

NANOPARTICLE SYNTHESIS FOR TARGETED DRUG DELIVERY: A REVIEW OF DESIGN STRATEGIES, FABRICATION METHODS, AND TRANSLATIONAL CHALLENGES

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Abstract

Nanoparticle (NP)-based drug delivery has emerged as one of the most active frontiers in pharmaceutical and materials chemistry, offering the ability to protect labile drugs, improve solubility, and direct therapeutic payloads to diseased tissue while sparing healthy organs. This review synthesizes current literature on the synthesis, functionalization, and targeting performance of nanoparticle carriers, with emphasis on organic systems (liposomes, polymeric nanoparticles, lipid nanoparticles), inorganic systems (gold, iron oxide, and mesoporous silica nanoparticles), and hybrid architectures. Bottom-up fabrication approaches, including nanoprecipitation, thin-film hydration, high-pressure homogenization, and microfluidic self-assembly, are compared against traditional top-down methods, with microfluidic mixing highlighted as the dominant strategy for achieving reproducible size distribution and encapsulation efficiency at scale. Targeting mechanisms are examined across two axes: passive accumulation via the enhanced permeability and retention (EPR) effect and active, ligand-mediated recognition of overexpressed receptors on target cells, alongside stimuli-responsive systems that release payloads in response to pH, redox potential, enzymatic activity, or external fields. The review then evaluates persistent barriers to clinical translation, including batch-to-batch variability, incomplete understanding of the protein corona, long-term toxicity of inorganic cores, and regulatory ambiguity surrounding nanomedicine characterization. Recent advances (2023–2025) in gold-nanoparticle chemotherapy conjugates, mesoporous silica stimuli-responsive carriers, and acoustically driven microfluidic liposome production are discussed as evidence of the field's rapid technical maturation. The review concludes that continued progress depends on standardizing characterization protocols, integrating artificial-intelligence-assisted formulation design, and strengthening interdisciplinary collaboration between chemists, pharmacologists, and

1. Introduction

Conventional drug administration is limited by systemic distribution: therapeutic agents circulate throughout the body regardless of where disease is located, producing off-target toxicity, rapid clearance, and, for poorly soluble compounds, low bioavailability. Nanotechnology addresses these limitations by encapsulating or conjugating drugs to carriers on the order of 1 to 200 nanometers, altering their pharmacokinetics, biodistribution, and cellular uptake (Di Stefano, 2023). Nanoscale carriers can be engineered from natural or synthetic polymers, lipids, or metallic and inorganic materials, and their surface chemistry can be tuned to prolong circulation time, evade immune clearance, and recognize specific molecular markers on target cells.

The therapeutic rationale for nanoparticle (NP) delivery rests on two complementary targeting strategies. Passive targeting exploits the enhanced permeability and retention (EPR) effect, in which the leaky vasculature and poor lymphatic drainage characteristic of solid tumors and inflamed tissue allow nanoscale carriers to accumulate preferentially at the disease site. Active targeting supplements this effect by decorating the nanoparticle surface with ligands antibodies, peptides, aptamers, or small molecules—that bind receptors overexpressed on diseased cells, improving cellular uptake and therapeutic selectivity (Mitchell et al., 2021). More recent designs incorporate stimuli-responsive elements that release the encapsulated drug only upon encountering the acidic, hypoxic, or enzyme-rich microenvironment of a tumor, or in response to an externally applied field such as light or a magnet.

The chemistry used to synthesize these carriers is as diverse as the materials themselves. Organic nanoparticles, including liposomes, solid lipid nanoparticles, and polymeric nanoparticles built from biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), dominate clinically approved formulations because of their biocompatibility. Inorganic nanoparticles, including gold, iron oxide, and mesoporous

silica nanoparticles, offer complementary advantages such as intrinsic imaging contrast, tunable optical properties for photo thermal therapy, and rigid, high-surface-area scaffolds for dense drug loading (Lopes et al., 2024; Elechalawar et al., 2024). Hybrid systems that combine organic shells with inorganic cores are an increasingly active area of synthesis research because they merge the biocompatibility of soft matter with the functional versatility of inorganic materials.

Despite substantial preclinical progress, only a modest fraction of nanoparticle formulations advances to clinical approval, a gap frequently attributed to manufacturing variability, incomplete toxicological characterization, and regulatory uncertainty (Metselaar & Lammers, 2020). This review therefore has three aims: (1) to summarize the principal chemical strategies used to synthesize targeted drug-delivery nanoparticles, (2) to evaluate the mechanisms by which these carriers achieve site-specific delivery, and (3) to critically assess the barriers that continue to separate laboratory-scale synthesis from clinical practice, drawing on literature published primarily between 2020 and 2025.

2. Literature Review

2.1 Organic Nanoparticle Systems

Liposomes remain the most clinically established nanocarrier class, owing to their phospholipid bilayer structure, which closely mimics biological membranes and permits encapsulation of both hydrophilic (aqueous core) and hydrophobic (bilayer-embedded) drugs. Polymeric nanoparticles, particularly those synthesized from PLGA and related biodegradable copolymers, offer tunable degradation rates and surface chemistry for covalent ligand attachment. A recent review of polymer characterization and fabrication methods emphasized that the physicochemical properties of the starting polymer—molecular weight, block ratio, and end-group chemistry—directly determine the resulting nanoparticle's size, drug-loading capacity, and release kinetics, and argued that standardized characterization

protocols are needed before polymeric carriers can be reliably compared across studies (as cited in the MDPI Polymers review on polymeric nanoparticle fabrication, 2025).

2.2 Inorganic and Hybrid Nanoparticle Systems

Gold nanoparticles (AuNPs) have attracted particular interest because their surface plasmon resonance enables simultaneous imaging and photothermal therapy alongside drug delivery. Lopes et al. (2024) reported the synthesis and characterization of GABA-functionalized gold, silver, and copper nanoparticles and evaluated their potential biomedical applications, while Elechalawar et al. (2024) demonstrated that a gold-nanoparticle-based targeted delivery system improved biodistribution and therapeutic efficacy against pancreatic cancer in preclinical models. Combination carriers are also advancing: Zenjanab et al. (2024) synthesized niosomes co-loaded with paclitaxel and gold nanoparticles using different coating agents to achieve combined chemo- and photothermal therapy against breast cancer, and Zhang et al. (2024) described the in situ synthesis of gold nanoparticles within chitin nanogels that exhibited stimulus-responsive drug release. Mesoporous silica nanoparticles (MSNs) constitute a separate inorganic platform valued

for their high surface area, tunable pore size, and ease of surface functionalization; recent work on hybrid MSN architectures has focused on integrating polymer, lipid, and biomolecule coatings to create redox-, pH-, enzyme-, and light-responsive delivery systems with improved stability and biological activity (PMC review of mesoporous silica and hybrid nanoparticles, 2025).

2.3 Targeting Mechanisms

Mitchell et al. (2021), in a widely cited Nature Reviews Drug Discovery article, distinguished between passive accumulation via the EPR effect and active, ligand-receptor-mediated targeting, and argued that the next generation of "precision nanoparticles" will require rational engineering of size, shape, surface charge, and ligand density rather than reliance on EPR alone, since EPR is heterogeneous across tumor types and patients. Surface decoration strategies reviewed by Nguyen and colleagues catalogued coating agents—including polyethylene glycol (PEG), serum albumins, and thrombin—used to confer stealth properties and biological stability to nanoparticle surfaces, reporting that magnetic nanoparticles coated with bovine or human serum albumin retained colloidal stability at physiological pH over extended incubation periods (Nguyen et al., 2024).

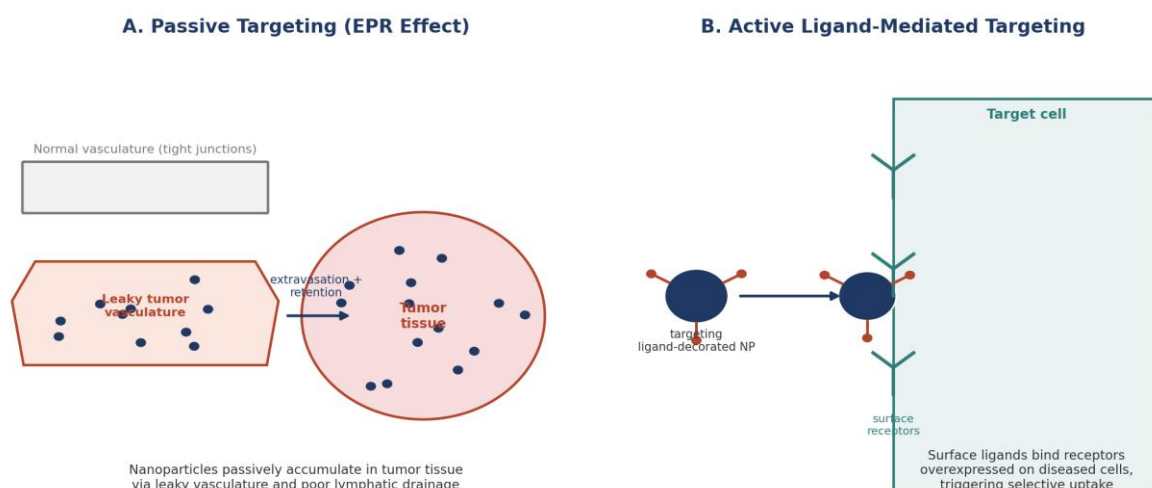


Figure 1. Schematic comparison of passive targeting via the EPR effect (A) and active, ligand-mediated targeting (B) in nanoparticle drug delivery.

Table 1. Comparison of major nanoparticle classes used in targeted drug delivery.

Nanoparticle Class	Representative Materials	Key Advantages	Key Limitations
Liposomes	Phospholipid bilayers (e.g., DSPC, cholesterol)	Biocompatible; carries hydrophilic and hydrophobic drugs; clinically established	Limited stability; potential rapid clearance without PEGylation
Polymeric nanoparticles	PLGA, PLA, chitosan	Tunable degradation; controllable release; easy ligand conjugation	Batch variability; residual solvent concerns
Gold nanoparticles	Au core, functionalized surface	Imaging + photothermal + drug delivery in one platform	Uncertain long-term biodistribution/clearance
Mesoporous silica nanoparticles	SiO ₂ with tunable pores	High surface area/loading; stimuli-responsive gating	Silica biodegradability and chronic toxicity still under study
Iron oxide nanoparticles	Fe ₃ O ₄ (magnetite)	MRI contrast; magnetically guided delivery	Potential oxidative stress; aggregation risk
Hybrid nanoparticles	Lipid-polymer, lipid-metal cores	Combines biocompatibility with functional core properties	Complex, multi-step synthesis; harder to standardize

Note. Compiled from Di Stefano (2023), Lopes et al. (2024), Elechalawar et al. (2024), and the mesoporous silica hybrid nanoparticle review (2025).

Table 2. Comparison of common nanoparticle synthesis methods.

Method	Approach	Size Control	Typical Use Case
Thin-film hydration (Bangham)	Bottom-up	Poor-moderate; high polydispersity	Traditional liposome preparation
Nanoprecipitation	Bottom-up	Moderate	Hydrophilic/hydrophobic drug entrapment in polymeric NPs
High-pressure homogenization	Top-down/bottom-up hybrid	Moderate	Solid lipid nanoparticles, emulsions
Microfluidic mixing	Bottom-up, self-assembly	High; narrow polydispersity, reproducible	Lipid nanoparticles, liposomes, siRNA/mRNA carriers
Green/biosynthesis	Bottom-up	Variable	Metal NPs (Au, Ag) using plant extracts, reduced toxicity

Note. Compiled from Bilati et al. (2005), Belliveau et al. (2012), and Mehraji and DeVoe (2024).

2.4 Fabrication Chemistry

Two general fabrication philosophies dominate the literature: top-down approaches that mechanically reduce bulk material to the nanoscale, and bottom-up, self-assembly approaches that build particles directly from molecular precursors. Bottom-up nanoprecipitation, first systematized for hydrophilic drug entrapment by Bilati et al. (2005), remains foundational, but batch nanoprecipitation and thin-film hydration ('Bangham') methods are increasingly being displaced by microfluidic mixing, which affords far tighter control over particle size distribution and encapsulation efficiency. Mehraji and DeVoe (2024), in a critical review published in *Lab on a Chip*, concluded that microfluidic platforms—by precisely controlling diffusive and advective mixing within microfabricated channels—now represent the state of the art for lipid-based nanoparticle production, though scaling manufacturing throughput while preserving particle uniformity remains an active engineering challenge. Belliveau et al. (2012) demonstrated one of the earliest high-impact applications of this approach, using microfluidic mixing to generate limit-size lipid nanoparticles for siRNA delivery, a synthesis strategy that later underpinned clinically deployed lipid-nanoparticle mRNA vaccine platforms.

3. Methodology

This review employed a narrative-synthesis approach informed by systematic search principles. Literature was identified through structured searches of PubMed/MEDLINE, ScienceDirect, SpringerLink, and the Royal Society of Chemistry (RSC) database, using combinations of the keywords "nanoparticle," "synthesis," "targeted drug delivery," "microfluidics," "liposome," "polymeric nanoparticle," "gold nanoparticle," "mesoporous silica," and "clinical translation." Priority was given to peer-reviewed articles published between 2020 and 2025 to ensure the review reflects the current state of the field, though several foundational methodological papers published before 2020 were retained where they remain the primary reference for a technique (e.g., nanoprecipitation, microfluidic siRNA-lipid nanoparticle synthesis).

Inclusion criteria required that a source (a) report original synthesis, characterization, or in vivo/in vitro performance data for a nanoparticle drug-delivery system, or (b) constitute a peer-reviewed review article synthesizing such data, and (c) be published in an indexed, peer-reviewed journal. Sources lacking verifiable authorship, journal indexing, or bibliographic completeness were excluded from citation. For each included study, information was extracted on nanoparticle composition, synthesis method, targeting strategy (passive, active, or stimuli-responsive), reported particle size and encapsulation efficiency where available, and translational stage (preclinical or clinical). Extracted data were organized thematically by nanoparticle class (organic, inorganic, hybrid) and by synthesis method (top-down versus bottom-up/self-assembly) to allow direct comparison across studies, consistent with the structure used in recent comprehensive nanoparticle drug-delivery reviews (e.g., the updated review framework applied in *Regenerative Engineering and Translational Medicine*, 2026). This thematic organization forms the basis of the Literature Review and Discussion sections that follow.

4. Discussion

Several patterns emerge from the surveyed literature. First, the field has clearly consolidated around microfluidic, bottom-up self-assembly as the preferred synthesis strategy for lipid- and polymer-based carriers, largely because it resolves the batch-to-batch variability that historically undermined confidence in nanoparticle manufacturing (Mehraji & DeVoe, 2024). This shift has direct chemical consequences: precise control over mixing time and solvent-to-aqueous-phase ratio governs nanoprecipitation kinetics and therefore final particle size, polydispersity, and drug encapsulation efficiency, parameters that were far harder to control using traditional bulk methods such as thin-film hydration.

Second, the choice between organic and inorganic cores continues to represent a trade-off between biocompatibility and function. Organic carriers such as liposomes and PLGA nanoparticles remain the most clinically

advanced platforms because their degradation products are generally well tolerated, but they typically offer limited intrinsic imaging or therapeutic functionality beyond drug release. Inorganic and hybrid systems, including gold and mesoporous silica nanoparticles, provide combined imaging, photothermal, and drug-delivery functionality that organic carriers cannot easily replicate, but questions remain about the long-term fate and toxicity of inorganic cores that are not readily metabolized (Elechalawar et al., 2024; PMC review of mesoporous silica and hybrid nanoparticles, 2025).

Third, the literature reveals a persistent gap between demonstrated preclinical targeting efficiency and clinical translation. Metselaar and Lammers (2020) identified five categories of translational barriers—practical and clinical feasibility, preclinical predictivity, and pharmaceutical development challenges among them—that must be addressed before a nanomedicine candidate can reach approval. Consistent with this, Hua et al. (2018) emphasized that the complexity of nanoparticle design must be minimized to allow reproducible manufacturing and characterization, since regulatory agencies evaluate nanomedicines on a case-by-case basis given the absence of standardized characterization frameworks. More recent analyses reinforce that this gap has not closed substantially: reviews covering the 2016–2025 period report that successful translation depends heavily on matching carrier physicochemical properties (size, surface charge, material composition) to the specific biological barrier being targeted, with liposomes and lipid nanoparticles remaining the most clinically validated platforms in part because their behavior in vivo is comparatively well characterized relative to newer inorganic and hybrid designs.

A further recurring theme is the tension between passive EPR-based targeting and active ligand-mediated targeting. While EPR-based accumulation was historically treated as sufficient justification for nanoparticle-based cancer therapy, Mitchell et al. (2021) argued that EPR heterogeneity across tumor types and even across patients with the same tumor type limits its reliability as a sole targeting mechanism,

motivating a shift toward actively targeted and stimuli-responsive designs. This helps explain the growing emphasis, evident across the sources reviewed here, on surface functionalization chemistry (PEGylation, protein coating, ligand conjugation) as a research priority independent of the core material being used.

Taken together, these findings suggest that future progress in nanoparticle drug delivery is less likely to come from entirely new core materials and more likely to come from improvements in three areas: (a) manufacturing reproducibility, particularly through continued refinement of microfluidic and other bottom-up synthesis platforms; (b) surface chemistry that more reliably predicts in vivo targeting behavior across patient populations; and (c) closer integration of preclinical toxicology and pharmacokinetic modeling into the earliest stages of formulation design, so that translational barriers are anticipated during synthesis rather than discovered after preclinical testing is complete.

5. Conclusion

Nanoparticle-based drug delivery has matured from a conceptually promising idea into a chemically sophisticated field encompassing organic, inorganic, and hybrid carrier systems synthesized through an increasingly standardized set of bottom-up, self-assembly techniques, chief among them microfluidic mixing. The reviewed literature demonstrates clear progress in the precision with which nanoparticle size, surface chemistry, and targeting ligand density can be controlled, and in the sophistication of stimuli-responsive release mechanisms that exploit the biochemical distinctiveness of diseased tissue. At the same time, the persistent gap between preclinical success and clinical approval indicates that synthesis chemistry alone cannot resolve the translational challenges facing the field; toxicology, manufacturing scale-up, and regulatory science must advance in parallel. The chemistry of nanoparticle synthesis is therefore best understood not as a solved problem but as an actively evolving discipline whose next advances will likely be defined as much by

reproducibility and characterization standards as by novel materials.

6. Recommendations

1. Prioritize microfluidic and other bottom-up self-assembly methods over traditional bulk techniques when reproducibility and narrow polydispersity are required, particularly for lipid- and polymer-based carriers intended for eventual clinical development.
2. Adopt standardized, consensus-based characterization protocols (dynamic light scattering, zeta potential, encapsulation efficiency, and in vivo biodistribution assays) across laboratories to make cross-study comparison and regulatory evaluation more tractable.
3. Invest in long-term toxicological studies of inorganic and hybrid nanoparticle cores, particularly regarding organ accumulation and clearance, before advancing gold-, silica-, or metal-based systems toward clinical trials.
4. Design active-targeting and stimuli-responsive systems as complements to, rather than replacements for, passive EPR-based accumulation, given documented heterogeneity in EPR across tumor types and patients.
5. Engage regulatory scientists early in the formulation-design process, following case-by-case, risk-based frameworks now emerging from the FDA, EMA, and MHRA, to reduce late-stage translational failures.
6. Explore artificial-intelligence-assisted formulation screening to accelerate optimization of polymer composition, ligand density, and synthesis parameters, an approach increasingly cited as a priority direction in recent nanomedicine reviews.

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