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Nanocarrier-Based Drug Delivery Systems: Recent Advances in Pharmaceutical Formulation and Clinical Translation

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Abstract:

Nanocarrier-based drug delivery systems have transformed the landscape of pharmaceutical formulation by improving solubility, stability, targeted delivery, and therapeutic index of small molecules, biologics, and nucleic acids. This review summarizes the classification of nanocarriers, formulation materials and methods, physicochemical characterization techniques, mechanisms of drug loading and release, clinical and preclinical applications, stimuli-responsive "smart" systems, and the challenges of clinical translation and regulation. We highlight notable clinical successes (e.g., pegylated liposomal doxorubicin and albumin-bound paclitaxel), discuss manufacturing and toxicity concerns, and present future directions including AI-guided design and personalized nanomedicine.

Keywords: nanocarriers, liposomes, polymeric nanoparticles, solid lipid nanoparticles, clinical translation, stimuli-responsive, liposomal doxorubicin, Abraxane®

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1. Introduction

Traditional drug formulations face persistent challenges: poor aqueous solubility of new chemical entities, rapid systemic clearance, off-target toxicity, poor penetration into target tissues (notably tumors and the CNS), and limited oral bioavailability for many biologics and nucleic acids.

Overcoming these limitations often requires higher systemic doses that exacerbate side effects and narrow therapeutic windows [1]. These unresolved problems motivated the development of engineered nanocarriers that can encapsulate therapeutic cargos, modify pharmacokinetics, and enable active or passive targeting approaches. Nanocarriers (1–1000 nm tunable range, most commonly 10–300 nm for systemic delivery) include lipid-based systems (liposomes, lipid nanoparticles), polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, micelles, and inorganic platforms (gold, silica). Their physicochemical tunability has enabled drug solubilization, protection from degradation, controlled release, and accumulation at pathological sites via enhanced permeability and retention (EPR) or ligand-mediated targeting [2]. Clinical acceptance of nanocarriers began with several decades-old approvals pivotal examples are pegylated liposomal doxorubicin (DOXIL®) and albumin-bound paclitaxel (Abraxane®), which validated the concept that nanoscale delivery can improve therapeutic indices in oncology. From academic proof-of-concept studies in the 1970s–1990s to first approvals in the mid-1990s and early 2000s, the nanomedicine field matured into diverse product classes liposomal chemotherapies, polymer-based depot formulations, and most recently lipid nanoparticles (LNPs) for nucleic acid vaccines and therapeutics [3]. The COVID-19 mRNA vaccines accelerated clinical acceptance of LNP platforms for nucleic acid delivery, catalyzing further investment and innovation in the field. Continued advances in materials science, microfluidic manufacturing, and predictive modeling accelerate translation from bench to clinic [4].

2. Classification of Nanocarrier Systems

This section summarizes the main nanocarrier families, their composition, typical size ranges, major advantages, and key challenges.Liposomes are phospholipid bilayer vesicles that encapsulate hydrophilic drugs in their aqueous core and lipophilic drugs within the bilayer [5]. PEGylation (surface grafting of polyethylene glycol) extends circulation half-life by reducing opsonization and RES clearance. Clinical examples: DOXIL® (pegylated liposomal doxorubicin). Advantages: biocompatibility, load a range of payloads, scalable manufacturing. Challenges: batch variability, stability, drug leakage, and manufacturing cost [6]. Niosomes are non-ionic surfactant vesicles similar to liposomes but often more chemically stable and cost-effective. They have been explored for topical, oral, and parenteral routes. Drawbacks include surfactant-related toxicity and limited clinical translation to date [7].Polymeric nanoparticles (PLGA, PEG-PLA, polycaprolactone, chitosan, etc.) can be formulated as nanospheres (drug dispersed through matrix) or nanocapsules (drug in core surrounded by polymer shell). Polymeric micelles form from amphiphilic block copolymers and are particularly useful for solubilizing hydrophobic drugs[8]. Advantages: controlled release, tunable degradation. Challenges: polymer residual solvents, reproducibility, and scale-up. Dendrimers are highly branched, monodisperse macromolecules with controlled surface functionalities for drug conjugation and targeting[9]. They offer precise architecture but

suffer from complex synthesis and sometimes toxicity from cationic surface groups.SLNs are colloidal carriers made from solid lipids; NLCs mix solid and liquid lipids to increase drug loading and reduce crystallization. They are attractive for controlled release and topical/ocular delivery with simpler scale-up than some polymeric systems [10]. Challenges include polymorphic transitions and drug expulsion during storage.Gold, silica, iron-oxide nanoparticles, and quantum dots have strong niche uses imaging, and hyperthermia, theranostics but regulatory and long-term safety remain significant concerns [11]. (Table 1)

Table 1: Comparison of different nanocarrier systems composition, typical size, advantages, and challenges

Nanocarrier	Typical composition	Size (nm)	advantages	Main challenges	Reference
Liposomes / PEGylated liposomes	Phospholipids ± cholesterol ± PEG	50–200	Biocompatible; can load hydrophilic & lipophilic drugs; clinically validated (DOXIL®).	Stability, leakage, manufacturing cost.	12
Polymeric NPs (PLGA, PEG-PLA)	Synthetic or natural polymers	50–300	Controlled release, wide tunability	Residual solvents, scale-up reproducibility.	13
Micelles	Amphiphilic block copolymers	10–100	Solubilize hydrophobic drugs	Stability upon dilution, rapid disassembly.	14
Dendrimers	Branched polymeric architectures	1–20 (molecular)	Precise surface functionality	Synthesis complexity, potential toxicity	15
SLNs / NLCs	Solid & liquid lipids + surfactant	50–500	Simple ingredients, controlled release	Polymorphism, drug expulsion	16
Inorganic NPs	Gold, silica, iron oxide	5–200+	Imaging/theranostics, tunable physical properties	Long-term biopersistence, regulatory hurdles	17

3. Materials and Methods in Nanocarrier Formulation

Materials selection in nanoparticle formulation isn't just about picking whatever sounds fancy in the lab it's a strategic game guided by desired biodistribution, release profile, biocompatibility, and of course, regulatory acceptance (because no one wants their brilliant formulation stuck in paperwork hell)[18]. Commonly used polymers such as PLGA, PEG, PLA, chitosan, and polycaprolactone form the backbone of many delivery systems due to their proven track record in safety and biodegradability. On the lipid side of things, phosphatidylcholine, cholesterol, and

ionizable lipids are key players, especially for lipid nanoparticle (LNP) formulations [19]. To keep these little carriers stable and functional, surfactants and stabilizers like Tween, Poloxamer, and DSPE-PEG are often added acting like bodyguards that enhance colloidal stability and minimize unwanted protein adsorption. Importantly, biodegradability, impurity profile, and the source of materials (synthetic vs. natural) play a decisive role in determining how smoothly a formulation can transition from the lab bench to clinical trials [20].

When it comes to fabrication techniques, the approach depends on the material and the desired end product. Solvent evaporation/emulsification remains a workhorse method where an organic polymer/drug solution is emulsified in water and the solvent is gently whisked away to form nanoparticles [21]. Nanoprecipitation (a.k.a. solvent displacement) offers a simpler, low-shear alternative, perfect for hydrophobic drugs that hate water. Microfluidics and controlled mixing bring precision and scalability to the table, making them a rising star in GMP manufacturing, especially for LNPs and liposomes. For lipid-based carriers like solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), high-pressure homogenization or ultrasonication is the method of choice [22]. Meanwhile, thin-film hydration combined with remote loading remains the gold standard for liposome prep yes, the same method behind blockbuster formulations like DOXIL®, leveraging ammonium sulfate gradients for high encapsulation efficiency. (Figure 1)

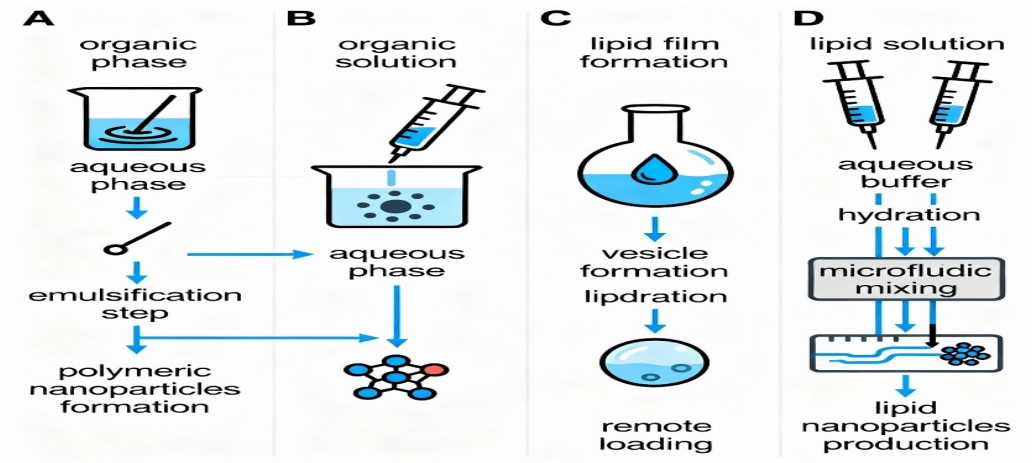


Figure 1: Schematic diagram illustrating solvent evaporation, nanoprecipitation, thin-film hydration/remote loading for liposomes, and microfluidic mixing for LNP formation.

4. Physicochemical Characterization Techniques

Accurate characterization of nanoparticles isn't just a "good-to-have" step it's absolutely essential for ensuring reproducibility, performance predictability, and, most importantly, safety during

clinical translation. If you can't describe what you've made down to its finest details, you can't trust it to behave predictably in a biological system.Particle size and distribution form the cornerstone of characterization [23]. Techniques like dynamic light scattering (DLS) provide information on hydrodynamic diameter and polydispersity index (PDI), helping determine how uniform your particles are. To complement this, nanoparticle tracking analysis (NTA) gives more precise concentration and distribution data because knowing just the average size isn't enough when therapeutic performance depends on size-dependent biodistribution and clearance [24].

Next, surface charge (zeta potential) steps in as the "mood indicator" of your formulation. A stable zeta potential helps predict colloidal stability and protein interactions in biological fluids. While cationic surfaces can boost cellular uptake, they also come with a catch higher toxicity and serum opsonization, which can accelerate clearance from the body.Morphological characterization takes the analysis a step further [25]. Using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), researchers can visualize the actual shape, lamellarity (especially crucial for liposomes), and aggregation state of the nanoparticles. This gives a clear window into structural integrity and helps explain functional behavior.When it comes to encapsulation efficiency and drug loading, precision is everything. Techniques like ultrafiltration or dialysis separate free drug from encapsulated drug, while HPLC and UV–vis spectroscopy quantify how much active ingredient is actually inside [26]. High encapsulation efficiency isn't just nice for the data sheet it minimizes excipient load and ensures dosing accuracy. Finally, physicochemical analyses provide deep insights into the internal structure and interactions within the formulation. FTIR/ATR identifies chemical interactions, differential scanning calorimetry (DSC) reveals thermal transitions and crystallinity (a big deal for SLNs and NLCs), and X-ray diffraction (XRD) confirms the solid-state structure [27]. Together, these methods create a full "characterization fingerprint" of the formulation one that ensures quality, consistency, and trustworthiness from lab bench to patient bedside. (Table 2)

Table 2: Analytical tools and primary readouts

Technique	Primary readout	Use case	Reference
DLS	Hydrodynamic diameter, PDI	Routine size/stat stability	28
NTA	Size distribution, particle concentration	Particle counting, heterogenous samples	29
TEM/SEM	Morphology, lamellarity	Structural confirmation	30

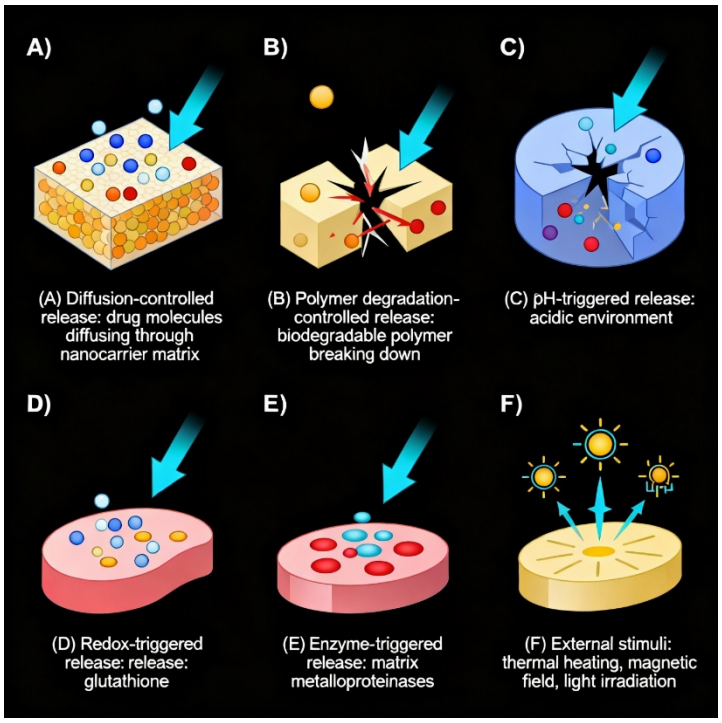
Zeta potential	Surface charge	Stability/interaction prediction	31
HPLC/UV	Drug quantification	Encapsulation efficiency, release	32
DSC/XRD	Thermal transitions/crystallinity	Solid-state properties	33

5. Mechanisms of Drug Loading and Release

Drug loading strategies and release mechanisms are the beating heart of smart drug delivery systems because making a perfect nanoparticle means nothing if your drug isn't loaded efficiently or released effectively at the right site. A well-designed system balances encapsulation efficiency, stability, and controlled release to maximize therapeutic impact while minimizing side effects [34]. Loading strategies can be broadly categorized into four main types, each with its own advantages and trade-offs. Passive encapsulation is the most straightforward method, where the drug is incorporated during particle formation itself. It's easy and cost-effective, but not always the best for hydrophilic drugs, which tend to escape the party early, resulting in lower encapsulation efficiency. To overcome this, remote or active loading takes a more tactical approach. By using ion gradients (like the famous ammonium sulfate gradient used for doxorubicin in DOXIL®), it achieves high drug-to-lipid ratios and improved stability. This is a go-to strategy for liposomes and LNP formulations[35].Another sophisticated option is drug conjugation, where the drug is covalently linked to a carrier or polymer backbone through a cleavable linker. These linkers can be pH-sensitive or enzyme-sensitive, ensuring the drug is only released in the target microenvironment like a biological "unlock code." Meanwhile, surface adsorption or complexation leverages electrostatic interactions to load molecules, particularly nucleic acids such as mRNA or siRNA, onto cationic lipids or polymers[36]. This is central to the design of modern lipid nanoparticles and polyplexes, which power some of the most advanced gene delivery systems today.Once the drug is snug inside the carrier, the next big question is: how does it get out? That's where release mechanisms come into play. In diffusion-controlled release, the drug simply diffuses through the matrix or lipid shell over time, offering a predictable and steady release. In contrast, degradation-controlled release relies on polymer biodegradation for example, the slow hydrolysis of PLGA to regulate drug liberation in a more time-dependent manner [37].But the real game-changer is stimuli-responsive release, where smart carriers respond to specific biological or external triggers like pH shifts, redox environments (e.g., high glutathione levels in the cytosol), enzymes (like matrix metalloproteinases), temperature, magnetic fields, or even light. This on-demand, site-specific release is crucial for boosting the therapeutic index of potent drugs delivering them exactly where

needed, when needed, and sparing the rest of the body unnecessary exposure. This is where nanomedicine starts to feel a lot like precision engineering, not just pharmaceutical science [38]. (Figure 2)

Figure 2: Schematic showing diffusion, polymer degradation, and stimuli-triggered release (pH, redox, enzymes, thermal, magnetic, light).



6. Nanocarrier Applications in Pharmaceutical Formulations

Nanocarriers have truly become the Swiss Army knife of modern drug delivery versatile, precise, and increasingly indispensable across multiple therapeutic areas. Their ability to improve drug solubility, enhance bioavailability, and target specific tissues or cells has opened the floodgates for innovative treatments that weren't possible with conventional dosage forms [39]. While research is ongoing in dozens of fields, a few therapeutic domains have taken the lead with strong preclinical and even clinical evidence backing their impact.The biggest and most established playground for nanocarriers is oncology. Cancer treatment is notoriously tricky because the drugs that can kill tumor cells often wreak havoc on healthy tissues too [40]. This is where nanocarriers shine. Approved nanomedicines like liposomal anthracyclines, pegylated liposomal doxorubicin, and albumin-bound paclitaxel have shown they can reduce systemic toxicities while enhancing tumor delivery, mainly through the enhanced permeability and retention (EPR) effect and direct interactions with

the tumor microenvironment. But and this is a big "but" EPR is inconsistent. It varies between tumor types and even between patients, which makes outcomes harder to predict. So while these formulations are a massive step forward, they're not a magic bullet just yet.Another area where nanocarriers have proven themselves is infectious diseases and vaccines. The world got a front-row seat to their power during the COVID-19 pandemic, when lipid nanoparticles (LNPs) made mRNA vaccines a reality at record speed. These LNP-based platforms protect fragile nucleic acids, deliver them effectively into cells, and allow for systemic or intramuscular vaccination. Beyond vaccines, lipid-based nanocarriers are also advancing in antifungal and antibacterial therapies areas that badly need new solutions to tackle resistance.Targeting the central nervous system (CNS) is another frontier [41]. The blood–brain barrier (BBB) is like an elite nightclub most drugs don't get past the bouncer. But surface-engineered liposomes, polymeric nanoparticles, and receptor-targeted systems (like those using transferrin receptor ligands) are being designed to sneak past. While success is still limited due to the BBB's complexity, clever strategies like intranasal delivery or transient BBB disruption are showing promise in bypassing this formidable barrier.In ophthalmic delivery, nanocarriers like solid lipid nanoparticles (SLNs), liposomes, and micelles are making big strides in improving corneal penetration and achieving sustained ocular drug delivery for both anterior and posterior segment diseases [42]. This is crucial because the eye's protective barriers make drug delivery notoriously difficult with traditional eye drops or injections.Finally, nanocarriers are expanding into oral, pulmonary, topical, and gene therapy applications. They can shield sensitive biologics from harsh gastrointestinal environments for oral delivery, provide controlled inhalation delivery directly to the lungs, and enable sustained topical release for skin and mucosal treatments. In gene therapy, LNPs and polymeric carriers have become the go-to vehicles for mRNA and other nucleic acid-based therapeutics, paving the way for precision medicine and next-gen treatments.In short, nanocarriers are no longer just a lab curiosity they're driving a therapeutic revolution, reshaping how we think about delivering drugs, genes, and vaccines to where they're needed most [43]. (Table 3)

Table 3: Representative nanocarrier-based drugs (marketed or in clinical trials)

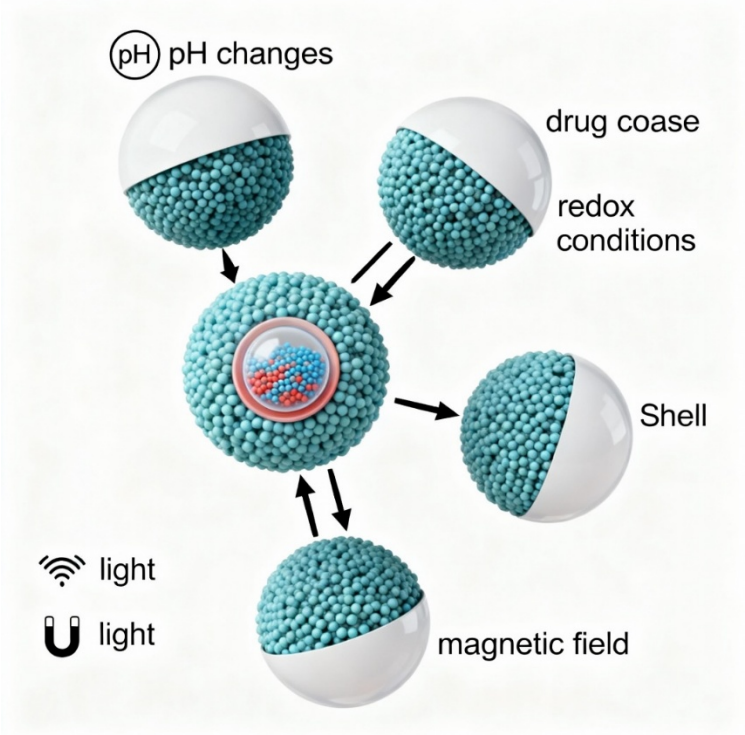
Product / candidate	Carrier type	Indication	Status / Notes	Reference
DOXIL® (doxorubicin liposomal)	PEGylated liposome	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	FDA-approved (1995) high clinical impact.	44
ABRAXANE® (nab-paclitaxel)	Albumin-bound nanoparticles	Breast, NSCLC, pancreatic cancer	FDA-approved (2005); protein-bound formulation eliminates Cremophor EL.	45
Onpattro® (patisiran)	LNP siRNA	Hereditary transthyretin-mediated amyloidosis	Approved LNP siRNA therapeutic (2018)	46

			demonstrates LNP clinical viability for nucleic acids.	
mRNA COVID-19 vaccines	Ionizable lipid nanoparticles	Vaccination	Emergency use & approval demonstrated rapid LNP deployment.	47

7. Stimuli-Responsive and Smart Nanocarriers

Stimuli-responsive nanocarriers, often nicknamed "smart" nanocarriers, are one of the coolest innovations in modern drug delivery because they don't just carry drugs passively; they *listen* to their environment and *respond* on cue. These carriers are engineered to release their therapeutic payload only when specific microenvironmental conditions or external stimuli are present. This makes them ideal for targeted, on-demand, and precision drug delivery something traditional drug formulations could never pull off [48].A classic example is pH-responsive systems, which exploit the naturally acidic tumor microenvironment or the low pH of endosomes inside cells. When these nanocarriers encounter acidic conditions, they undergo structural changes or bond cleavage, triggering a controlled drug release right at the disease site minimizing collateral damage to healthy tissues [49].Then there are redox-responsive systems, which cleverly use disulfide linkers that remain stable in the bloodstream but break apart in the presence of high intracellular glutathione levels something that's often elevated in tumor cells. This results in selective intracellular release, making it particularly useful for cancer therapies.Enzyme-sensitive systems take advantage of tumor- or disease-associated enzymes, like matrix metalloproteinases (MMPs), which degrade specific linkers or coatings to free the drug [50]. This is like setting a molecular trap that only activates in diseased tissues.But the magic doesn't stop at internal triggers. External stimuli can also be harnessed to control drug release with impressive precision. For example, light-responsive systems use photocleavable linkers that break upon irradiation, thermosensitive liposomes release drugs at elevated temperatures (useful in localized hyperthermia), and magnetic fields can be used to heat or guide particles to the target site basically remote-controlling your drug delivery like a sci-fi gadget [51].Pushing the envelope further, multi-stimuli-responsive systems combine two or more triggers say pH + enzyme, or redox + heat for greater specificity and tighter control over when and where drugs are released. This reduces the risk of off-target effects and allows for highly personalized therapy.However, with all this sophistication comes a not-so-fun reality check: manufacturing complexity and regulatory hurdles. Designing a "smart" nanocarrier is one thing; proving its consistency, safety, and scalability is another. But despite these challenges, stimuli-responsive systems remain a hot topic in nanomedicine because they represent the next leap toward truly intelligent, precision therapeutics [52]. (Figure 3)

Figure 3: Diagram showing nanocarriers releasing cargo in response to extracellular pH, intracellular redox state, and external light or magnetic field.



8. Clinical Translation and Regulatory Challenges

Translating lab-scale formulations to GMP manufacturing requires robust, reproducible processes. Microfluidic mixing has emerged as a preferred scalable method for LNPs and liposomes, delivering tight control over particle size and lamellarity. However, scale-up introduces challenges in solvent removal, sterilization, and batch-to-batch variability [53]. Nanocarrier toxicity can be driven by carrier materials (e.g., cationic lipids cause membrane perturbation), impurities, and accumulation in RES organs (liver, spleen). Immunogenicity, complement activation-related pseudoallergy (CARPA), and long-term organ deposition are regulatory concerns that require chronic toxicity and biodistribution studies. Physical instability (aggregation), chemical degradation, payload leakage, and lipid polymorphism affect shelf-life and require stabilization strategies (lyophilization, cryoprotectants, optimized lipid blends) [54].Regulatory agencies (FDA, EMA) evaluate nanomedicines under existing frameworks but ask for detailed characterization of particle attributes, manufacturing control, and safety. Established regulatory precedents for

liposomal drugs and LNPs simplify pathways in some cases, but novel materials and complex multifunctional systems face greater scrutiny [55]. Lists and summaries of FDA-approved nanomedicines help guide developers; several compiled resources summarize approved nano-enabled drugs and their indications. Approved nanomedicines (DOXIL®, Abraxane®, Onpattro® among others) illustrate both the promise and the pitfalls of nanocarriers improved delivery and reduced certain toxicities, but also unexpected adverse effects and manufacturing complexities that delayed or limited broader clinical impact. These lessons highlight the need for robust physicochemical control, early safety profiling, and clinically meaningful endpoints in trials [56].

Table 4: Selected FDA-approved nanocarrier formulations and primary indications (representative subset)

Product	Carrier type	Indication	FDA approval year	Notes	Reference
DOXIL®	PEGylated liposomal doxorubicin	Ovarian cancer, Kaposi's sarcoma	1995	Landmark liposomal oncology drug.	57
ABRAXANE®	Nab-paclitaxel (albumin-bound)	Breast, NSCLC, pancreatic cancer	2005	Removed need for Cremophor EL; improved tolerability in some settings. (FDA Access Data)	58
Onpattro®	LNP (siRNA)	Hereditary ATTR amyloidosis	2018	First approved siRNA LNP therapeutic.	59
Multiple mRNA vaccines	Ionizable lipid nanoparticles	Infectious disease vaccination	2020–2021 (EU/US EUA/approvals)	Rapid deployment of LNP platforms for mRNA vaccines.	60

				(OAE Publishing)	

9. Future Perspectives and Emerging Trends

Machine learning and AI can accelerate formulation optimization by predicting relationships among composition, process parameters, and critical quality attributes (size, encapsulation, stability). AI-driven approaches reduce experimental burden and can propose novel material combinations for targeted biodistribution [61].Tailoring nanocarrier composition and targeting ligands to patient-specific tumor biology (biomarker-driven targeting) and combining diagnostic and therapeutic functions (theranostics) are promising directions. Patient stratification will be essential to demonstrate clinical benefit given heterogeneity in EPR and tumor microenvironments.LNPs and polymeric nanocarriers have matured as practical platforms for mRNA and siRNA delivery [62]. Further improvements in ionizable lipid safety, endosomal escape, and organ-specific delivery will broaden therapeutic applications (inborn errors, oncology, and vaccines). Development of robust, standardized assays for nanoparticle identity, potency, and safety will accelerate regulatory review [63]. Collaborative consortia among academia, industry, and regulators are expected to streamline best practices.

10. Conclusion

Nanocarrier-based drug delivery systems have advanced from bench-top curiosities to clinically validated medicines that improve therapeutic outcomes in multiple domains. While landmark approvals such as pegylated liposomal doxorubicin and albumin-bound paclitaxel demonstrate real-world value, broad clinical impact requires overcoming challenges in manufacturing scale-up, reproducibility, long-term safety, and patient-specific variability in delivery (e.g., EPR variability). Emerging tools especially microfluidic manufacturing, stimuli-responsive materials, and AI-guided design promise to accelerate translation. Continued multidisciplinary efforts are required to realize personalized, multifunctional nanotherapies that are safe, effective, and economically viable.

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