and retention effect sufficient for curing cancer?. *Bioconjugate chemistry*. 2016 Oct 19;27(10):2225-38.
101. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Advanced drug delivery reviews*. 2014 Feb 1;66:2-5.
102. Park JW, Hong K, Kirpotin DB, Colbern G, Shalaby R, Baselga J, Shao Y, Nielsen UB, Marks JD, Moore D, Papahadjopoulos D. Anti-HER2 immunoliposomes: enhanced efficacy attributable to targeted delivery. *Clinical Cancer Research*. 2002 Apr 1;8(4):1172-81.
103. Leamon CP, Reddy JA. Folate-targeted chemotherapy. *Advanced drug delivery reviews*. 2004 Apr 29;56(8):1127-41.
104. Sudimack J, Lee RJ. Targeted drug delivery via the folate receptor. *Advanced drug delivery reviews*. 2000 Mar 30;41(2):147-62.
105. Keefe AD, Pai S, Ellington A. Aptamers as therapeutics. *Nature reviews Drug discovery*. 2010 Jul;9(7):537-50.
106. Farokhzad OC, Cheng J, Teply BA, Sherifi I, Jon S, Kantoff PW, Richie JP, Langer R. Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. *Proceedings of the National Academy of Sciences*. 2006 Apr 18;103(16):6315-20.
107. Peng Y, Wong WK, Hu Z, Cheng Y, Yuan D, Khan SA, Zhao D. Room temperature batch and continuous flow synthesis of water-stable covalent organic frameworks (COFs). *Chemistry of Materials*. 2016 Jul 26;28(14):5095-101.
108. Tannock IF, Rotin D. Acid pH in tumors and its potential for therapeutic exploitation. *Cancer research*. 1989 Aug 15;49(16):4373-84.
109. Bahiram U, Ahire M, Ahire S, Mahajan S. Biomedical Applications of Nanoparticles Derived from Curcumin & Resveratrol. *International Journal of Pharmacognosy*. 2024;6(2):53-9
110. Timko BP, Dvir T, Kohane DS. Remotely triggerable drug delivery systems. *Advanced materials*. 2010 Nov 24;22(44):4925-43.





WISELEAF SCIENTIFIC VENTURES

111. Cedervall T, Lynch I, Lindman S, Berggård T, Thulin E, Nilsson H, Dawson KA, Linse S. Understanding the nanoparticle–protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. *Proceedings of the National Academy of Sciences*. 2007 Feb 13;104(7):2050-5.
112. Ahire SM, Pawar PS, Jadhav SP, Shewale VV, Patil CD, Mahajan SK, Vishwas S. Nanotechnology-driven antioxidants and immunomodulators for polycystic ovary syndrome (PCOS) therapy. *Nanotechnology NextGen: From Treatment to Transformation in Polycystic Ovary Syndrome (PCOS)*. 2025 Jul 15:184.
113. Caracciolo G, Farokhzad OC, Mahmoudi M. Biological identity of nanoparticles in vivo: clinical implications of the protein corona. *Trends in biotechnology*. 2017 Mar 1;35(3):257-64.
114. Rodriguez PL, Harada T, Christian DA, Pantano DA, Tsai RK, Discher DE. Minimal "Self" peptides that inhibit phagocytic clearance and enhance delivery of nanoparticles. *Science*. 2013 Feb 22;339(6122):971-5.
115. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacological reviews*. 2001 Jun 1;53(2):283-318.
116. Owens III DE, Peppas NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. *International journal of pharmaceutics*. 2006 Jan 3;307(1):93-102.
117. Ishida T, Kiwada H. Accelerated blood clearance (ABC) phenomenon upon repeated injection of PEGylated liposomes. *International journal of pharmaceutics*. 2008 Apr 16;354(1-2):56-62.
118. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. *Nature reviews Clinical oncology*. 2010 Nov;7(11):653-64.
119. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. *Nature materials*. 2013 Nov;12(11):958-62.
120. Zheng N, Sun DD, Zou P, Jiang W. Scientific and regulatory considerations for generic complex drug products containing nanomaterials. *The AAPS journal*. 2017 May;19(3):619-31.
121. Jadhav SP, Ahire SM, Pawar PS, Mahajan SK, Sonawane DD. Exploring Natural Oils: Role in Antimicrobial Activity and Preservation. *Asian Journal of Research in Pharmaceutical Sciences*. 2026 Jan 5;16(1):59-64.





WISELEAF SCIENTIFIC VENTURES

122. Bagul RD, Ahire SM, Sonwane DD, Mahajan SK. Emerging Application of Pluot in Nutraceutical and Cosmetic Formulation. *Research Journal of Pharmacognosy and Phytochemistry*. 2026 Jul;18:3.
123. Stern ST, McNeil SE. Nanotechnology safety concerns revisited. *Toxicological sciences*. 2008 Jan 1;101(1):4-21.
124. Wang J, Maniruzzaman M. A global bibliometric and visualized analysis of bacteria-mediated cancer therapy. *Drug Discovery Today*. 2022 Oct 1;27(10):103297.
125. Zhao L, Skwarczynski M, Toth I. Polyelectrolyte-based platforms for the delivery of peptides and proteins. *ACS Biomaterials Science & Engineering*. 2019 Sep 15;5(10):4937-50.
126. Beg S, Rahman M, Jain A, Saini S, Hasnain MS, Swain S, Imam S, Kazmi I, Akhter S. Emergence in the functionalized carbon nanotubes as smart nanocarriers for drug delivery applications. In *Fullerens, graphenes and nanotubes 2018 Jan 1* (pp. 105-133). William Andrew Publishing.
127. Sharma P, Kumar Mehra N, Jain K, Jain NK. Biomedical applications of carbon nanotubes: a critical review. *Current drug delivery*. 2016 Sep 1;13(6):796-817.
128. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. *Nanomedicine*. 2010 Jun 1;5(4):523-8.
129. Pawar SP, Ahire MS, Shewale VV, Jadhav S, Mahajan KS, Sonawane DD. Silver nanoparticles: A comprehensive review on synthesis, properties and applications. *Research Journal of Pharmaceutical Dosage Forms and Technology*. 2025;17(4):279-85.
130. Sun T, Zhang YS, Pang B, Hyun DC, Yang M, Xia Y. Engineered nanoparticles for drug delivery in cancer therapy. *Nanomaterials and neoplasms*. 2021 Jul 22;31-142.
131. Stephan MT, Stephan SB, Bak P, Chen J, Irvine DJ. Synapse-directed delivery of immunomodulators using T-cell-conjugated nanoparticles. *Biomaterials*. 2012 Aug 1;33(23):5776-87.
132. Xu CF, Chen GJ, Luo YL, Zhang Y, Zhao G, Lu ZD, Czarna A, Gu Z, Wang J. Rational designs of in vivo CRISPR-Cas delivery systems. *Advanced drug delivery reviews*. 2021 Jan 1;168:3-29.
133. Ahire SM, Pawar PS, Jadhav SP, Mahajan SK. Herbal Nutraceuticals and Functional Applications of *Celosia argentea* and Allied Botanicals.





WISELEAF SCIENTIFIC VENTURES

134.Irvine DJ, Dane EL. Enhancing cancer immunotherapy with nanomedicine. Nature Reviews Immunology. 2020 May;20(5):321-34.

