Nanotechnology-Based Drug Delivery Systems: Formulation, Characterisation, Therapeutic Applications and Future Perspectives

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ABSTRACT

Nanotechnology has reshaped pharmaceutical drug delivery over the past three decades by allowing therapeutic agents to be carried in engineered particulate systems typically between 10 and 1000 nm in diameter. At this scale, materials acquire properties that bulk formulations cannot reproduce: an enormous surface-area-to-volume ratio that accelerates dissolution, a size regime that permits extravasation through leaky tumour vasculature and uptake by endocytic pathways, and a surface that can be chemically modified to control circulation time and tissue distribution. This review examines the principles underlying pharmaceutical nanotechnology and surveys the major carrier classes, including polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, polymeric micelles and dendrimers, comparing their loading capacity, release behaviour, stability and clinical maturity. A critical account of the existing literature is provided, identifying both the substantial progress made in solubility enhancement, targeting and controlled release and the persistent gap between preclinical promise and clinical delivery, most visibly in the modest tumour accumulation actually achieved by systemically administered nanoparticles. Preparation methods from nanoprecipitation and emulsification through high-pressure homogenisation, ultrasonication, ionic gelation and thin-film hydration are compared, followed by the characterisation techniques used to establish particle size, surface charge, morphology, drug loading, solid-state behaviour and release kinetics. Therapeutic applications are reviewed across oncology, infectious disease, cardiovascular and neurological disorders, metabolic and inflammatory disease, vaccines, nucleic acid delivery and ocular and topical routes, with particular attention to the lipid nanoparticle platforms that enabled messenger RNA vaccination. Advantages, nanotoxicological considerations, stability and scale-up constraints and regulatory expectations are then discussed, followed by emerging directions in stimuli-responsive, biomimetic, theranostic and computationally designed nanocarriers.

Keywords: nanotechnology; nanoparticles; drug delivery; liposomes; polymeric nanoparticles; lipid nanoparticles; targeted delivery; nanomedicine; clinical translation.

I INTRODUCTION

The therapeutic performance of a drug depends as much on where and when it arrives as on what it does when it gets there. A conventional dosage form distributes its payload according to the physicochemical properties of the molecule and the physiology of the body, with little scope for intervention. The consequences are familiar: poorly soluble compounds are absorbed erratically, cytotoxic agents damage healthy tissue as readily as diseased tissue, short-half-life drugs require frequent dosing, and molecules that cannot cross the blood–brain barrier or the intestinal epithelium are simply unavailable at their target [7,25].

Nanotechnology addresses this by separating the drug from its distribution behaviour. When a molecule is loaded into a nanoscale carrier, its fate in the body is governed largely by the carrier rather than by the drug itself. Size, surface charge, surface chemistry and mechanical properties of the particle determine how long it circulates, which tissues it

reaches, which cells take it up and how quickly it releases its contents. These are engineering variables that a formulator can manipulate, whereas the properties of the drug molecule are fixed [9,31].

The field has a substantial clinical record. Liposomal amphotericin B and liposomal doxorubicin have been in routine use since the 1990s, albumin-bound paclitaxel since 2005, and iron–carbohydrate nanoparticle complexes for decades before that. More than fifty nanomedicine products have received regulatory approval, and the deployment of lipid nanoparticle messenger RNA vaccines from 2020 onwards represented the largest-scale application of a nanoparticulate delivery system in medical history [16,17,32].

At the same time, the field has been marked by a persistent gap between preclinical expectation and clinical delivery. A widely discussed meta-analysis found that the median proportion of an injected nanoparticle dose reaching a solid tumour was well below one per cent, prompting substantial reappraisal of the enhanced permeability and retention effect on which much oncology nanomedicine had been predicated [18]. Understanding both what nanotechnologies reliably delivers and where its limitations lie is therefore essential to using it well.

This review covers the fundamentals of pharmaceutical nanotechnology, the principal carrier classes and their comparative properties, a critical reading of the existing literature, preparation and characterisation methods, therapeutic applications across major disease areas, and the safety, manufacturing and regulatory considerations that govern translation. Emerging directions including stimuli-responsive, biomimetic and theranostic systems and computationally guided design are considered in closing.

II FUNDAMENTALS OF PHARMACEUTICAL NANOTECHNOLOGY

2.1 Concept and principles

Pharmaceutical nanotechnology concerns the design and use of materials with at least one dimension in the nanometre range for therapeutic and diagnostic purposes. Although the strict definition of nanomaterials sets an upper limit of 100 nm, the pharmaceutical literature conventionally extends the range to approximately 1000 nm, since carriers of 100–500 nm retain the behaviours of interest and are frequently the most practical to manufacture [22,25].

Three physical consequences of small size drive the pharmaceutical utility of these systems. The first is surface area. Because the surface-area-to-volume ratio scales inversely with radius, reducing particle diameter from 10 μm to 100 nm increases the specific surface area a hundredfold, which accelerates dissolution proportionally under the Noyes–Whitney relationship and raises apparent saturation solubility through the Ostwald–Freundlich effect [15]. The second is biological access. Particles below roughly 200 nm can extravasate through the discontinuous endothelium of tumour and inflamed tissue, and particles in the 20–200 nm range are efficiently internalised by clathrin- and caveolin-mediated endocytosis, providing entry routes closed to larger material [3,18]. The third is surface engineering. A nanoparticle presents a large, chemically addressable surface to which stabilisers, hydrophilic polymers, targeting ligands and imaging agents can be attached, allowing circulation time and tissue distribution to be tuned independently of the drug [4,30].

2.2 Classification of pharmaceutical nanocarriers

Nanocarriers are classified most usefully by the material from which the matrix is built. Polymeric systems include nanospheres, in which drug is dispersed throughout a solid polymer matrix, nanocapsules, in which a liquid core is enclosed by a polymer shell, and polymeric micelles formed by self-assembly of amphiphilic block copolymers. Lipid-based systems include liposomes, solid lipid nanoparticles, nanostructured lipid carriers,

nanoemulsions and the ionisable lipid nanoparticles used for nucleic acid delivery. Inorganic systems include gold, silica, iron oxide and quantum dot carriers, valued mainly for their optical and magnetic properties in diagnostic and theranostic applications. Dendrimers occupy a separate category as precisely defined, monodisperse branched macromolecules. Drug nanocrystals, consisting of pure drug stabilised by a thin surfactant layer with no carrier matrix at all, are a further distinct class used primarily for solubility enhancement [7,22,25].

Table 1. Classification and principal characteristics of pharmaceutical nanocarriers.

Carrier class	Composition	Typical size	Drug type suited	Distinguishing feature
Polymeric nanoparticles	PLGA, PLA, PCL, chitosan, albumin	100–500 nm	Hydrophobic and hydrophilic	Tunable, sustained release via polymer degradation
Liposomes	Phospholipids and cholesterol bilayers	50–500 nm	Both, in bilayer or aqueous core	Amphiphilic; encapsulates both drug types simultaneously
Solid lipid nanoparticles	Solid lipid stabilised by surfactant	50–500 nm	Lipophilic	Solid matrix; controlled release; solvent-free production
Nanostructured lipid carriers	Solid lipid blended with liquid lipid	50–500 nm	Lipophilic	Imperfect matrix; higher loading, less expulsion
Nanoemulsions	Oil droplets stabilised by surfactant	20–200 nm	Lipophilic	Kinetically stable liquid core; rapid release
Polymeric micelles	Amphiphilic block copolymers	10–100 nm	Strongly lipophilic	Self-assembling; very small; core–shell architecture
Dendrimers	Branched macromolecules (PAMAM, PPI)	1–15 nm	Both, encapsulated or conjugated	Monodisperse, precisely defined generation and surface
Inorganic nanoparticles	Gold, silica, iron oxide, quantum dots	5–200 nm	Surface-conjugated	Optical and magnetic properties; theranostic use
Drug nanocrystals	Pure drug with surfactant layer	100–1000 nm	Poorly soluble	No carrier matrix; very high drug content

PLGA = poly(lactic-co-glycolic acid); PCL = polycaprolactone; PAMAM = polyamidoamine. Compiled from references [7,22,23,25].

2.3 Physicochemical properties of nanoparticles

Particle size is the single most consequential attribute. It determines biodistribution, since particles above roughly 200 nm are efficiently cleared by the mononuclear phagocyte system in liver and spleen while those below approximately 6 nm undergo rapid renal elimination, leaving an intermediate window in which prolonged circulation is achievable. Size also governs cellular uptake efficiency, tissue penetration and release rate through its effect on diffusion path length [3,26,29]. The polydispersity index quantifies the width of the size distribution on a scale from 0 to 1. Values below 0.3 are generally considered acceptable for pharmaceutical nanocarriers and values below 0.1 indicate a nearly monodisperse population. A broad distribution is problematic beyond simple inelegance, because different size fractions distribute differently in vivo, so a polydisperse preparation behaves as a mixture of products rather than as one [26].

Zeta potential is the electrical potential at the plane of hydrodynamic shear and predicts colloidal stability. Magnitudes above 30 mV in either direction usually provide sufficient electrostatic repulsion to prevent aggregation, although sterically stabilised systems remain stable at much lower values. Charge also influences biological behaviour: cationic particles interact strongly with the anionic cell membrane and are taken up efficiently but are more cytotoxic and are cleared rapidly from circulation, while anionic and near-neutral particles circulate longer [22,26]. Surface chemistry determines the composition of the protein corona that forms within seconds of contact with biological fluid, and it is this corona rather than the engineered surface that cells actually encounter, an insight that has substantially revised thinking about targeting [29,30].

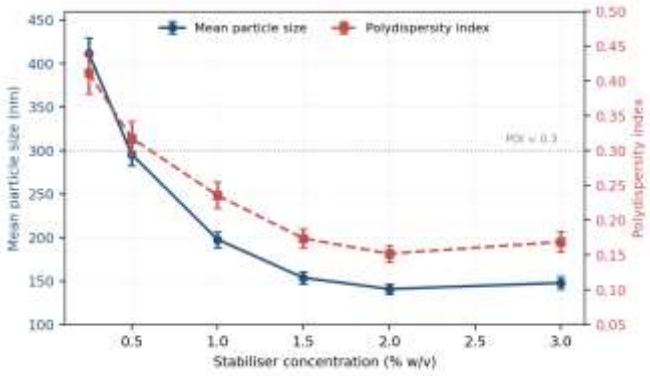


Figure 1. Influence of stabiliser concentration on the mean particle size and polydispersity index of a model nanoparticle formulation. Both fall as stabiliser is increased until the interface is saturated, beyond which no further benefit is obtained. Illustrative profiles constructed from trends reported in references [1,24,26]; error bars represent SD, n = 3.

2.4 Drug loading and encapsulation

Two related but distinct parameters describe how much drug a carrier holds. Encapsulation efficiency expresses the proportion of the drug offered to the formulation that is actually incorporated:

$$EE\ (\%) = [(W_{total} - W_{free}) / W_{total}] \times 100 \quad (1)$$

where W_total is the total quantity of drug added and W_free the quantity recovered unentrapped after separation by ultracentrifugation, ultrafiltration or dialysis. Drug loading capacity instead expresses the payload relative to the mass of the carrier system:

$$DL\ (\%) = [W_{encapsulated} / (W_{encapsulated} + W_{carrier})] \times 100 \quad (2)$$

Reporting both matters. A formulation may achieve 95% encapsulation efficiency using a large excess of polymer and still have a drug loading of only 2%, which means the patient must receive fifty times more excipient than drug. Loading capacity above roughly 10% is generally desirable for practical dosage forms, and values above 20% are difficult to achieve for most matrix systems [23,24].

Drug can be incorporated during particle formation, by dissolving it in the organic or lipid phase before dispersion, or after formation by incubation and passive or active loading. Active loading exploits a transmembrane gradient, most commonly an

ammonium sulfate or pH gradient across a liposome bilayer, which drives weakly basic drugs such as doxorubicin into the aqueous core where they precipitate as a gel and cannot escape. This mechanism achieves encapsulation efficiencies approaching 100% and loading far beyond what passive methods allow, and it underpins the commercially successful liposomal anthracycline products [5,10].

III TYPES OF NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

3.1 Polymeric nanoparticles

Polymeric nanoparticles are prepared from biodegradable synthetic polymers, principally poly(lactic-co-glycolic acid), polylactic acid and polycaprolactone, or from natural polymers such as chitosan, alginate, gelatin and albumin. PLGA is the most extensively used because it degrades by hydrolysis to lactic and glycolic acid, both entering normal metabolic pathways, and because degradation rate can be tuned from weeks to months through the lactide-to-glycolide ratio and polymer molecular weight. Release from these systems combines diffusion through the matrix with polymer erosion, giving sustained profiles that few other carriers match. Albumin-bound paclitaxel demonstrated that a protein-based nanoparticle could eliminate the need for the Cremophor EL vehicle and its associated hypersensitivity reactions, and remains one of the clearest commercial successes in the field [2,23,24].

3.2 Liposomes

Liposomes are vesicles consisting of one or more phospholipid bilayers enclosing an aqueous core, and they are the most clinically established nanocarrier class. Their amphiphilic architecture allows hydrophilic drugs to be held in the aqueous compartment and lipophilic drugs within the bilayer, sometimes simultaneously. Composition determines behaviour: cholesterol content controls bilayer rigidity and leakage, the phase transition temperature of the phospholipid governs release, and surface modification with polyethylene glycol reduces opsonisation and extends circulation half-life from minutes to many hours, producing the so-called stealth liposomes that made liposomal doxorubicin clinically viable. Limitations include physical and chemical instability on storage, drug leakage, and relatively complex manufacture requiring sterilisation strategies compatible with a fragile bilayer [5,10,12].

3.3 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles consist of a lipid that remains solid at body temperature, dispersed in aqueous surfactant solution. They offer controlled release, physical stability, production without organic solvent by high-pressure homogenisation, and excipients with excellent tolerability. Their weakness is structural: a pure lipid crystallises into a well-ordered lattice that accommodates little drug, and polymorphic transition towards the stable β form during storage expels the drug that was incorporated [12,13,15].

Nanostructured lipid carriers were developed specifically to solve this. Blending the solid lipid with 5–40% of a spatially incompatible liquid lipid produces a matrix with crystal imperfections or discrete oil compartments in which drug can be accommodated, raising loading capacity substantially and suppressing expulsion. The liquid lipid also lowers melt viscosity, which reduces particle size during homogenisation. These carriers have been widely applied to oral delivery of poorly soluble drugs, where dissolution enhancement, protection from degradation and partial lymphatic uptake act together [14,20].

3.4 Nanoemulsions

Nanoemulsions are kinetically stable dispersions of oil in water, or water in oil, with droplet diameters typically between 20 and 200 nm. Unlike microemulsions they are not thermodynamically stable and require energy input to form, but the small droplet size makes them transparent and resistant to creaming and sedimentation. They provide high solubilisation capacity for lipophilic drugs, rapid release, and straightforward manufacture, and are used across oral, parenteral, topical and ocular routes. Ostwald ripening, the growth of larger droplets at the expense of smaller ones driven by the

higher solubility of material in small droplets, is the characteristic long-term failure mode [19,23].

3.5 Polymeric micelles

Amphiphilic block copolymers self-assemble above their critical micelle concentration into core–shell structures with a hydrophobic core solubilising the drug and a hydrophilic corona, usually polyethylene glycol, providing colloidal stability and reduced recognition by phagocytes. Diameters of 10–100 nm are smaller than most other carriers, favouring tissue penetration. The principal vulnerability is dilution: on intravenous injection the micelle concentration may fall below the critical micelle concentration, causing disassembly and premature drug release. Cross-linking the core or shell, and selecting copolymers with very low critical micelle concentration, are the usual countermeasures [21,27].

3.6 Dendrimers

Dendrimers are synthesised by iterative branching from a central core, producing monodisperse macromolecules of precisely defined molecular weight, size and surface functionality. Successive generations increase size and surface group number geometrically, and drug can be held in internal cavities or conjugated to surface groups. The precision of the architecture is scientifically attractive, allowing structure–activity relationships to be established with unusual clarity. Clinical translation has been slowed by the cytotoxicity of cationic amine-terminated dendrimers, which disrupt cell membranes, and by the cost and complexity of multi-step synthesis; surface modification with polyethylene glycol, acetyl or carboxyl groups substantially reduces the toxicity [8,11].

3.7 Inorganic nanoparticles and drug nanocrystals

Two further classes complete the picture. Inorganic carriers built from gold, mesoporous silica, iron oxide or quantum dots are valued less for their loading capacity than for physical properties the organic systems cannot provide: gold particles absorb near-infrared light and convert it to heat for photothermal therapy, superparamagnetic iron oxide provides magnetic resonance contrast and permits magnetic guidance, and mesoporous silica offers an exceptionally high surface area with pores that can be capped by stimulus-responsive gatekeepers. Their principal drawback is that most are not biodegradable, so long-term accumulation in liver, spleen and lymph nodes is a genuine and incompletely resolved concern for chronic use [22,31].

Drug nanocrystals occupy the opposite extreme, consisting of pure drug particles stabilised only by a thin adsorbed surfactant or polymer layer. Because there is no carrier matrix, drug content approaches 100%, which makes them uniquely suited to high-dose poorly soluble compounds where any matrix system would produce an unacceptably large dosage form. They are produced by wet media milling, high-pressure homogenisation or controlled precipitation, and their benefit derives entirely from surface area and elevated saturation solubility rather than from any change in distribution. Several oral products based on this technology are marketed, making nanocrystals one of the commercially more successful applications of pharmaceutical nanotechnology [14,25].

Table 2. Comparative assessment of the principal nanocarrier systems.

System	Drug loading	Release profile	Physical stability	Scalability	Clinical maturity
Polymeric nanoparticles	Moderate (5–20%)	Sustained, diffusion plus erosion	Good; lyophilisable	Moderate; solvent removal required	Several approved products

Liposomes	High with active loading	Tunable by lipid composition	Moderate; leakage and hydrolysis	Established but complex	Most mature; many approvals
Solid lipid nanoparticles	Low (< 5–10%)	Sustained	Expulsion on polymorphic transition	Good; solvent-free	Mainly preclinical and cosmetic
Nanostructured lipid carriers	Higher (10–30%)	Biphasic: burst then sustained	Better than SLN	Good; solvent-free	Preclinical, some cosmetic products
Nanoemulsions	High for lipophilic drugs	Rapid	Ostwald ripening over time	Excellent	Approved parenteral and topical products
Polymeric micelles	Moderate, drug-dependent	Rapid to moderate	Disassembly below CMC	Good	Approved in some regions; trials ongoing
Dendrimers	Moderate; defined stoichiometry	Depends on conjugation chemistry	Excellent	Poor; multi-step synthesis	Largely preclinical

CMC = critical micelle concentration. Compiled from references [5,10,13,14,19,21,23,27].

IV LITERATURE REVIEW

4.1 Development of nanotechnology-based delivery systems

The field developed in three broadly identifiable phases. The first, from the 1960s to the late 1980s, established that vesicular and particulate carriers could encapsulate drugs and alter their distribution, but the resulting systems were cleared from circulation within minutes by the mononuclear phagocyte system. The second phase, from around 1990, solved this through surface modification with polyethylene glycol, producing long-circulating carriers and enabling the first commercially successful products. The third phase, from roughly 2000 onwards, has pursued active targeting through ligand conjugation, stimulus-responsive release and multifunctional constructs, with results that have been scientifically productive but clinically more equivocal than the preceding phase [4,12,17].

4.2 Nanocarriers for solubility and bioavailability enhancement

This is the application with the most consistent and reproducible success, largely because the mechanism is physical rather than biological and therefore less dependent on complex in vivo behaviour. Reduction to the nanoscale increases dissolution rate through surface area and reduces the diffusion layer thickness, while carrier systems additionally present the drug in an amorphous or molecularly dispersed state and protect it from precipitation. Reported improvements in oral bioavailability for BCS Class II and IV compounds commonly fall between two- and five-fold across polymeric, lipid and nanocrystal systems, and nanocrystal technology in particular has delivered several marketed oral products [15,20,25].

4.3 Targeted and controlled delivery

Passive targeting relies on the enhanced permeability and retention effect, in which the discontinuous endothelium and impaired lymphatic drainage of solid tumours allow nanoparticles to extravasate and accumulate. Active targeting adds a ligand such as folate, transferrin, an antibody fragment or an aptamer that binds a receptor overexpressed on the target cell. The evidence supports a nuanced conclusion: ligand conjugation reliably increases cellular internalisation once a particle has reached the tumour, but generally does not increase the quantity of particle delivered to the tumour, because

that is determined by circulation time and vascular access rather than by cell-surface affinity [4,28,30].

Controlled release has been demonstrated convincingly across carrier types, with profiles ranging from hours to months depending on matrix composition. Release from most nanocarriers is biphasic, with an initial burst attributable to surface-associated drug followed by sustained release from the core, and the burst fraction is one of the more difficult parameters to control reproducibly [6,23].

4.4 Applications across therapeutic areas

Oncology dominates the published literature by a wide margin, reflecting both the severity of dose-limiting toxicity with conventional chemotherapy and the vascular abnormalities that make tumours uniquely accessible to particulate carriers. Antimicrobial applications form the second largest group, addressing intracellular pathogens, biofilms and resistant organisms. Central nervous system delivery, cardiovascular applications, metabolic disease, inflammatory conditions, vaccines and nucleic acid delivery follow. The relative volume of publication does not track clinical success: nucleic acid delivery, a comparatively small literature until recently, produced the most consequential clinical application of the past decade [25,29,32].

4.5 Multifunctional nanocarriers

Recent work increasingly combines functions within one construct: targeting ligand, stimulus-responsive linker, imaging agent and one or more therapeutic payloads. Theranostic particles that permit simultaneous treatment and monitoring, and hybrid lipid–polymer systems combining the biocompatibility of a lipid shell with the release control of a polymer core, are representative. The scientific appeal is clear, but each additional function adds synthesis steps, characterisation requirements and regulatory complexity, and the marginal clinical benefit of the later additions has not generally been demonstrated [8,30,31].

4.6 Critical analysis and research gaps

Several weaknesses recur across the literature and deserve explicit statement. First, the analysis of tumour delivery data across a decade of publications found a median delivery efficiency of approximately 0.7% of the injected dose, a figure that reframes much of the preceding optimism about passive targeting and indicates that the dominant barrier is biological distribution rather than carrier design [18]. Second, animal models systematically overstate the enhanced permeability and retention effect: rapidly grown subcutaneous xenografts have more permeable and more uniform vasculature than spontaneous human tumours, so preclinical results do not transfer reliably [28,30].

Third, reporting standards are inconsistent. Particle size measured by dynamic light scattering, by nanoparticle tracking analysis and by electron microscopy give systematically different values, yet method details are often omitted, and encapsulation efficiency is reported without specifying the separation technique that defines it. Fourth, publication bias towards positive results means the formulations that failed, which are as informative as those that succeeded, rarely appear. Fifth, in vitro release methods are not standardised, and dialysis-based methods in particular can be membrane-limited rather than release-limited, producing profiles that reflect the apparatus rather than the formulation [22,26].

The gaps that follow are correspondingly clear: a need for predictive in vitro models and animal models that reflect human tumour biology; standardised, comparable characterisation and reporting; better understanding of the protein corona and how to engineer for it rather than around it; scalable and reproducible manufacturing suitable for complex multifunctional constructs; and long-term safety data for materials intended for chronic administration [28,29,30].

V FORMULATION AND PREPARATION APPROACHES

Preparation methods divide broadly into top-down approaches, which reduce larger material to the nanoscale by applying energy, and bottom-up approaches, which build particles from molecularly dispersed starting material. The choice determines achievable size, distribution width, solvent requirement and scalability [1,24].

5.1 Nanoprecipitation

Also called solvent displacement, this method dissolves polymer and drug in a water-miscible organic solvent such as acetone or acetonitrile and adds the solution to an aqueous phase containing stabiliser under stirring. Rapid diffusion of the solvent into water causes local supersaturation and spontaneous polymer precipitation into nanoparticles by the Marangoni effect. The method requires little energy, gives small particles with narrow distributions, and is highly reproducible. It is restricted to drugs and polymers soluble in water-miscible solvents, gives dilute suspensions requiring concentration, and encapsulates hydrophilic drugs poorly since they diffuse into the aqueous phase during formation [1,24].

5.2 Emulsification methods

In single emulsion solvent evaporation, polymer and drug are dissolved in a water-immiscible solvent, emulsified into aqueous surfactant solution by sonication or high-shear mixing, and the solvent removed by evaporation under stirring or reduced pressure. The double or multiple emulsion variant, in which an internal aqueous phase containing a hydrophilic drug or protein is first emulsified into the organic polymer solution before the second emulsification, extends the technique to water-soluble payloads. Encapsulation efficiency for the internal phase is often modest and protein stability at the two interfaces requires careful attention. Emulsification–diffusion uses a partially water-miscible solvent saturated with water, with dilution driving solvent diffusion and particle formation; it gives narrow distributions but needs large water volumes [23,24].

5.3 High-pressure homogenisation

Fluid is forced at 100–2000 bar through a gap of a few micrometres, where shear, turbulence and cavitation break droplets or particles down to the nanoscale. It is the dominant method for lipid nanoparticles and nanoemulsions and the only one demonstrated at full industrial scale. In the hot variant the drug is dissolved in molten lipid, a hot pre-emulsion is formed and homogenised above the lipid melting point, and cooling produces solid particles; the cold variant processes solidified, milled lipid below room temperature and is used for thermolabile and hydrophilic drugs at the cost of larger, more polydisperse particles. Three to five cycles are usually optimal, since further cycles can increase size through coalescence [13,15].

5.4 Ultrasonication

Probe or bath sonication uses acoustic cavitation to disperse a coarse emulsion. The equipment is inexpensive and near-universally available, making it the standard laboratory screening method, but distributions are broad, a microparticle fraction is frequently present, processing is slow, and metal shed from the probe can contaminate the product. It is rarely appropriate beyond bench scale [13,24].

5.5 Ionic gelation

Ionic gelation exploits electrostatic cross-linking between an ionic polymer and a multivalent counter-ion. Chitosan nanoparticles formed by adding sodium tripolyphosphate to acidic chitosan solution are the archetype, and alginate with calcium ions is the anionic equivalent. The method operates in water at ambient temperature without organic solvent or high energy, which makes it particularly suitable for proteins, peptides and nucleic acids that would not survive harsher processing. Particles are physically rather than covalently cross-linked, so they are sensitive to pH and ionic strength [23,25].

5.6 Thin-film hydration

The standard method for liposomes. Phospholipids, cholesterol and any lipophilic drug are dissolved in chloroform or a chloroform–methanol mixture, the solvent is removed on a rotary evaporator to leave a thin lipid film on the flask wall, and the film is hydrated above the lipid phase transition temperature with aqueous buffer containing any hydrophilic drug. Hydration produces large multilamellar vesicles which are then reduced in size and lamellarity by extrusion through polycarbonate membranes of defined pore size, or by sonication. Extrusion gives reproducible, narrow distributions and is the preferred size-reduction step. Microfluidic mixing has become an important alternative, particularly for the ionisable lipid nanoparticles used in nucleic acid delivery, where rapid, controlled

mixing of an ethanolic lipid stream with an aqueous nucleic acid stream produces highly reproducible particles and is readily scaled by parallelisation [10,32].

5.7 Emerging technologies and method comparison

Supercritical fluid processing uses carbon dioxide as solvent or antisolvent, avoiding organic solvent residue and producing dry powder directly. Electrospraying and electrospinning generate particles and fibres under an electric field. Membrane emulsification presses the dispersed phase through defined pores for tight size control with low energy input. Continuous microfluidic platforms allow real-time control and straightforward scale-out. Method choice in practice is governed by the thermal and chemical stability of the payload, the target size and distribution, regulatory tolerance for residual solvent, and the intended production scale [24,25,32].

Table 3. Comparison of preparation methods for nanoparticulate drug delivery systems.

Method	Principle	Organic solvent	Typical size	Suited to	Key limitation
Nanoprecipitation	Solvent displacement, spontaneous precipitation	Water-miscible required	100–300 nm	Polymeric NPs, lipophilic drugs	Poor for hydrophilic drugs; dilute product
Single emulsion–solvent evaporation	Emulsification then solvent removal	Water-immiscible required	100–500 nm	Polymeric NPs, lipophilic drugs	Residual solvent; energy-intensive
Double emulsion (w/o/w)	Two-stage emulsification	Required	150–600 nm	Proteins, peptides, hydrophilic drugs	Low internal-phase encapsulation; interfacial stress
Emulsification–diffusion	Solvent diffusion on dilution	Partially miscible required	50–250 nm	Polymeric NPs	Large water volumes; concentration step
High-pressure homogenisation	Shear, turbulence, cavitation	None	50–300 nm	SLN, NLC, nanoemulsions	Thermal stress in hot variant
Ultrasonication	Acoustic cavitation	None or minimal	100–600 nm	Laboratory screening	Broad distribution; probe contamination
Ionic gelation	Electrostatic cross-linking	None	100–500 nm	Chitosan, alginate; biologics	pH and ionic strength sensitivity
Thin-film hydration + extrusion	Lipid film hydration, size reduction	Required for film step	80–200 nm	Liposomes	Multi-step; solvent removal validation
Microfluidic mixing	Controlled rapid nanoprecipitation	Ethanol typically	50–150 nm	Lipid nanoparticles, mRNA delivery	Equipment cost; scale-out rather than scale-up

Supercritical fluid	$scCO_2$ as solvent or antisolvent	None	50–500 nm	Thermolabile drugs; dry powders	High capital cost and complexity

VI CHARACTERISATION AND EVALUATION

6.1 Particle size and polydispersity index

Dynamic light scattering is the standard technique, measuring fluctuations in scattered light intensity caused by Brownian motion and converting the derived diffusion coefficient into a hydrodynamic diameter through the Stokes–Einstein relationship. It is rapid and requires little sample, but it is intensity-weighted and therefore biased towards larger particles, so a small aggregate population can dominate the reported mean. Nanoparticle tracking analysis provides a number-weighted distribution and resolves mixed populations better, and electron microscopy gives the projected geometric size of the dried particle, which is generally smaller than the hydrodynamic diameter because the latter includes the solvation layer. Reporting the technique alongside the value is therefore essential, and disagreement between methods is informative rather than an error [22,26].

6.2 Zeta potential

Zeta potential is determined from electrophoretic mobility measured by laser Doppler velocimetry, and is related to it through Henry's equation:

$$U_E = (2 \varepsilon \zeta f(\kappa a)) / (3 \eta) \quad (3)$$

where U_E is the electrophoretic mobility, ε the dielectric constant of the medium, ζ the zeta potential, η the viscosity, and $f(\kappa a)$ Henry's function, taken as 1.5 for aqueous media under the Smoluchowski approximation and 1.0 for non-aqueous media under the Hückel approximation. Because zeta potential depends strongly on pH and ionic strength, a single value reported without those conditions is of limited use. A titration across pH, as illustrated in Figure 2, is far more informative, since it locates the isoelectric point at which the particle carries no net charge and colloidal stability is at its minimum [22,26].

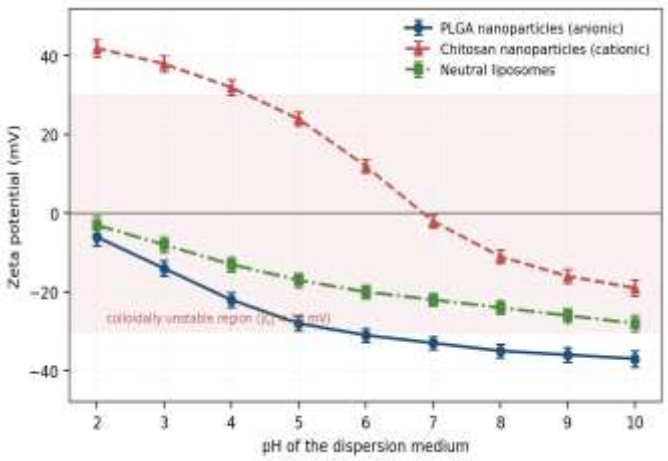


Figure 2. Zeta potential as a function of medium pH for anionic, cationic and near-neutral nanocarriers. The shaded band indicates the region within which electrostatic repulsion is generally insufficient to prevent aggregation; the cationic system passes through its isoelectric point near pH 7. Illustrative profiles constructed from trends reported in references [22,26]; error bars represent SD, n = 3.

6.3 Surface morphology

Transmission electron microscopy, usually with negative staining using phosphotungstic acid or uranyl acetate, reveals particle shape, internal structure and lamellarity, and cryogenic TEM avoids the drying artefacts that distort soft lipid and polymer particles. Scanning electron microscopy provides surface topography, and atomic force microscopy gives three-dimensional surface profiles under near-physiological conditions without staining. Microscopy is an essential orthogonal check on light scattering, since anisometric or aggregated particles are misrepresented by an equivalent-sphere diameter [22,24].

6.4 Drug loading and encapsulation efficiency

Free drug is separated from encapsulated drug by ultracentrifugation, centrifugal ultrafiltration through a membrane of appropriate molecular weight cut-off, size-exclusion chromatography or dialysis, and both fractions are quantified by validated HPLC or UV spectrophotometry. The

separation method materially affects the result, since drug loosely associated with the particle surface may be recovered as encapsulated by one technique and free by another, and the method should always be stated. Equations 1 and 2 above define the two parameters [23,24].

6.5 Solid-state and spectroscopic characterisation

Fourier-transform infrared spectroscopy detects interactions between drug, carrier and stabiliser through shifts or attenuation of characteristic bands, particularly carbonyl, hydroxyl and amine stretching, and the absence of new bands supports physical rather than chemical incorporation. Differential scanning calorimetry reveals the physical state of the drug: disappearance of the sharp crystalline melting endotherm indicates that the drug is amorphous or molecularly dispersed within the carrier, while depression and broadening of the carrier melting peak reflects reduced crystalline order and nanoscale dimensions. The recrystallisation index derived from normalised enthalpy quantifies matrix crystallinity and predicts storage behaviour for lipid systems. X-ray diffraction provides direct confirmation, with loss of the characteristic sharp drug reflections and appearance of a diffuse halo indicating conversion to the amorphous state; for lipid carriers, wide-angle scattering identifies the polymorphic form and small-angle scattering the lamellar organisation, making it the most informative single test for expulsion risk on storage [13,14,24].

6.6 In vitro drug release

Dialysis bag diffusion is the most widely used method, with the dispersion placed inside a membrane and immersed in receptor medium at 37 °C under stirring. Its weakness is that the membrane can become the rate-limiting barrier, producing profiles that reflect the apparatus rather than the formulation; sample-and-separate and reverse dialysis methods avoid this and should be preferred where feasible. Sink conditions are maintained with a solubiliser, and biorelevant media give a more physiologically meaningful picture than compendial buffers. Release data are fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models, the last expressed as:

$$M_t / M_\infty = k \cdot t^n \quad (4)$$

where M_t/M_∞ is the fraction released at time t, k the release rate constant incorporating structural and geometric characteristics, and n the release exponent. For spherical carriers, $n \leq 0.43$ indicates Fickian diffusion, values between 0.43 and 0.85 indicate anomalous transport combining diffusion with matrix relaxation or erosion, and $n \geq 0.85$ indicates case-II transport. Most nanocarriers give exponents in the anomalous range [6,23].

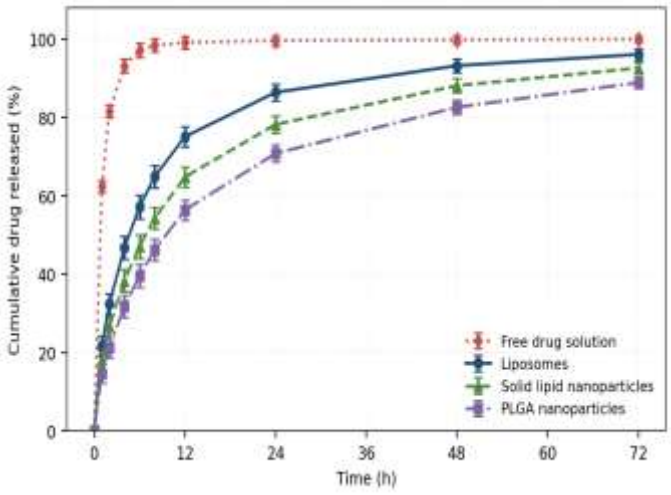


Figure 3. Representative in vitro release profiles of a model drug from three nanocarrier types compared with free drug solution, determined by dialysis at 37 °C under sink conditions. All carriers show the characteristic biphasic pattern of an initial burst followed by sustained release. Illustrative profiles constructed from trends reported in references [6,10,23]; error bars represent SD, n = 3.

Table 4. Characterisation parameters and typical acceptance expectations for nanoformulations.

Parameter	Technique	Typical target	Information obtained
Particle size	DLS, NTA, TEM, SEM	50–300 nm depending on route	Hydrodynamic and geometric diameter

Polydispersity index	DLS	< 0.3, preferably < 0.2	Width and homogeneity of the distribution
Zeta potential	Laser Doppler electrophoresis	|ζ| > 30 mV for electrostatic systems	Surface charge; predicted colloidal stability
Morphology	TEM, cryo-TEM, SEM, AFM	Spherical, discrete, non-aggregated	Shape, lamellarity, surface texture
Encapsulation efficiency	Separation followed by HPLC or UV	> 70–80%	Proportion of added drug incorporated
Drug loading	As above, normalised to carrier mass	> 5–10%	Payload per unit mass of formulation
Physical state of drug	DSC, XRD	Amorphous or molecularly dispersed	Crystallinity; polymorphic form
Drug–carrier interaction	FTIR, Raman	No new bands or major shifts	Chemical compatibility
In vitro release	Dialysis, reverse dialysis, sample-and-separate	Biphasic; sustained over the target period	Release rate, mechanism, kinetic model
Residual solvent	Headspace GC	Within ICH Q3C limits	Process-related impurity control
Storage stability	ICH conditions, size and assay over time	< 10–15% change	Shelf life; aggregation and leakage risk
Sterility and endotoxin	Pharmacopoeial methods	Compliant for parenteral products	Suitability for injection

DLS = dynamic light scattering; NTA = nanoparticle tracking analysis. Compiled from references [22,23,24,26].

VII THERAPEUTIC APPLICATIONS

7.1 Cancer therapy

Oncology has been the primary driver of nanomedicine. The rationale is that dose-limiting toxicity, not insufficient potency, restricts most cytotoxic regimens, so any redistribution of drug away from healthy tissue translates into therapeutic benefit. Liposomal doxorubicin demonstrated the principle definitively: encapsulation reduces the peak free plasma concentration responsible for cardiotoxicity while maintaining or improving antitumour efficacy, and the cardiac safety advantage has been reproduced consistently. Albumin-bound paclitaxel eliminated the Cremophor EL vehicle and its hypersensitivity reactions and permits higher dosing. Liposomal irinotecan and liposomal cytarabine–daunorubicin have followed [2,3,8].

The honest assessment is that approved oncology nanomedicines have generally improved tolerability more than they have improved survival, and that active targeting has not yet delivered the step change once anticipated. The delivery data indicate why: if under one per cent of the injected dose reaches the tumour, improvements in cellular uptake at the tumour cannot compensate. Current effort is directed at overcoming the biological barriers to delivery itself, including stromal density, elevated interstitial fluid pressure and phagocytic clearance, rather than at further refinement of the particle surface [18,28,30].

7.2 Antimicrobial delivery

Nanocarriers address several distinct antimicrobial problems. Intracellular pathogens including Mycobacterium tuberculosis, Salmonella and Leishmania reside within macrophages, precisely the cells that phagocytose nanoparticles most efficiently,

so the clearance mechanism that frustrates tumour delivery becomes an advantage. Biofilms exclude free antibiotics but can be penetrated by suitably sized and charged particles. Liposomal amphotericin B remains the clearest success, reducing the nephrotoxicity that severely limits the conventional deoxycholate formulation and permitting higher, more effective dosing. Nanoparticulate delivery has also been explored to shorten tuberculosis regimens through sustained release and to restore activity against resistant organisms [7,17,25].

7.3 Cardiovascular Disease

Applications include targeted delivery of thrombolytics to reduce systemic bleeding risk, delivery of anti-inflammatory and antiproliferative agents to atherosclerotic plaque, which is accessible to nanoparticles because plaque macrophages actively take them up, and nanoparticle coatings on stents for localised drug elution. Delivery to the myocardium after infarction has been explored using both passive accumulation in the injured region and ligand-mediated targeting. Most work remains preclinical, with the notable exception of stent coatings, which are established clinically [22,30].

7.4 Neurological disorders

The blood–brain barrier excludes essentially all large molecules and most small ones, and remains the central obstacle in neurotherapeutics. Nanoparticles have been engineered to cross it by receptor-mediated transcytosis, using transferrin, insulin or low-density lipoprotein receptor ligands, by adsorptive transcytosis with cationic surfaces, and by surfactant coatings such as polysorbate 80 that adsorb apolipoproteins from plasma and mimic lipoprotein particles. Intranasal administration provides an alternative route along the olfactory and trigeminal nerves that bypasses the barrier entirely and has attracted increasing attention. Applications span glioma, Alzheimer's and Parkinson's disease, stroke and epilepsy, though transport efficiency remains low and clinical translation limited [21,25].

7.5 Diabetes, metabolic and inflammatory disease

Oral insulin delivery is a long-standing objective, requiring protection from gastric acid and proteolysis together with transport across the intestinal epithelium; chitosan and PLGA nanoparticles have shown measurable hypoglycaemic effects in animals but bioavailability remains low and variable. Glucose-responsive systems that release insulin in proportion to ambient glucose concentration represent a more ambitious closed-loop approach. In inflammatory disease, the leaky vasculature of inflamed tissue provides a passive accumulation mechanism analogous to that in tumours, and nanoparticulate glucocorticoids and anti-tumour necrosis factor agents have been investigated in rheumatoid arthritis and inflammatory bowel disease, where colon-targeted formulations exploit both particle size and local pH [7,25,30].

7.6 Vaccines and nucleic acid delivery

This is where nanotechnology has had its greatest recent clinical impact. Nucleic acids are large, highly anionic and rapidly degraded by nucleases, and cannot enter cells unaided; a delivery vehicle is not an enhancement but a prerequisite. Ionisable lipid nanoparticles solved the problem through a mechanism that depends on pH-dependent charge: the ionisable lipid is neutral at physiological pH, which limits toxicity and prolongs circulation, but becomes protonated in the acidifying endosome, where it interacts with anionic endosomal lipids to destabilise the membrane and release the nucleic acid into the cytosol. The approved small interfering RNA product patisiran established the platform clinically, and the messenger RNA vaccines deployed from 2020 demonstrated it at a scale of billions of doses [29,32].

Nanoparticles also function as vaccine adjuvants and antigen carriers more generally, protecting antigen from degradation, promoting uptake by antigen-presenting cells, providing depot release and enabling co-delivery of antigen with immunostimulatory molecules. Virus-like particles and self-assembling protein nanoparticles extend the same principles [29].

7.7 Ocular and topical delivery

The eye presents formidable barriers: rapid tear turnover, blinking, the corneal epithelium and the blood–retinal barrier together mean that under five

per cent of an instilled dose typically reaches intraocular tissue. Nanocarriers improve precorneal retention through mucoadhesion, enhance corneal permeation and provide sustained release, and formulations for glaucoma, ocular inflammation and posterior segment disease have been investigated extensively. In dermal and transdermal delivery, nanocarriers increase the concentration of drug in the stratum corneum, provide reservoir effects within skin, reduce irritation from the free drug and improve chemical stability of labile actives; deformable vesicles and lipid nanoparticles have been the most studied [14,25].

Table 5. Selected approved nanomedicine products and their delivery rationale.

Product type	Active agent	Carrier system	Principal clinical rationale
Liposomal anthracycline	Doxorubicin	PEGylated liposome	Reduced cardiotoxicity at comparable efficacy
Liposomal antifungal	Amphotericin B	Liposome	Substantially reduced nephrotoxicity; higher dosing possible
Protein-bound taxane	Paclitaxel	Albumin nanoparticle	Avoids Cremophor EL vehicle and its hypersensitivity reactions
Liposomal topoisomerase inhibitor	Irinotecan	Liposome	Prolonged exposure; improved tolerability
Nanocrystal oral products	Various poorly soluble drugs	Drug nanocrystals	Improved dissolution, absorption and reduced food effect
siRNA therapeutic	Patisiran	Ionisable lipid nanoparticle	Delivery and endosomal escape of siRNA to hepatocytes
mRNA vaccines	SARS-CoV-2 spike mRNA	Ionisable lipid nanoparticle	Protection of mRNA and cytosolic delivery to immune cells
Iron replacement	Iron–carbohydrate complexes	Colloidal iron nanoparticle	Controlled iron release; reduced free-iron toxicity

Product availability and approved indications vary by jurisdiction; local prescribing information should be consulted. Compiled from references [16,17,29,32].

VIII ADVANTAGES, CHALLENGES AND SAFETY CONSIDERATIONS

8.1 Advantages

The benefits are well established and mechanistically understood. Solubility and bioavailability enhancement follows from increased surface area, reduced diffusion layer thickness, elevated apparent saturation solubility and presentation of the drug in an amorphous state. Controlled and sustained release follows from the physical barrier the matrix presents to diffusion and from its degradation rate, allowing dosing intervals to be extended and plasma concentration fluctuation to be reduced. Target-specific delivery, whether passive or ligand-mediated, redistributes drug away from healthy tissue. Reduced systemic toxicity is the most consistently demonstrated clinical benefit, as the anthracycline and amphotericin B examples show, and arises because encapsulation lowers the peak free drug concentration to which sensitive tissue is exposed. Additional advantages include protection of labile payloads, the ability to deliver molecules that cannot otherwise enter cells, and co-delivery of multiple agents with matched pharmacokinetics [3,7,25,31].

8.2 Nanotoxicity and biocompatibility

Nanoparticles can exhibit toxicity distinct from that of the same material in bulk form, and the mechanisms are reasonably well characterised: oxidative stress from surface reactive species,

membrane disruption by cationic surfaces, lysosomal dysfunction following endocytic uptake, complement activation-related pseudoallergy on intravenous administration, and inflammatory responses to persistent material. Cationic particles and dendrimers are consistently the most cytotoxic classes, and surface modification to reduce charge is the standard mitigation. Biodegradable materials that clear by known metabolic routes, such as PLGA and phospholipids, present a far more favourable profile than persistent inorganic materials, for which long-term accumulation in liver, spleen and lymph nodes remains inadequately characterised [14,29,31].

8.3 Stability and storage

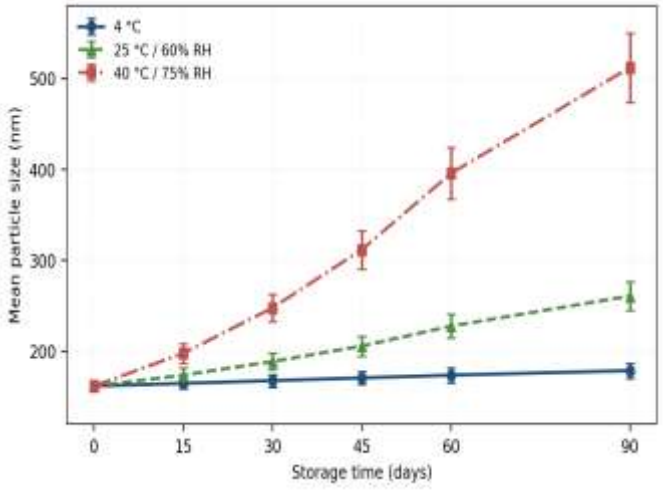


Figure 4. Change in mean particle size of an aqueous nanodispersion over 90 days at three storage conditions. Growth is minimal under refrigeration and pronounced under accelerated conditions, which is why most aqueous nanodispersions require cold storage or conversion to a dry powder. Illustrative profiles constructed from trends reported in references [13,23,26]; error bars represent SD, n = 3.

Nanodispersions are thermodynamically unstable by nature and the characteristic failure modes are predictable: aggregation and Ostwald ripening increase particle size, drug leaks from the carrier over time, lipids and polymers hydrolyse or oxidise, and lipid matrices undergo polymorphic transition that expels drug. Figure 4 illustrates the temperature dependence of particle growth that dictates storage conditions for most aqueous nanodispersions. Conversion to a dry powder by lyophilisation with a cryoprotectant such as trehalose, mannitol or sucrose, or by spray drying, removes most of these pathways and is the usual route to an acceptable shelf life, but the drying step must itself be optimised since particles readily fuse during freezing or drying if inadequately protected [13,23,26].

8.4 Manufacturing and scale-up

Scale-up is among the most underestimated obstacles. Laboratory methods relying on sonication, small-volume solvent diffusion or manual extrusion do not transfer to production scale, and those that do, principally high-pressure homogenisation and microfluidic mixing, still show batch-scale-dependent differences in shear distribution, temperature profile and residence time that alter particle size and distribution. Aseptic processing is a further constraint, since terminal heat sterilisation destabilises most nanocarriers and sterile filtration is impractical for particles approaching the filter pore size, which effectively requires aseptic manufacture throughout. Batch-to-batch reproducibility of complex multifunctional constructs, and the analytical methods needed to demonstrate it, are frequently the limiting factor in translation [23,28,30].

8.5 Regulatory considerations

Nanomedicines are regulated as drug products rather than under a separate framework, but the critical quality attributes that must be controlled are more numerous and less standardised than for conventional formulations. Regulators expect characterisation of size and distribution, surface charge, morphology, drug loading, free versus encapsulated drug, in vitro release, stability and impurity profile, and expect the analytical methods to be justified. Establishing in vitro–in vivo correlation is difficult because no standardised release method reflects in vivo behaviour reliably. Generic versions present a particular difficulty, since demonstrating equivalence of a complex particulate system requires more than plasma concentration comparison, and follow-on liposomal and iron nanoparticle products have proved contentious for exactly this reason [28,30].

Table 6. Principal challenges in nanomedicine development and current mitigation approaches.

Challenge	Underlying cause	Mitigation approaches
Low tumour delivery efficiency	Phagocytic clearance; stromal barriers; high interstitial pressure	Stealth coatings, size optimisation, stromal modulation, biomimetic surfaces
Poor preclinical–clinical translation	Xenograft vasculature unrepresentative of human tumours	Orthotopic and spontaneous tumour models; patient stratification by imaging
Protein corona alteration of targeting	Rapid plasma protein adsorption masks ligands	Corona-aware design; pre-coating; ligand density optimisation
Physical instability on storage	Aggregation, ripening, leakage, polymorphic transition	Lyophilisation with cryoprotectant; cold storage; matrix optimisation
Scale-up variability	Shear and mixing differ between bench and production	Continuous manufacture; microfluidic scale-out; process analytical technology
Sterilisation constraints	Heat destabilises carriers; filtration impractical near pore size	Aseptic processing throughout; gamma irradiation where compatible
Toxicity of cationic materials	Membrane disruption and lysosomal damage	Surface charge reduction; PEGylation; biodegradable materials
Regulatory and equivalence uncertainty	Complex CQAs; no standardised release method	Early regulatory engagement; biorelevant release method development

CQA = critical quality attribute. Compiled from references [18,28,29,30,31].

IX RECENT ADVANCES AND FUTURE PERSPECTIVES

Stimuli-responsive carriers release their payload in response to a trigger rather than by passive diffusion. Internal triggers exploit differences between diseased and healthy tissue: the reduced pH of tumour interstitium and endosomes, elevated intracellular glutathione acting on disulfide linkers, and overexpressed enzymes such as matrix metalloproteinases. External triggers include light, ultrasound, magnetic field and heat, and offer spatial and temporal control that internal triggers cannot. The design challenge is achieving a response sharp enough to be useful, since the differences between target and non-target tissue are often modest [6,31].

Multifunctional and theranostic constructs combine therapy with imaging in a single particle, allowing biodistribution to be visualised in the individual patient and treatment adjusted accordingly. This has a specific and defensible clinical use: imaging could identify which patients accumulate nanoparticles in their tumours and are therefore likely to respond, addressing the heterogeneity that has confounded oncology nanomedicine trials. Personalised nanomedicine extends the same logic, matching carrier design to tumour vascular characteristics, receptor expression or genetic profile [8,28,30].

Biomimetic and cell-derived carriers represent one of the more conceptually interesting recent directions. Coating a synthetic core with a membrane derived from erythrocytes, platelets, leukocytes or cancer cells transfers the surface proteome of the

source cell, including the markers that prevent phagocytic clearance, so the particle inherits biological identity rather than approximating it chemically. Extracellular vesicles and exosomes are being developed as naturally occurring carriers with intrinsic tropism, though isolation, characterisation and scale-up remain difficult [30,31].

Computational and machine learning approaches are increasingly used to design nanocarriers. Models trained on published formulations predict particle size, encapsulation efficiency and release profile from composition and process parameters, allowing candidate formulations to be ranked before any laboratory work, and high-throughput screening combined with predictive modelling has been used to identify drug–excipient pairs that self-assemble into nanoparticles. These methods do not replace experiment but substantially reduce the screening burden [31].

Clinical translation and commercialisation remain the binding constraint. The lipid nanoparticle vaccines demonstrated that a complex nanoparticulate product can be manufactured at extraordinary scale under regulatory scrutiny when the incentive is sufficient, which is an important existence proof. The lessons that appear to matter are that platforms succeed where they solve a problem with no alternative solution, that biodegradable and metabolically familiar materials translate more readily than novel ones, and that manufacturing simplicity is a stronger predictor of success than sophistication of design. The realistic outlook is incremental but genuine progress, with the largest near-term gains likely in nucleic acid delivery, vaccines and local or regional administration rather than in systemic tumour targeting [17,28,32].

X CONCLUSION

Nanotechnology has established a permanent and substantial place in pharmaceutical drug delivery. Its central contribution is to decouple the distribution of a drug from the properties of the drug molecule, placing that behaviour instead under the control of a carrier whose size, charge, surface chemistry and degradation rate the formulator can engineer. From this follow the benefits that have been demonstrated most reliably: enhanced dissolution and oral bioavailability for poorly soluble compounds, controlled and sustained release, protection of labile payloads, and reduced systemic toxicity for agents with narrow therapeutic indices.

A balanced assessment must also record where expectations have not been met. Systemic targeting of solid tumours has delivered far less than was anticipated two decades ago, and the evidence now indicates that the limiting factor is biological distribution rather than insufficient sophistication of particle design. Preclinical models overstate the effects on which much of the field was predicated, characterisation and reporting remain insufficiently standardised, and scale-up and reproducibility continue to obstruct translation of the more complex constructs.

The most productive direction is therefore not further elaboration of multifunctional carriers but closer attention to the barriers that actually limit delivery, coupled with standardised characterisation, more predictive models and manufacturing designed in from the outset rather than retrofitted. The lipid nanoparticle platform that enabled messenger RNA vaccination illustrates what the field achieves when a genuine unmet need, a mechanistically well-understood carrier and a manufacturable process coincide, and it offers a reasonable template for what successful nanomedicine looks like.

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