



Next-Generation Nanocarrier Systems for Targeted Drug Delivery: Advances in Lipid, Polymeric, Metal-Based, and Green Nanoparticles

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Abstract: Nanocarrier-based drug delivery has evolved from a concept into a clinically proven platform technology, with lipid nanoparticle (LNP)- based messenger RNA vaccine delivery systems and a wide array of polymeric and metallic nanomedicines as just a few examples. The review aims to be a synthesis of recent advances in the four main classes of nanocarriers: lipid-based (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, and ionizable-lipid LNPs); polymeric (poly (lactic-co-glycolic acid), chitosan, polymeric micelles and dendrimers); metal-based (gold and iron oxide nanoparticles); and green-synthesised nanoparticles (via plants, algae and microbes). For each class, the review discusses synthesis strategies, targeting mechanisms (passive enhanced permeability and retention versus active ligand-mediated targeting), and representative preclinical and clinical applications. It compares these approaches with other systems to highlight trade-offs in biocompatibility, payload flexibility, targeting accuracy, and manufacturing scalability. The review discusses key translational obstacles in depth, including inter-patient EPR heterogeneity, reproducibility of green-synthesis batches, and gaps in regulatory standardisation, as well as novel solutions such as stimuli-responsive design, microfluidic manufacturing, and image-guided dosing. Based on the overall picture emerging from the review, the future of targeted therapeutics depends on nanocarriers that can adapt to the tumour/tissue microenvironment, with a stronger mechanistic understanding of the tumour/tissue environment.

Keywords: Nanocarriers; Lipid Nanoparticles; Polymeric Nanoparticles; Metal Nanoparticles; Green Synthesis; Targeted Drug Delivery; Nanomedicine.

Nomenclature:

LNP: Lipid Nanoparticle
EPR: Enhanced Permeability and Retention
SLNs: Solid Lipid Nanoparticles
NLCs: Nanostructured Lipid Carriers
SPIONs: Superparamagnetic Iron Oxide Nanoparticles
MRI: magnetic resonance imaging
IGDS: Imaging-Guided Dose Selection
QbD: Quality-By-Design

I. INTRODUCTION

Conventional pharmacotherapy is often limited by poor aqueous solubility, non-specific biodistribution, rapid systemic clearance and dose-limiting off-target toxicity. Drug delivery systems based on nanocarriers (1-200 nm) can overcome these drawbacks by controlling drug pharmacokinetics, protecting labile therapeutic cargo, and targeting delivery to the site of interest [1,2].

The clinical turning point for nanomedicine came with the dissemination of SARS-CoV-2 mRNA vaccines formulated with ionizable-lipid nanoparticles (LNPs), which showed that a rationally designed lipid nanocarrier can efficiently escape endosomes and deliver strong immunogenicity on a population scale [3,4]. The success has stimulated rejuvenated interest across four major families of nanocarriers: lipid-based, polymeric, metal-based, and, more recently, so-called "green" or biologically synthesised nanoparticles, which use plant, algal, or microbial reducing agents instead of toxic chemical reagents [5-8].

There are two complementary strategies for achieving tumour/tissue selectivity, namely passive targeting, based on the enhanced permeability and retention (EPR) effect resulting from leaky tumour vasculature and impaired lymphatic drainage, and active targeting, which relies on ligands bound to the surface that bind to the receptors expressed in excess on diseased cells, such as antibodies, peptides, aptamers or small molecules [9,10]. Although the EPR paradigm has been used in preclinical design for decades, recent clinical re-evaluations suggest that EPR magnitude varies widely by tumour type and patient, encouraging the adoption of active targeting, stimulus-responsive release, and image-guided dosing strategies [9,10]. Figure 1 shows passive and active tumour-targeting mechanisms.



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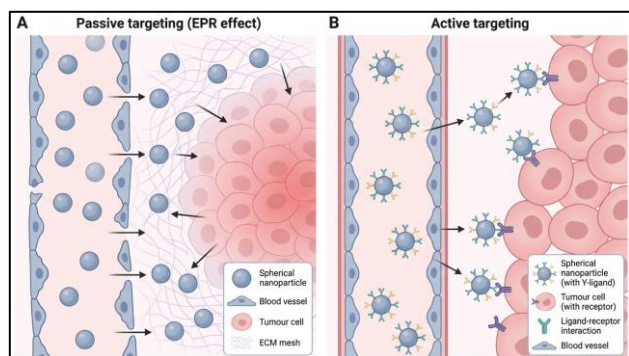
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[Fig.1: Passive Versus Active Tumour-Targeting Mechanisms]

Legend: Side-by-side cross-sectional schematic of a tumour blood vessel illustrating (A) passive targeting via the enhanced permeability and retention (EPR) effect, showing nanoparticle extravasation through fenestrated endothelium into the tumour interstitium, and (B) active targeting, showing surface-conjugated ligands (antibody/peptide/aptamer) binding to overexpressed receptors on tumour cell membranes.

Sources: Concept based on references [2,9,10].

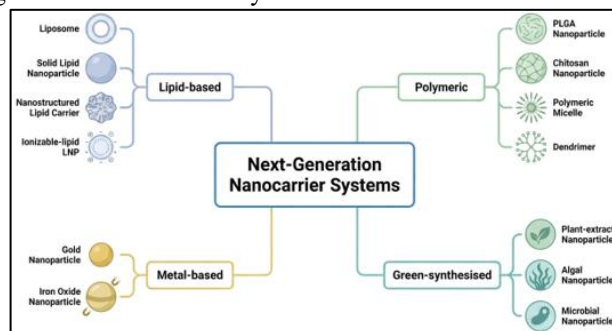
This comparative, integrated review presents currently available nanocarriers based on lipid, polymeric, metal-based, and green-synthesised systems, and compiles literature published between 2020 and 2025. Section 2 discusses the methodology; Section 3 covers lipid-based systems; Section 4 covers polymeric systems; Section 5 covers metal-based systems; and Section 6 covers green-synthesised nanoparticles. Section 7 compares the systems in Tables 1-3, Section 8 discusses translation issues, and Section 9 offers future perspectives.

II. METHODOLOGY

In this narrative review, we compiled literature from January 2020 to mid-2025 on drug delivery systems using nanocarriers. Structured searches were performed in PubMed/MEDLINE, Scopus, Web of Science and Google Scholar, using combinations of the search terms "nanocarrier", "lipid nanoparticle", "liposome", "polymeric nanoparticle", "PLGA", "chitosan nanoparticle", "dendrimer", "gold nanoparticle", "iron oxide nanoparticle", "SPION", "green synthesis", "biogenic nanoparticle", "targeted drug delivery" and "enhanced permeability and retention", using the Boolean operators (AND/OR).

We included peer-reviewed reviews, original research studies, and clinical trial reports on lipid-based, polymeric, metal-based, or green-synthesised nanocarriers used to deliver drugs, genes, and vaccines, including their synthesis, physicochemical characterisation, targeting strategy, and preclinical/clinical applications. We excluded studies not in English or without full-text data (e.g., conference abstracts), as well as those not directly related to therapeutic or diagnostic drug delivery (e.g., purely industrial or environmental applications of nanoparticles). To anchor the comparative analysis in Section 8, we hand-searched the reference lists of key reviews for primary studies, including clinical evaluations of the BNT162b2 mRNA vaccine, which were pivotal to the study.

The search and selection approach is broad, cross-platform, and spans four structurally different classes of nanocarriers; therefore, it did not follow a systematic methodology, instead using a narrative approach and was not conducted in accordance with PRISMA guidelines. The selected studies were qualitatively synthesised and grouped into nanocarrier classes (Sections 4-7), and representative studies, pros, cons, and references were summarised in comparative tables (Section 8). [Figure 2](#) shows the Classification of next-generation nanocarrier systems



[Fig.2: Classification of Next-Generation Nanocarrier Systems]

Legend: Schematic classification tree showing the four nanocarrier classes discussed in this review, lipid-based (liposomes, SLNs, NLCs, ionizable-lipid LNPs), polymeric (PLGA, chitosan, micelles, dendrimers), metal-based (gold, iron oxide) and green-synthesised (plant-, algal-, microbe-mediated), with representative payloads (small molecule, peptide/protein, nucleic acid) indicated for each branch.

Sources: Adapted from concepts discussed in references [1-3,5-8,11].

III. LIPID-BASED NANOCARRIERS

Lipid-based nanocarriers are the most clinically advanced nanoplatform, ranging from first-generation liposomes to solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and, most recently, ionizable-lipid LNPs optimised for nucleic-acid delivery [2,3,11]. Liposomes are bilayer vesicles formed from phospholipids and cholesterol that can encapsulate and carry both lipophilic (embedded in the bilayer) and hydrophilic (aqueous core) drugs; PEGylated liposomal doxorubicin (PEG-LD) is a clinically approved benchmark nanomedicine [2].

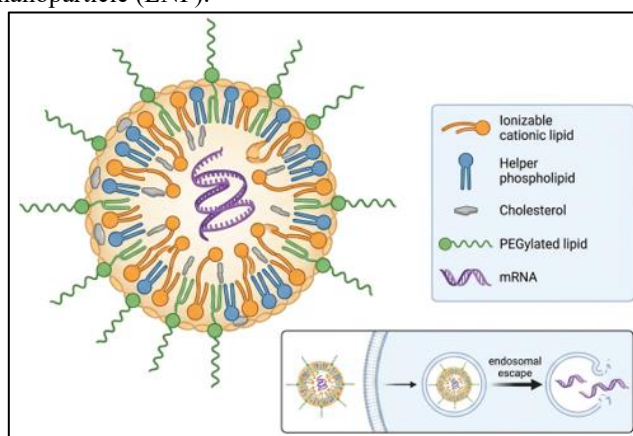
SLNs replace emulsions, which contain a liquid oil phase within a solid lipid matrix, to improve physical stability and control drug release. In contrast, NLCs contain a mixture of solid and liquid lipids to reduce drug expulsion during storage and increase drug loading. A comparative study by Viegas et al. showed that NLCs typically have higher drug-loading capacity than first-generation SLNs and are more stable in the long term. Still, SLNs have the advantage of being easier to produce on a larger scale [11].

The most recent development that has revolutionised the field is the ionizable-lipid LNP, which consists of an ionizable cationic lipid, a helper phospholipid, and cholesterol and a PEGylated lipid. These four components condense





nucleic acids at low pH during formulation, keep the formulation near neutral at physiological pH, reduce toxicity, and improve endosomal escape after internalisation [3]. Tenchov et al. highlighted 30 years of LNP development, from early liposomal variants to clinically available mRNA vaccine platforms, with iterative changes in lipid composition, particle size, and PEG-lipid ratio shaping the transfection efficiency and immunogenicity of each generation [3]. In the Phase I/II clinical evaluation of an LNP-formulated mRNA vaccine candidate, BNT162b2, the platform demonstrated a robust neutralising-antibody response with an acceptable reactogenicity profile, providing the clearest evidence to date of the lipid nanocarrier's clinical translatability [4]. [Figure 3](#) shows the Structural architecture of an ionizable-lipid nanoparticle (LNP).



[Fig.3: Structural Architecture of an Ionizable-Lipid Nanoparticle (LNP)]

Legend: *Cutaway schematic of an ionizable-lipid nanoparticle showing its four core components, ionizable cationic lipid, helper phospholipid, cholesterol, and PEGylated lipid, self-assembled around an encapsulated mRNA payload, with an inset depicting endosomal escape after cellular uptake.*

Sources: Architectural concept based on references [3,4].

Beyond vaccines, lipid nanocarriers are also used for cancer immunity, as they can carry immunomodulatory agents, checkpoint-pathway modulators, and siRNA payloads to re-engineer the tumour immune microenvironment [2]. Key remaining challenges include long-term colloidal and chemical stability during storage, cold-chain dependence for RNA-LNPs, and limited understanding of lipid nanoparticle biodistribution beyond the liver (Table 1 [near here]).

IV. POLYMERIC NANOCARRIERS

Polymeric nanocarriers include biodegradable polyester nanoparticles, natural polysaccharide nanoparticles, amphiphilic block-copolymer micelles, and hyperbranched dendrimers, which offer different control over drug release and particle surface functionalisation [1,12-16].

Poly(lactic-co-glycolic acid) (PLGA) is the most widely studied synthetic polymer because it is biodegradable and degrades at a tuneable rate (determined by the lactide: glycolide ratio) that regulatory agencies readily accept. PEG Particle Nanotechnology (PEG-PLGA) also prolongs the systemic circulation time of the particles by sterically protecting the particle surface from opsonisation and allows

the subsequent conjugation of ligands for active targeting. Zhang et al. exhaustively reviewed the various applications of PEG-PLGA nanoparticles in oncology, including single- and dual-functional nanoparticles (folate, transferrin, hyaluronic acid, aptamers) that target tumour tissue for selective accumulation and co-integrating imaging agents for theranostic properties [1].

A cationic polysaccharide derived from chitin, known as chitosan, shows mucoadhesive properties due to electrostatic interaction with the negatively charged mucosal surface and its ability to transiently open epithelial tight junctions, which increases the oral and mucosal bioavailability of poorly absorbed drugs, peptides, and nucleic acids [12,17]. Mikušová and Mikuš compiled a list of chitosan-nanoparticle applications for oral, nasal, ocular, and pulmonary delivery routes. They noted that the main, mild, organic-solvent-free method for preparing the particles was ionic gelation with tripolyphosphate, which suits labile biologics [12].

Polymeric micelles form by spontaneous self-aggregation of amphiphilic block copolymers in aqueous solutions and have a hydrophobic core suitable for encapsulating poorly water-soluble drugs and a hydrophilic corona that provides colloidal stability and long circulation times [15,16]. Kotta et al. reviewed recent advances in micelle preparation and characterisation, extending micelle use beyond solubilising small molecules to delivering nucleic acids and proteins/peptides via oral, parenteral, transdermal, or intranasal routes [15,16].

Dendrimers are hyperbranched macromolecules with well-defined size, structure, and surface functional groups, obtained by iterative divergent or convergent synthesis, resulting in monodisperse nanostructures with a controllable number of functional groups per surface generation [13,14]. Mittal et al. discussed dendrimer applications in gene delivery, dendrimer drug conjugation, and dendrimer-based imaging agents, including the clinically approved Dendrimer-Lysine, a lysine-dendrimer product [13] that demonstrates dendrimer translational feasibility. Apartsin's 2023 special-issue overview also identified novel dendrimer applications in Alzheimer's disease diagnostics, siRNA/dendriplex formulations, and cancer nanomedicine, as well as generation-dependent cationic surface toxicity, which PEGylation often overcomes, as the main limitation to widespread clinical use [14].

V. METAL-BASED NANOCARRIERS

Metal and metal-oxide nanoparticles can deliver the drug and possess intrinsic physical properties (optical - gold, magnetic - iron oxide or catalytic) that allow simultaneous diagnostic and therapeutic (theranostic) use [18-23].

Gold nanoparticles (AuNPs) have tunable surface plasmon resonance, simple thiol-based surface chemistry for conjugating various ligands, and a proven ability to produce a photothermal effect under near-infrared irradiation. Yafout et al. summarised recent achievements in delivering conventional chemotherapy agents via aptamer- and antibody-functionalized AuNPs that can specifically target tumour cells and release drugs at the low pH of the



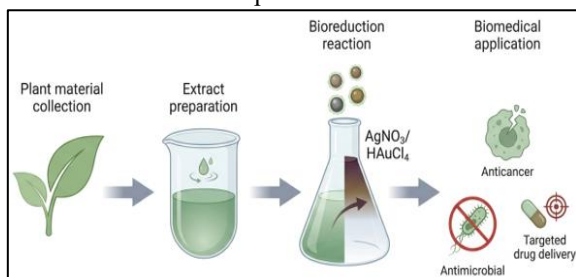
endosomal compartment and tumour microenvironment [18]. AuNP conjugates have also been investigated as immunomodulatory adjuvants when combined with checkpoint-inhibitor therapy, leveraging their ability to activate APCs [19].

Maghemite nanoparticles, and more specifically superparamagnetic iron oxide nanoparticles (SPIONs), enable magnetically guided drug delivery, magnetic hyperthermia, and T2-weighted magnetic resonance imaging (MRI) contrast enhancement. Stanicki et al. examined the physicochemical factors (core size, surface coating, hydrodynamic diameter) that influence SPION biodistribution and the rate at which drugs are released from the core. They concluded that surface functionalisation with biocompatible polymers (dextran, polyethylene glycol) is critical to prevent opsonisation and extend the circulation time [21]. Vasić et al. further developed this research to create multifunctional biocomposites containing SPIONs with combined imaging and targeted-release ability, and Ebadi et al. presented a formulation of magnetic nanoparticles coated with layered double hydroxide that showed structural stability and controlled release for hepatocellular carcinoma therapy using sorafenib as the therapeutic agent [22,23]. Manescu et al. [20] also investigated the oncological application of magnetic nanoparticles, where hyperthermia induction is associated with the co-delivery of chemotherapeutic agents.

The main but non-exclusive translational challenges on the metal-based platforms include long-term biopersistence of the inorganic core, limited renal clearance when the hydrodynamic diameter exceeds a critical value, and non-reproducibility of the chemistry of the surface coating, which are all factors that contribute to the slower pace of regulatory approval compared to organic (lipid/polymeric) platforms [21,22].

VI. GREEN-SYNTHESISED NANOPARTICLES

Green (biogenic) synthesis uses plant extracts, algal biomass, or microbial cultures containing endogenous phytochemicals (flavonoids, phenolics, terpenoids) that act as both reducing and stabilising agents and replace hazardous chemical reducing and capping agents [5-8]. This is a cheap, non-toxic and environmentally friendly alternative to the traditional chemical or physical methods of making nanoparticles. Figure 4 shows the green synthesis pathway of plant-mediated metal nanoparticles.



[Fig.4: Green Synthesis Pathway of Plant-Mediated Metal Nanoparticles]

Legend: Process-flow schematic depicting green synthesis of metal nanoparticles: plant material extraction, mixing plant extract with a metal salt precursor solution, phytochemical-mediated bioreduction to metal nanoparticles

capped with a phytochemical corona, and downstream biomedical applications (antimicrobial, anticancer, drug delivery).

Source: Concept based on references [5-8].

Medicinal plants have been used to synthesise silver nanoparticles (AgNPs), and a wide range of antibacterial, antifungal, and wound-healing bioactivities has been reported to derive from both the metallic core and the phytochemical corona surrounding the nanoparticles [6]. Similarly, Vidyasagar et al. classified green AgNP synthesis methods using algae and seaweed extracts, as well as flower extracts, and studied how biogenic surface coatings affect targeted drug delivery performance and systemic toxicity profiles [7]. More recently, Madhusudan et al. investigated the preparation of AgNPs using green methods and incorporated them into natural and synthetic polymers with antimicrobial agents, observing a synergistic effect between AgNPs and antimicrobial agents in terms of antimicrobial activity, as well as enhanced colloidal stability and potential applications in wound-healing materials and topical drug delivery [8].

Silver isn't the only metal that can be synthesised using plants; gold nanoparticles can be synthesised using plants too, and Nisha et al. [5] reviewed their effects on apoptosis induction, cell-cycle arrest, and immune modulation in tumour cell models, as well as their compatibility with chemically synthesised AuNPs. These studies position green nanoparticles as an increasingly promising, sustainable alternative to traditional metal-nanoparticle synthesis methods. Still, the key challenge for reproducible, regulatory-compliant production is the lack of standardisation of plant extract composition, reaction parameters (such as pH, temperature, and raw-material concentration), and particle-size distribution [6-8].

VII. COMPARATIVE ANALYSIS OF NANOCARRIER PLATFORMS

Table 1 summarises representative examples and the main advantages and disadvantages of the four classes of nanocarriers mentioned above. Lipid-based carriers are widely used for clinical translation, as they are now common practice in the field. At the same time, polymeric systems have the highest potential for surface engineering and controlled release. Metal-based platforms offer unique therapeutic and diagnostic functions, but their longer regulatory pathways reflect their biopersistence; green-synthesised nanoparticles offer a sustainable alternative with low toxicity but still require standardisation, especially at scale.

Table 1 compiles a comparative overview of different classes of nanocarriers: lipid, polymeric, metal, and green nanocarriers.

VIII. CHALLENGES AND CLINICAL TRANSLATION

Although preclinical and pre-prodrug trials have advanced significantly, progress toward full regulatory approval of nanomedicines remains low relative to the number of nanomedicine designs





published, often referred to as the "translational gap" [10,24]. One of the most significant factors is the variation in the EPR effect between different types of tumours and different patients: Kim and co-workers showed that dense ECM, increased IFP, and vascular heterogeneity are important factors that reduce the efficacy of nanoplateform extravasation in clinical tumours compared to murine xenografts, therefore hampering direct extrapolation from preclinical to clinical models [9]. Similarly, Lammers suggested that targeting tumour cells should not be a standard design rule for nanomedicine. Instead, combination applications of active targeting, vascular normalisation, and imaging-guided dose selection (IGDS) should be promoted as context-, tumour-, and patient-specific approaches [10].

The second big hurdle is manufacturing reproducibility. Fabricating lipid and polymeric nanoparticles by microfluidic and nanoprecipitation methods is highly sensitive to flow-rate ratios, mixing geometry, and solvent-exchange kinetics, which can shift particle size, polydispersity, and encapsulation efficiency between batches. These parameters are more commonly being standardised in quality-by-design (QbD) frameworks and continuous-flow microfluidic platforms [1,11].

Biodistribution and clearance vary widely depending on carrier chemistry. Organic (lipid, polymeric) nanocarriers typically biodegrade into biocompatible metabolites. In contrast, inorganic cores (gold, iron oxide) can persist in reticuloendothelial organs beyond the clinically relevant time frame and require careful optimisation of core size, surface coating, and dose to keep the core below renal clearance thresholds, if possible [21-23].

Another challenge for all nanocarrier types, but especially for green-synthesised nanoparticles, is the lack of standardisation of physicochemical properties, which depend on plant phytochemical content, extraction methods, and season. Consistent clinical translation across the four platforms requires harmonised characterisation panels (including particle size, zeta potential, encapsulation efficiency, endotoxin content, and residual reducing-agent quantification) and greater engagement with regulatory science initiatives (e.g., FDA and EMA nanomedicine guidance) [25].

IX. FUTURE PERSPECTIVES AND CONCLUSIONS

Each of the nanocarriers mentioned above has its own unique set of desirable properties that are complementary, and nanocarriers with hybrid designs, such as lipid-polymer hybrid nanoparticles, polymer-coated metal cores and phytochemical-functionalised metallic nanoparticles, are becoming increasingly common, as the boundaries between these classes are becoming progressively less distinct. The clinical efficacy of ionizable-lipid mRNA vaccines shows that rationally designed nanocarriers can have therapeutic effects at the population level, and that other nanocarrier classes can adopt regulatory and manufacturing frameworks for these mRNA vaccines.

The future will likely involve three converging trends: stimulus-responsive and actively targeted designs to overcome the variability of passive (EPR-based) targeting; continuous flow, quality-by-design manufacturing to

improve batch-to-batch consistency across nanocarrier types, including green-synthesised nanocarriers; and integrating image-guided dosing with patient stratification to tailor nanomedicine administration. Achieving these directions will require ongoing multidisciplinary efforts among pharmaceutical scientists, materials chemists, clinicians, and regulatory agencies to bring the significant preclinical potential of next-generation nanocarriers into clinical practice.

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