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Comparative Studies on Organic and Inorganic Nanocarriers: Distinct Platforms for Drug Delivery

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Abstract

Nanocarrier technology has transformed drug delivery by improving the solubility, stability, and targeted transport of therapeutic agents. This study provides a comparative analysis of organic, inorganic, and hybrid nanocarriers, examining their structural features, drug-loading capacity, release behaviour, biocompatibility, and clinical applicability. Organic nanocarriers, including liposomes and micelles, are distinguished by their biodegradability, low toxicity, and established clinical use, though they often suffer from limited stability and drug-loading capacity. Inorganic nanocarriers iron oxide nanoparticles, quantum dots, gold nanoparticles, carbon nanotubes, graphene, and mesoporous silica nanoparticles offer superior mechanical strength, high surface area, tunable porosity, and unique optical, magnetic, and thermal properties that enable advanced theranostic applications such as imaging-guided therapy, photothermal and photodynamic treatment, and stimuli-responsive drug release. However, their long-term toxicity, non-biodegradability, and unresolved regulatory status remain significant barriers to translation. Hybrid nanocarriers, which integrate organic and inorganic components within a single platform, have emerged to combine the biocompatibility of organic systems with the functionality and stability of inorganic materials, enabling synergistic multi-drug and multi-therapy strategies for overcoming drug resistance. The findings indicate that no single platform is universally superior; rather, nanocarrier selection must be tailored to the therapeutic goal, payload characteristics, and required route of administration, with hybrid systems representing the most promising direction for future clinical translation.

Keywords: Nanomedicine, Nanocarriers, Liposomes, Micelles, Drug Delivery.

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Introduction

Nanomedicine has emerged as a transformative approach to modern therapeutics, addressing long-standing limitations of conventional drug formulations, including poor aqueous solubility, non-specific biodistribution, rapid systemic clearance, and dose-limiting toxicity (Cheng, Zaki, Hui, Muzykantov, & Tsourkas, 2012, p. 903). *Nanomaterials* are broadly defined as materials with sizes ranging between 1 and 100 nm (Navya, et al., 2019, p. 24), a definition consistent with the US Food and Drug Administration's characterization of nanoscale materials, for which the typical particle size is also 1–100 nm (Choi & Han, 2017, p. 50). At this size regime, particles exhibit distinctive structural, chemical, mechanical, magnetic, electrical, and biological properties that differ fundamentally from those observed in the macroscopic and atomic realms (Goldberg, Langer, & Jia, 2007, p. 242). Because the surface area of a particulate material increases by several orders of magnitude as particle size is reduced to the nanometer scale, nanoscale carriers possess an exceptionally large interactive interface with their biological surroundings (Singh, Biswas, Shukla, & Maiti, 2019, p. 33).

Nanocarriers confer a well-documented set of advantages over free drugs: they circumvent problems of solubility and stability, protect payloads from degradation by proteases and other enzymes while prolonging systemic half-life, improve drug distribution and targeting, enable sustained release at disease sites, and permit co-delivery of multiple agents to help reduce drug resistance (Navya, et al., 2019, p. 24). Their small size, good stability, ability to improve the solubility of poorly water-soluble drugs, and capacity to reduce drug toxicity further underpin their therapeutic appeal (Shi, et al., 2021, p. 10748). These attributes, together with the finding that particles smaller than 100 nm can be readily internalized by endocytic vesicles suggesting a preferred size range of roughly 10–100 nm for drug delivery have driven intensive development of nanoscale carriers over the past two decades (Goldberg, Langer, & Jia, 2007, p. 242).

Efforts to render nanocarriers "stealthy" in the bloodstream have been central to this progress. As early as 1977, Abuchowski and colleagues showed that covalent conjugation of polyethylene glycol to

a model protein decreased its immunogenicity and increased its circulating time, inaugurating the strategy now known as PEGylation (Amoozgar & Yeo, 2012, p. 220). PEG coatings shield nanoparticles from aggregation, opsonization, and phagocytosis, prolonging systemic circulation time (Suk, Xu, Kim, Hanes, & Ensign, 2015, p. 28), and can extend the circulation half-life of nanoparticles to more than 40 hours (Amoozgar & Yeo, 2012, p. 220). By preventing adsorption of blood serum proteins, this stealth layer also enhances the probability of particle permeation into tumor tissue via the enhanced permeability and retention effect, and provides a versatile platform for attaching targeting moieties (Mout, Moyano, Rana, & Rotello, 2012, p. 2541). The clinical impact of such engineering is measurable: as of 2016, 78 nanomedicines were on pharmaceutical markets worldwide, with a further 63 approved as drugs or in the approval process (Choi & Han, 2017, p. 50).

The nanocarrier toolbox spans three broad families distinguished by composition. *Organic* nanocarriers lipid-based and macromolecular assemblies such as liposomes, polymeric nanoparticles, micelles, dendrimers, and solid lipid nanoparticles offer good biocompatibility and multiple opportunities for drug functionalization on their surface or within their interior, though they tend to be less stable (Chehelgerdi, et al., 2023, p. 195). *Inorganic* nanocarriers, by contrast, bring inherent conductivity, magnetism, and optical properties, together with tunable size, structure, and shape, that have made them a focus of therapeutic diagnosis (Song, Vikulina, Parakhonskiy, & Skirtach, 2023, p. 1078841). *Hybrid* nanocarriers, which integrate organic and inorganic components classifiable as inorganic–inorganic, organic–inorganic, and bio–inorganic nanohybrids (Choi, Rejinold, Piao, & Choy, 2021, p. 5044) combine the complementary advantages of both families, offering improved biocompatibility and stability (Chehelgerdi, et al., 2023, p. 195) and serving as versatile platforms for drug delivery in cancer, bone regeneration, and neurological disorders (Manatunga, Godakanda, Silva, & Silva, 2019), as well as for gene therapy, phototherapy, and theranostics (Seaberg, et al., 2021).

Despite this promise, clinical translation has proceeded more slowly than anticipated. FDA-approved nanodrugs have succeeded in reducing life-threatening toxicities of their active ingredients, yet they have so far yielded limited improvement in overall patient survival, and nanocarriers remain subject to immune system interactions that can cause premature clearance, immune activation, and toxicity (Anchordoquy, et al., 2017, p. 14). Additional hurdles include batch-to-batch variability, the absence of standardized characterization strategies, scale-up difficulties, and premature release of encapsulated cargoes (Elsabahy, Heo, Lim, Sun, & Wooley, 2015, p. 10999), as well as stringent and complex regulatory pathways that demand precise characterization of size, shape, surface charge, and stability (Chehelgerdi, et al., 2023, p. 259). Pharmacokinetic data are infrequently disclosed for nanoparticle formulations, and biological barriers such as the heterogeneous distribution of the vasculature in solid tumors further impede efficient delivery (Huang, et al., 2024, p. 66). Long-term safety questions, particularly regarding heavy metal components in some inorganic systems, remain unresolved (Chehelgerdi, et al., 2023, p. 195).

Given these considerations, the present review comparatively evaluates organic, inorganic, and hybrid nanocarriers for drug delivery, examining their design principles, physicochemical characteristics, therapeutic applications, pharmacokinetic behaviour, and clinical translation status, with the aim of clarifying the strengths and limitations of each family and identifying the most promising directions for future development.

Organic nanocarriers

Systemic drug administration is constrained by four long-standing pharmacological problems: poor aqueous solubility of many therapeutic agents, rapid clearance of small molecules from circulation, non-specific biodistribution that produces off-target toxicity, and poor penetration across biological barriers such as the intestinal epithelium, the blood–brain barrier, or the stratum corneum of the skin (Prasad, Achazi, Böttcher, Haag, & Sharma, 2017, p. 22121). Encapsulating a drug within a discrete nanoscale vehicle is a direct response to these problems, and among the available carrier architectures, *organic vesicular systems* are particularly well suited to the task because their amphiphilic building blocks self-assemble into structures that can simultaneously accommodate hydrophilic and hydrophobic payloads (Ren, Nie, Zhu, & Zhang, 2022, p. 4861).

Vesicular nanocarriers form when amphiphilic lipids or surfactants organize into one or more closed bilayers surrounding an aqueous core (Patra, et al., 2018; Zhang, et al., 2022). The resulting bilayer architecture allows an exceptionally broad range of guest molecules to be packaged: hydrophilic drugs dissolve in the internal aqueous compartment, hydrophobic drugs partition into the lipid bilayers, and amphiphilic molecules can be accommodated at either interfacial region (Choi & Han, 2017; Afzal, et al., 2022). Liposomes, the prototypical vesicular carriers, are spherical vesicles with one or more phospholipid bilayers, typically 50–450 nm in size, while niosomes are vesicles constructed from non-ionic surfactants (often combined with cholesterol) rather than phospholipids (Patra, et al., 2018; Zhang, et al., 2022). Both classes enclose an aqueous compartment and share the lipid-bilayer organizing principle, but niosomes are reported to be more

chemically stable, lower in cost, and lower in toxicity than phospholipid-based systems (Kaur & Kumar, 2018, p. 42).

The versatility of lipid vesicles is further extended by a family of deformable variants designed to overcome specific biological barriers. **Ethosomes** incorporate ethanol to soften the bilayer, increasing membrane flexibility and enabling delivery through intact skin into deep skin layers and the systemic circulation (Patra, et al., 2018; Park, 2013). **Transferosomes** are ultradeformable vesicles in which an "edge activator" typically a surfactant such as sodium cholate or Tween 80 destabilizes the bilayer just enough to permit the vesicle to squeeze through pores that rigid liposomes cannot traverse (Patra, et al., 2018). **Invasomes** add a penetration-enhancing terpene to the phospholipid mix to drive transdermal absorption (Park, 2013). All three classes share a common practical advantage: they expand the routes of administration available to vesicular carriers, including transdermal and topical routes, which sidestep the gastric degradation and hepatic first-pass metabolism that limit oral bioavailability (Yang, et al., 2017, p. 6).

The clinical importance of organic vesicular carriers is most clearly demonstrated by liposomes. As of the early 2010s, liposomes were already the dominant class of clinically approved nanopharmaceuticals, mainly because they are biocompatible, biodegradable, structurally versatile, and non-toxic (Farokhzad & Langer, 2009; Park, 2013). Doxil® (liposomal doxorubicin), approved in 1995, established that liposomal formulation can markedly reduce the cardiotoxicity of free doxorubicin while preserving therapeutic activity (Choi & Han, 2017; Farokhzad & Langer, 2009). Abraxane® (paclitaxel bound to albumin), approved in 2005, demonstrated that protein-mediated solubilization can circumvent the Cremophor-vehicle hypersensitivity associated with the conventional paclitaxel formulation and improve the therapeutic index of an otherwise poorly tolerated drug (Farokhzad & Langer, 2009; Afzal, et al., 2022). Both products became landmark reference points for the field and remain widely cited.

The superiority of organic vesicles over simpler nanoparticulate designs can be traced to four specific physicochemical properties: (i) membrane composition can be tuned by adjusting the lipid-to-cholesterol ratio to control bilayer rigidity and release kinetics, allowing sustained drug release over hours to weeks (Patra, et al., 2018; Waheed, et al., 2022); (ii) the bilayer provides high biocompatibility, with phospholipids being natural components of cell membranes and therefore minimally immunogenic in conventional formulations (Farokhzad & Langer, 2009; Park, 2013); (iii) deformability, modulated by lipid composition and surfactant additives, enables penetration across tight barriers such as skin or mucosa (Patra, et al., 2018; Park, 2013); and (iv) cargo protection preserves drug integrity in systemic circulation until the carrier delivers payload at the diseased site, sharply reducing systemic side effects (**Fig. 1**) (Waheed, et al., 2022; Afzal, et al., 2022).

These advantages explain why organic vesicles remain the workhorse architecture for the vast majority of approved nanopharmaceuticals, and why, despite the rising interest in inorganic and hybrid systems, vesicular carriers continue to dominate the clinical pipeline (Anselmo & Mitragotri, 2015, p. 1041). The next subsections review the principal organic nanocarrier families in more detail and contrast their performance with inorganic alternatives.

Clinical applications of liposomes and micelles

Liposomes are the most clinically established family of nanocarriers (Beltrán-Gracia, López-Camacho, Higuera-Ciapara, Velázquez-Fernández, & Vallejo-Cardona, 2019, p. 2). The FDA approval of Doxil®, a PEGylated liposomal doxorubicin, in 1995 made it the first liposome-based drug delivery system approved for human use (Kemp & Kwon, 2021, p. 40), and it has since been approved for Kaposi's sarcoma, ovarian cancer, multiple myeloma, and metastatic breast cancer (Belfiore, et al., 2018, p. 5). DaunoXome® (liposomal daunorubicin) followed in 1996 for HIV-associated Kaposi's sarcoma, Myocet® (non-PEGylated liposomal doxorubicin) received EMA approval in 2000 for metastatic breast cancer, and Marqibo® (liposomal vincristine) was approved in 2012 for acute lymphoblastic leukemia (Belfiore, et al., 2018, p. 5). Onivyde® (liposomal irinotecan, approved 2015 for metastatic pancreatic cancer) and Vyxeos™ (a liposomal co-formulation of daunorubicin and cytarabine, approved 2017 for acute myeloid leukemia) illustrate the trend toward combination and engineered bilayer designs (Belfiore, et al., 2018; Li, et al., 2024, p. 5). Together these constitute seven liposomal therapeutics approved for cancer Doxil, DaunoXome, Marqibo, DepoCyt, Myocet, Mepact, and Onivyde although DepoCyt has since been discontinued (Kemp & Kwon, 2021, p. 40); in total, roughly 15 liposome and lipid-based formulations are approved for human use, six of them for cancer (Kraft, Freeling, Wang, & Ho, 2013, p. 31).

The clinical footprint of these products is considerable: liposomal doxorubicin and daunorubicin are used to treat more than 300,000 patients each year, and Doxil was reported to raise doxorubicin levels in Kaposi's sarcoma tissue by as much as 22-fold relative to healthy skin (Kraft, Freeling, Wang, & Ho, 2013, p. 31). A consistent lesson from three decades of use is that liposomal encapsulation reliably improves safety, whereas efficacy gains are indication-specific most clearly for Doxil in Kaposi's sarcoma and Vyxeos in acute myeloid leukemia and many of the 220 clinical trials now involving liposome products are designed to

position approved formulations within combination chemotherapy protocols, as exemplified by Onivyde (Crommelin, Hoogevest, & Storm, 2019, p. 259). Beyond oncology, liposomal reformulation proved decisive for antifungal therapy: the dose-limiting nephrotoxicity of amphotericin B earned it the nickname "ampho-terrible," and three lipid-based products are now in clinical use Abelcet® (ribbon-like lipid complex), Amphotec® (disk-like colloidal dispersion), and AmBisome® (the only true liposome of the three), with Abelcet receiving FDA approval in November 1995 (Min, Caster, Eblan, & Wang, 2015, p. 11160). AmBisome, composed of hydrogenated soy phosphatidylcholine, cholesterol, and distearoylphosphatidylglycerol with amphotericin B at a 2:1:0.8:0.4 molar ratio (Farjadian, et al., 2018, p. 103), was the first nanomedicine approved in Europe and is used for cryptococcal meningitis, aspergillus and candida infections, and visceral leishmaniasis (Foulkes, et al., 2020, p. 4659). Lipid platforms have also reached anesthesia (Diprivan®) and preventive vaccination (Epaxal® against hepatitis A) (Foulkes, et al., 2020; Li, et al., 2024, p. 4659), and more than six decades after the first description of liposomes in 1965, lipid nanoparticles culminated in the 2018 approval of Onpattro™ (patisiran), the first siRNA drug, and the 2021 approvals of the mRNA COVID-19 vaccines mRNA-1273 and Comirnaty® (Hou, Zaks, Langer, & Dong, 2021; Li, et al., 2024, p. 1079). Current surveys of marketed liposomal products extend the list to liposomal thalidomide, cytarabine, and paclitaxel including a liposomal paclitaxel indicated for non-small-cell lung cancer (Izadiyan, et al., 2025, p. 1251).

Polymeric micelles present a different picture: no micellar formulation has yet matched the liposome's portfolio of approvals, but several have reached advanced clinical trials, almost exclusively for intravenous anticancer therapy (Lü & Park, 2012; Hwang, Ramsey, & Kabanov, 2020, p. 218). Genexol-PM®, a PEG–poly(D,L-lactide) micelle encapsulating paclitaxel, is the most clinically advanced. In a phase I dose-escalation study in South Korea, 21 patients received 135–390 mg/m² Genexol-PM without corticosteroid or antihistamine premedication; no acute hypersensitivity reactions occurred, and the maximum tolerated dose of 390 mg/m² exceeded those of Taxol® (200 mg/m²) and Abraxane® (300 mg/m²) (Hwang, Ramsey, & Kabanov, 2020, p. 131). Preclinically, the formulation tripled the maximum tolerated dose of paclitaxel (Parveen, Arjmand, & Tabassum, 2019, p. 24710). Genexol-PM has since advanced to phase II–IV evaluation for recurrent breast cancer, unresectable locally advanced or metastatic pancreatic cancer, and advanced urothelial cancer (Chang, Ma, Xu, Xie, & Ju, 2021, p. 707337), and a phase IIb study in advanced non-small-cell lung cancer combining Genexol-PM 230 mg/m² with cisplatin 60 mg/m² demonstrated only non-inferiority to conventional paclitaxel plus cisplatin (Stirland, Nichols, Miura, & Bae, 2013, p. 1055).

A series of next-generation micelles is following the same path (Hwang, Ramsey, & Kabanov, 2020, p. 130). NK911, comprising PEG, doxorubicin, and poly(aspartic acid), and SP1049C, a Pluronic-based doxorubicin micelle, both entered clinical trials for cancer; SP1049C completed phase II in patients with metastatic esophageal and gastroesophageal junction adenocarcinoma refractory to standard chemotherapy, receiving 75 mg/m² doxorubicin every three weeks, and was shown to bypass P-glycoprotein-mediated drug resistance (Kamaly, Xiao, Valencia, Radovic-Moreno, & Farokhzad, 2012, p. 2978). NK105 (PEG-modified poly(α,β-aspartate) micellar paclitaxel) reached phase III in recurrent or metastatic breast cancer, and NK012 (micellar SN-38) has been evaluated in phase II trials for triple-negative breast cancer, refractory solid tumors, and metastatic colorectal cancer in combination with 5-fluorouracil (Chang, Ma, Xu, Xie, & Ju, 2021, p. 707337). Cisplatin delivery is addressed by NC-6004, a PEG–polyglutamic acid micelle that reduced cisplatin nephrotoxicity and neurotoxicity while increasing tumor Cmax 2.5-fold, now in phase III testing with gemcitabine for advanced and metastatic pancreatic cancer (Oerlemans, et al., 2010, p. 2572); its oxaliplatin analog NC-4016 entered phase I in advanced solid tumors and lymphoma (Chang, Ma, Xu, Xie, & Ju, 2021, p. 707337). Docetaxel formulations Docetaxel-PM (mPEG-PLA) and Cripecdocetaxel, a thermosensitive PEG–poly micelle are in phase I–II trials for head and neck squamous cell carcinoma and solid tumors (Chang, Ma, Xu, Xie, & Ju, 2021, p. 707337).

Taken together, the clinical record shows a division of labor: liposomes and lipid nanoparticles constitute a mature, broadly approved platform spanning oncology, antifungal therapy, anesthesia, gene silencing, and vaccines, whereas polymeric micelles remain an intensely investigated anticancer platform distinguished by their ability to solubilize poorly water-soluble cytotoxics, improve dose tolerance, and circumvent efflux-mediated resistance, with Genexol-PM as the leading proof of concept (He, et al., 2022), (Lü & Park, 2012, p. 218).

Advanced applications of micelles and liposomes

Beyond the passive accumulation that governs first-generation carriers, contemporary research on liposomes and micelles has moved toward increasingly sophisticated designs built on four pillars: active targeting, stimuli-responsive release, theranostic integration, and combination therapy (Hartshorn, et al., 2017, p. 32).

Active targeting with antibodies and ligands. The convergence of liposome technology with monoclonal antibody engineering produced *immunoliposomes*, first developed in the 1980s and

widely regarded as a milestone in the evolution of multifunctional liposomes (Madni, et al., 2014). Targeting ligands confer improved cellular uptake once the carrier reaches the target, although ligand-targeted nanomedicines remain subject to the same physiological localization as their unmodified counterparts and therefore exhibit broadly comparable biodistribution (Eloy, Petrilli, Trevizan, & Chorilli, 2017). Antibody engineering has refined the targeting module itself: less immunogenic fragments, notably the single-chain variable fragment (scFv), are now commonly used for liposome functionalization (Eloy, Petrilli, Trevizan, & Chorilli, 2017). In a representative preclinical example, liposomes conjugated to antibodies against EphA2 and enclosing a docetaxel prodrug reduced antitumor drug toxicity, improved overall tolerability, maintained desirable drug exposure in cancer tissue, and markedly improved antitumor activity relative to both non-nanodelivery and non-targeted nanodelivery controls (Wang, et al., 2024). Immunoliposomes have demonstrated preferential binding to tumor cells and antitumor properties in animal models (Maclean, Symonds, & Ward, 1997), and the field has advanced to the point that one immunoliposomal formulation is now manufactured under GMP-compliant conditions for preclinical studies (Kontermann, 2006). Polymeric micelles are equally amenable to such engineering, since their surfaces can be readily modified with functional moieties to improve bioavailability, circulation time, tumor specificity, and anticancer activity (Zhou, Zhang, Yang, & Wu, 2018).

Stimuli-responsive liposomes. Smart liposomes release their payloads in response to endogenous triggers mildly acidic pH, elevated glutathione levels, upregulated enzymes or exogenous ones, including hyperthermia, light, magnetic fields, and ultrasound (**Fig. 2**) (Ashrafizadeh, et al., 2022; Torres, Oses, Rabasco, González-Rodríguez, & García, 2025).

pH-sensitive liposomes can mediate endosomal escape through the proton sponge effect, and formulations responding to both pH and redox have shown greater drug-release capacity at the tumour site than single-stimulus systems (Ashrafizadeh, et al., 2022). Thermosensitive liposomes release their cargo above 40 °C under hyperthermia, while magneto-responsive and light-responsive variants respond to magnetic fields and irradiation, respectively (Ashrafizadeh, et al., 2022). Dual- and multi-responsive liposomes, which integrate several of these triggers, offer greater precision, improved therapeutic outcomes, and reduced systemic toxicity (Torres, Oses, Rabasco, González-Rodríguez, & García, 2025). Translation, however, remains limited: although physical stimuli-responsive liposomes have been a research hotspot, very few preclinical candidates have entered clinical trials, constrained by practical hurdles such as the choice of light source and wavelength settings, the availability of phospholipids with suitable stimuli-responsive properties, and the potential toxicity of synthesized lipids (Wang, et al., 2024).

Stimuli-responsive micelles. Polymeric micelles can likewise be engineered as "smart" nanocarriers that respond to intra- and extracellular biological stimuli (acidic pH, altered redox potential, upregulated enzymes) as well as external physical stimuli (magnetic field, light, temperature, ultrasound), typically by switching chain hydrophobicity/hydrophilicity, degradability, or ionizability (Zhou, Zhang, Yang, & Wu, 2018; Wei, Sun, Zhu, & Fu, 2023). Tumor-microenvironment-responsive polymer nanosystems offer high sensitivity, broad applicability across tumor types, functional versatility, and improved biosafety relative to conventional carriers (Wei, Sun, Zhu, & Fu, 2023). Emerging concepts include sequential and cascade drug release, NIR-II imaging, and multifunctional formulations that couple therapy with diagnostics (Wei, Sun, Zhu, & Fu, 2023).

Theranostics. Embedding imaging agents alongside drugs within a single carrier enables real-time monitoring of drug delivery, release, and efficacy, and is regarded as a key route to personalized medicine: only patients showing high target-site accumulation and a good early response would continue a given nanotherapy (Lammers, Aime, Hennink, Storm, & Kießling, 2011). Both liposomes and polymersomes are versatile theranostic platforms that efficiently load drugs and contrast agents via covalent or non-covalent interactions (Janib, Moses, & MacKay, 2010). Micelles are attractive for imaging because they form relatively uniform structures and can incorporate multiple functionalities, though lacking an aqueous core they require contrast agents to be bound to the polymer, conjugated to an anchor molecule, or entrapped within the dense hydrophobic core (Janib, Moses, & MacKay, 2010). A notable example is an HSPC-supported liposome co-encapsulating indocyanine green and doxorubicin and functionalized with a humanized antibody against MUC-1, which combined tumor-specific targeted therapy with optoacoustic tomography diagnosis in a murine breast cancer model (Xing, Hwang, & Lu, 2016).

Combination therapy and chemoimmunotherapy. Because single-agent treatment is frequently inadequate against chemoresistant tumors, nanocarriers increasingly co-deliver drug combinations to achieve synergistic effects (Pan, Rostamizadeh, Filipczak, & Torchilin, 2019). Micelles are particularly well suited to this task: one amphiphilic copolymer system accommodated three functional domains a PEG shell for prolonged circulation, electrostatic doxorubicin loading, and paclitaxel within a hydrophobic deoxycholate-modified core inducing synergistic apoptosis in A549 lung adenocarcinoma

cells and selective tumor accumulation in vivo (Hu, Sun, Wang, & Gu, 2015). mPEG-PLGA core–shell nanoparticles co-encapsulating paclitaxel and doxorubicin similarly enhanced cellular uptake and coordinated drug release (Hu, Sun, Wang, & Gu, 2015). pH-sensitive polymeric micelles co-delivering doxorubicin and docetaxel have been developed specifically for breast cancer, exploiting the hydrophilic shell/hydrophobic core architecture to deliver drugs of differing solubility simultaneously (Farhoudi, et al., 2024). At the frontier, a microfluidics-engineered nanocarrier combining polymeric prodrugs of three chemotherapeutics with a cascade-responsive block copolymer achieved ratiometric drug loading, synchronized drug release, and effective inhibition of tumor growth and metastasis, demonstrating the feasibility of individualized combination chemotherapy (Li, et al., 2022). On the immunotherapy side, co-encapsulating doxorubicin with the immunomodulator indoximod in liposomes (DOX/IND-liposomes) significantly enhanced the anti-breast-cancer immune response compared with doxorubicin-loaded liposomes alone (Mu, Chu, Liu, & Zhang, 2020).

Taken together, these strategies are transforming liposomes and micelles from passive drug depots into multifunctional platforms capable of carrying more than one therapeutic and diagnostic agent simultaneously (Madni, et al., 2014). Yet each added layer of complexity introduces new translational barriers very few stimuli-responsive candidates have reached the clinic (Wang, et al., 2024), and the optimal drug ratios within co-delivery carriers remain poorly understood and highly variable across reported systems (Pan, Rostamizadeh, Filipczak, & Torchilin, 2019). The next generation of vesicular and micellar nanomedicines will likely converge active targeting, triggered release, imaging, and combination payloads into single architectures, with theranostic monitoring guiding treatment decisions toward genuinely personalized therapy (Lammers, Aime, Hennink, Storm, & Kießling, 2011).

Inorganic nanocarriers

Inorganic nanocarriers including metallic (gold, silver, iron oxide), silica-based, carbon-based (carbon nanotubes, graphene, quantum dots), and lanthanide systems now form a significant fraction of current drug delivery systems, distinguished by precise control of size and shape, tuneable physicochemical properties, controlled surface chemistry, and diverse multifunctionality (Navya, et al., 2019, p. 33). Derived from materials such as gold, iron, silica, and lanthanides, they exhibit physicochemical characteristics absent from their bulk counterparts high surface-to-volume ratio, long-term stability, and optical responsiveness that make them promising platforms for drug loading and targeted release (Luther, et al., 2020, p. 189). Gold nanoparticles can be fabricated as nanoshells, nanospheres, nanocages, and nanorods with photothermal properties arising from oscillating free electrons (Waheed, et al., 2022, p. 398), while metal nanoparticles possess surface plasmon resonance that liposomes, dendrimers, and micelles do not offer, along with good biocompatibility and versatile surface functionalization (Patra, et al., 2018, p. 82).Cancer multidrug resistance is one of the main obstacles to successful cancer treatment, frequently leading to therapeutic failure of both chemotherapy and radiotherapy (**Fig. 3**) (Lin, Mi, Chu, Zhang, & Liu, 2016).

Its clinical roots lie in tumor-cell mechanisms such as the overexpression of efflux transporters notably P-glycoprotein, an MDR protein that pumps cytotoxics back out of cells before they can act (Kesharwani, et al., 2023, p. 111) together with dysregulated apoptotic pathways (Emran, et al., 2022, p. 891673). Against this backdrop, inorganic nanocarriers have emerged as uniquely positioned platforms: unlike organic carriers, they combine high drug-loading capacity with intrinsic physicochemical functions that enable both therapy and imaging within a single particle, offering a genuine theranostic route to circumvent MDR (Lin, Mi, Chu, Zhang, & Liu, 2016).

These features make inorganic nanocarriers highly stable carriers with electronic and optical properties useful for cancer imaging and theranostics (Chehelgerdi, et al., 2023, p. 195). Mesoporous silica, for example, combines easy functionalization, high drug storage capacity, and a simple production process (Wang, et al., 2024, p. 202), and among inorganic systems, silica has drawn particular attention for its robustness (Vallet-Regí, Schüth, Lozano, Colilla, & Manzano, 2022, p. 5390). Nevertheless, translation remains limited: very few inorganic nanoparticle systems have entered the clinic (Anselmo & Mitragotri, 2015, p. 1041), constrained by low solubility and potential toxicity of gold- and iron-based particles (Vallet-Regí, Schüth, Lozano, Colilla, & Manzano, 2022, p. 5390), tissue accumulation, unsatisfactory treatment outcomes (Wang, et al., 2024, p. 202), and concerns over long-term toxicity, immunogenicity, and tissue damage (Bayda, et al., 2017).

Mesoporous silica nanoparticles have been engineered to enhance chemotherapeutic efficacy while simultaneously overcoming MDR and inhibiting metastasis (He & Shi, MSN Anti-Cancer Nanomedicines: Chemotherapy Enhancement, Overcoming of Drug Resistance, and Metastasis Inhibition, 2013), and more sophisticated designs couple this cargo capacity with photothermal functionality for example, hollow mesoporous silica capsules housing gold nanorods and doxorubicin that release their payload under near-infrared control to reverse MDR in resistant hepatocellular carcinoma cells (Yang, et al., 2021). Gold-based systems similarly combine chemo–photothermal

therapy with MDR reversal through pH-responsive, P-glycoprotein-inhibiting surface engineering (Kesharwani, et al., 2023, p. 111), while porous silicon and silicon-nanowire hybrids decorated with iron oxide and gold nanoparticles integrate magnetic targeting, NIR-triggered release, and magnetic-resonance imaging to enhance drug accumulation in resistant breast cancer cells (Li, et al., 2019). Even the carrier materials themselves can act as effectors: silver nanoparticles downregulate anti-apoptotic genes (Bcl-2, Bcl-xL) and upregulate pro-apoptotic genes, directly sensitizing resistant cells (Emran, et al., 2022, p. 891673).

Because inorganic nanoparticles can simultaneously act as drug carriers, imaging antennas, and therapeutic effectors, they enable the multimodal, synergistic strategies required to break resistance where conventional medicine fails (Casals, Gustà, Cobaleda-Siles, García, & Puntes, 2017, p. 7). Their imaging capability further allows treatment responses drug resistance and therapeutic efficacy to be monitored in real time, which is expected to inform the rational design of next-generation nanocarriers for clinical translation (Lin, Mi, Chu, Zhang, & Liu, 2016).

Iron Oxide Nanoparticles

Iron oxide nanoparticles and in particular superparamagnetic iron oxide nanoparticles, composed of γ-Fe_2O_3 (maghemite) or Fe_3O_4 (magnetite) with cores ranging from 10 to 100 nm are among the most clinically advanced inorganic nanocarriers (Wahajuddin & Arora, 2012). At this size, each particle contains only a single magnetic domain and behaves as a small, thermally agitated magnet; because superparamagnetic particles retain no remnant magnetization once the external field is removed, they allow precise remote control of their action (Mahmoudi, Sant, Wang, Laurent, & Sen, 2010, p. 24). This property is exploited for magnetic drug targeting, magnetic resonance imaging contrast enhancement, and magnetic hyperthermia, in which alternating magnetic fields are used to generate localized heating for the destruction of cancer cells (Chenthamara, et al., 2019, p. 29).

Among magnetic nanoparticles, iron oxide is the most preferred material, being biocompatible, biodegradable, and intrinsically superparamagnetic (Chenthamara, et al., 2019, p. 29). Particles are typically coated with polymers such as dextran, starch, or polyethylene glycol, which stabilize the core against aggregation and provide chemical handles for the conjugation of therapeutic agents, further improving blood distribution profiles (Wahajuddin & Arora, 2012). These features have established SPIONs as nonviral gene vectors, MRI diagnostic agents, and drug delivery vehicles, with particular promise in brain, breast, prostate, and pancreatic tumors (Wahajuddin & Arora, 2012; Dulińska-Litewka, et al., 2019).

Iron oxide nanoparticles also constitute one of the few inorganic platforms to have reached the market: Feraheme® (ferumoxytol, approved in the US in 2009, Canada in 2011, and Europe in 2012 for iron-deficiency anemia), Combidex®/Sinerem® as MRI agents, Nanotherm® for cancer treatment, and Lumirem® for gastrointestinal imaging have all received regulatory approval (Huang, Hsu, Koo, & Cormode, 2021, p. 796). Ferumoxytol remains the most investigated FDA-approved iron oxide nanoparticle, now repurposed off-label as an MRI contrast agent in numerous clinical trials (Ehlerding, Grodzinski, Cai, & Liu, 2018, p. 2108). Nevertheless, translation is tempered by the high uptake of SPIONs by macrophages (Dulińska-Litewka, et al., 2019) and by toxicological concerns including altered gene expression profiles, disturbance of iron homeostasis, and oxidative stress, which must be resolved before these particles move fully from bench to bedside (Wahajuddin & Arora, 2012).

Quantum Dots

Quantum dots are nanoscale semiconductor crystals, typically composed of hundreds to thousands of atoms of group II–VI elements (e.g., CdSe, CdTe) or group III–V elements (e.g., InP, InAs) (Zrazhevskiy, Sena, & Gao, Designing multifunctional quantum dots for bioimaging, detection, and drug delivery, 2010, p. 4327). Unlike organic fluorophores, they combine size-tunable light emission, superior signal brightness, resistance to photobleaching, and broad absorption spectra that allow simultaneous excitation of multiple fluorescence colors (Smith, Duan, Mohs, & Nie, 2008, p. 1226). Their tunable optical properties extend into the near-infrared (>650 nm) region, and their high quantum yield, chemical stability, and narrow emission bands make them attractive for multiplexed detection and live-cell and in vivo imaging (Matea, et al., 2017).

Because their large surfaces offer an ideal platform for attaching multiple functionalities, QDs have been developed beyond imaging into theranostic vehicles: linking targeting ligands such as antibodies, peptides, or small molecules enables high-affinity labeling of tumor biomarkers, while co-attached therapeutic and diagnostic agents support integrated drug delivery with real-time monitoring (Smith, Duan, Mohs, & Nie, 2008, p. 1226). Their nanoparticle character can also afford long systemic circulation times and enhanced permeability and retention effects favorable for drug delivery (Wegner & Hildebrandt, 2015, p. 4804).

Clinical translation, however, remains limited: although QDs are being recruited into clinical trials, their power in the clinic is still underestimated, constrained by unresolved questions of toxicity particularly the release of toxic Cd^{2+} ions and formation of reactive oxygen intermediates from cadmium-based cores (Abdellatif, Younis, Alsharidah, Rugaie, & Tawfeek, 2022; Wegner &

Hildebrandt, 2015, p. 1951). Capping CdSe cores with a ZnS shell and stable coatings markedly reduces this cytotoxicity (Zrazhevskiy & Gao, Multifunctional quantum dots for personalized medicine, 2009, p. 423), and non-heavy-metal alternatives such as InGaP have been proposed to mitigate risk (Pinaud, et al., 2005, p. 1685), yet standardization and long-term safety data are still required before QDs move fully from bench to bedside (Chinen, et al., 2015, p. 10556).

Gold Nanoparticles

Gold nanoparticles are among the most extensively investigated inorganic nanocarriers for cancer applications, owing to their tunable and highly sensitive optical and electronic properties in particular, surface plasmon resonance which make them widely used in bio-imaging and phototherapy (Guo, et al., 2017). Because colloidal gold exhibits localized surface plasmon resonance, gold nanoparticles absorb light at specific wavelengths, generating photoacoustic and photothermal effects that are useful for hyperthermic cancer treatment and medical imaging; modifying their shape and size shifts this resonance, allowing excitation within the near-infrared tissue-transparency window (Vines, Yoon, Ryu, Lim, & Park, 2019, p. 167). Their photothermal property, especially pronounced in gold nanorods, converts absorbed light into heat and results in tumor cell destruction, and gold particles can be engineered into nanoshells, nanorods, and nanocages that absorb light in the ~700–1200 nm "water window," where absorption by aqueous tissues is minimal (Kesharwani, et al., 2023; Kesharwani, et al., 2023, p. 99). On this basis, gold nanoparticles now function as contrast agents for dark-field, photoacoustic, and optical coherence tomography imaging, and simultaneously as therapeutic agents for drug and gene delivery and photothermal therapy, forming multifunctional theranostic nanoplatforms (Choi, Liu, Lee, & Chen, 2011, p. 335). Their nano-scale size also permits passive tumor accumulation through the leaky tumor vasculature and safe renal excretion (Vines, Yoon, Ryu, Lim, & Park, 2019, p. 167).

Carbon-Based Nanocarriers

Carbon-based nanocarriers comprise a family of allotropes spanning 0D fullerenes and carbon nanodots, 1D carbon nanotubes, 2D graphene and graphene oxide, and 3D nanodiamonds (Panwar, et al., 2019). Since 2004, carbon nanotubes have been extensively explored as drug delivery carriers for the intracellular transport of chemotherapy drugs, proteins, and genes, with in vivo cancer treatment demonstrated in several animal studies (Liu, Robinson, Tabakman, Yang, & Dai, 2011). Graphene's high planar surface enables exceptionally high drug-loading capacity (Cheng, Li, Dey, & Chen, 2021), while surface functionalization of CNTs improves their solubility, biocompatibility, and reduces toxicity (Debnath & Srivastava, 2021). Beyond passive drug transport, CNTs act as near-infrared photothermal ablation agents and as antigen-presenting carriers for antitumor immunotherapy (Senapati, Mahanta, Kumar, & Maiti, 2018). Their clinical translation, however, remains constrained by unresolved long-term toxicity and regulatory and scalability challenges (Nandhini, Elumalai, Manickam, Bakthavatchalam, & Tamilselvan, 2024).

Carbon Nanotubes

Carbon nanotubes are one of the most promising carbon-based nanomaterials for biomedical use, possessing high surface-to-volume ratio, electrical and thermal conductivity, mechanical strength, biocompatibility, ease of functionalization, and distinctive optical properties that together make them attractive drug and gene delivery carriers (Zare, et al., 2021). Their very large specific surface area allows binding of many therapeutic molecules anticancer agents such as docetaxel, doxorubicin, methotrexate, paclitaxel, and gemcitabine, as well as plasmid DNA, micro-RNA, and siRNA enabling targeted delivery to tumor cells and intracellular compartments (Tang, et al., 2021). Because functionalization improves their solubility, biocompatibility, and reduces toxicity (Singh, et al., 2012), while their strong near-infrared absorption makes them efficient photothermal and photoacoustic agents (Maiti, Tong, Mou, & Yang, 2019), CNTs now support multifunctional theranostic strategies. However, their non-biodegradability, nanotoxicological concerns, and the absence of widespread FDA approval continue to limit clinical translation (Zare, et al., 2021).

Graphene

Graphene and its oxidized derivative, graphene oxide, have become highly competitive carbon-based drug delivery systems, with drug delivery now the most-studied biomedical application of graphene (Orecchioni, Cabizza, Bianco, & Delogu, 2015, p. 715). GO's reactive carboxyl and hydroxyl groups enable conjugation with polymers, biomolecules, and inorganic nanoparticles, imparting strong multifunctionality (Shen, Zhang, Liu, & Zhang, 2012, p. 284), while the large specific surface area of the graphene sheet, together with π–π stacking, electrostatic, and hydrophobic interactions with aromatic drug molecules, permits exceptionally high loading of poorly water-soluble anticancer agents such as doxorubicin and docetaxel (Shareena, McShan, Dasmahapatra, & Tchounwou, 2018, p. 59). Since Dai and colleagues first explored nanoscale GO as a carrier for water-insoluble aromatic anticancer drugs PEGylated NGO loaded with SN38 proved 1000-fold more potent than CPT-11 against HCT-116 cells functionalized graphene systems have been applied to chemotherapeutic drug targeting, photothermal and photodynamic therapy, and cancer imaging (Shen, Zhang, Liu, & Zhang, 2012, p. 284). Combined with high loading

efficiency, low toxicity, and good water solubility, these properties position GO-based nanocarriers as ideal candidates for chemotherapy, gene, and combination delivery

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles are ordered porous materials that have attracted increasing attention for their potential biomedical applications (Tang, Li, & Chen, 2012). Their well-defined, tunable physicochemical properties particle size, pore size, pore volume, surface area, and surface functionality provide cavities capable of hosting and releasing a wide variety of biomolecules and therapeutic agents, and this versatility in size, morphology, and texture has fueled their application as controlled drug delivery nanocarriers (Manzano & Vallet-Regí, 2019, p. 4). MSNs can be synthesized through a relatively simple, cost-effective process, with morphology, pore size, pore volume, and particle size tailored by controlling synthesis parameters (Narayan, Nayak, Raichur, & Garg, 2018). Because their structure, morphology, size, and surface properties are facilely tunable for drug loading, controlled release, and multifunctionalization (He & Shi, Mesoporous silica nanoparticle based nano drug delivery systems: synthesis, controlled drug release and delivery, pharmacokinetics and biocompatibility, 2011), MSNs offer significant advantages over traditional drug nanocarriers (Tang, Li, & Chen, 2012). They load both small molecules and macromolecules such as proteins and siRNA, and recent framework modifications have extended their use to drug-resistant chemotherapy and antimicrobial therapy; however, an incomplete understanding of their interaction with biological systems still poses a major hurdle to clinical translation (Narayan, Nayak, Raichur, & Garg, 2018).

Hybrid nanocarriers

Hybrid nanocarriers unite organic and inorganic building blocks within a single nanoassembly, and have been developed expressly to integrate the merits of both components while minimizing their intrinsic drawbacks (Yang, et al., 2021). One influential design framework distinguishes "barge" versus "tanker" architectures, in which liposomal, micellar, porous silica, polymeric, viral, noble-metal, and nanotube systems are incorporated either within or at the surface of a nanoparticle core (Sailor & Park, 2012). Lipid-enveloped hybrids composed of a hydrophilic PEG shell, a polymeric or inorganic core, and an intervening lipid mono- or bilayer combine the long circulation and biocompatibility of liposomes with the high drug-loading capacity and stability of nanoparticles (Tan, Li, Guo, & Zhang, 2012). Because such platforms can co-deliver multiple therapeutic agents acting through different mechanisms (He, Lu, & Lin, 2015), they support synergistic chemo-, photothermal-, photodynamic-, and immunotherapeutic combinations (Yang, et al., 2021; Lee, et al., 2023), and have been shown to enhance treatment efficacy while simultaneously reducing drug resistance (Yao, et al., 2020). Nevertheless, fabrication reproducibility, immunogenicity, and long-term fate remain unresolved challenges on the path to clinical translation (Manatunga, Godakanda, Silva, & Silva, 2019; Singh, et al., 2026).

Conclusion

This comparative study has examined organic, inorganic, and hybrid nanocarriers as distinct platforms for drug delivery, evaluating their structural features, loading capacities, release kinetics, biocompatibility, and translational readiness. The analysis confirms that each class carries inherent trade-offs that determine its suitability for specific therapeutic applications. Organic nanocarriers particularly liposomes and micelles remain the most clinically established platforms, valued for their biodegradability, biocompatibility, and long-circulating behavior; their chief limitations lie in physical stability and modest drug-loading capacity. Inorganic nanocarriers, including iron oxide nanoparticles, quantum dots, gold nanoparticles, carbon nanotubes, graphene, and mesoporous silica nanoparticles, offer exceptional surface area, tunable porosity, and distinctive optical, magnetic, and thermal properties. These features enable high payload loading, stimuli-responsive release, and integrated theranostic functions such as imaging-guided therapy and photothermal and photodynamic treatment. Yet their clinical advancement is constrained by concerns over long-term toxicity, non-biodegradability, and unresolved regulatory pathways. Hybrid nanocarriers have emerged as a compelling middle ground, uniting the biocompatibility of organic systems with the structural robustness and functionality of inorganic materials. Their capacity to co-deliver multiple therapeutic agents through complementary mechanisms has shown promise in synergistic combination therapy and in countering drug resistance. Ultimately, no single nanocarrier platform is universally optimal; effective design requires matching the carrier to the therapeutic agent, the disease context, and the intended delivery route. Future progress depends on standardized safety assessment, scalable manufacturing, and rigorous clinical evaluation, with hybrid platforms representing the most promising trajectory toward translation.

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Figures:

Fig. 1:
Structural organization of liposomes and niosomes (27).

Fig. 2:
Advanced applications of micelles and liposomes (56).

Fig. 3:
A) Schematic representation of multifunctional inorganic nanoparticles designed to co-deliver multiple therapeutic agents. B) Schematic representation of multifunctional inorganic nanoparticles engineered to reverse multidrug resistance in cancer cells (Lin, Mi, Chu, Zhang, & Liu, 2016).

Fig. 4:
Biomedical uses of (a) Fullerene. (b) Nanodiamonds. (c) Graphene Nanomaterials. (d) Carbon Nanotubes. (e) Carbon Nanodots (98).