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A REVIEW OF THE CLINICAL TRANSLATION OF NANOEMULSIONS, DOXIL AND LIPID NANOPARTICLES

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ABSTRACT

Nanomedicine has reshaped the clinical use of therapeutics by changing how payloads are formulated, protected, distributed and released. Yet despite decades of innovation, only a limited number of nanocarrier platforms have achieved sustained clinical impact. Here, we examine nanoemulsions, Doxil and lipid nanoparticles (LNPs) as three clinically validated platforms spanning increasing levels of carrier dependence. Nanoemulsions primarily solve formulation and administration constraints. Doxil reprograms the pharmacokinetics and toxicity of an established drug. LNPs enable nucleic acid therapeutics whose clinical activity depends on carrier-mediated protection, delivery and intracellular release. This reveals a central principle of translational nanomedicine: clinical value emerges when carrier function addresses an indispensable therapeutic need, rather than when nanoscale complexity is pursued as an end in itself. We further discuss how biological identity, tissue transport, cellular processing, payload release and manufacturability determine whether this functional advantage is retained in patients. Framing nanomedicines according to therapeutic dependence on the carrier provides a clinically grounded basis for understanding past successes and guiding the design of the next generation of translatable nanotherapeutics.

Keywords: nanomedicine, nanoemulsions, Doxil and lipid nanoparticles, clinically approved drugs

INTRODUCTION

The clinical story of nanocarriers intervene by reshaping how therapeutic payloads are formulated, protected, transported, recognized, and released. This ability has moved nanomedicine from a formulation concept into a clinically used technology across nutrition, anesthesia, oncology, vaccination, gene silencing, and mRNA therapy. The field now contains many clinically approved nanomedicines, including liposomes [1], albumin nanoparticles [2], polymeric systems [3], iron oxide particles [4], nanoemulsions [5,6], and lipid nanoparticles [7]. This review focuses on nanoemulsions, Doxil and lipid nanoparticles due to their defined three levels of carrier dependence in clinical translation. In nanoemulsions, the carrier acts as a formulation solution. In Doxil, the carrier acts as a pharmacokinetic modifier. In LNPs, the carrier becomes an essential enabler of a new therapeutic modality.

Nanoemulsions represent the most practical level of carrier dependence. Their clinical value lies in converting hydrophobic, lipid-based, or locally irritating agents into stable and administrable products. Oil-in-water emulsions achieve this by dispersing the payload within nanoscale oil droplets stabilized by biocompatible emulsifiers [8,9]. This principle underlies lipid emulsions for parenteral nutrition [10], propofol emulsions for anesthesia [11], topical and ocular formulations [12], and oil-in-water vaccine adjuvants [13]. In these cases, the carrier does not need to prove precise disease targeting to be clinically valuable. It succeeds because it makes a difficult agent usable, tolerable, scalable, and compatible with accepted routes of administration.

Doxil represents a deeper level of carrier dependence, where the nanocarrier redesigns the pharmacology of an existing drug [14]. Doxorubicin is highly active against cancer, but its clinical use is limited by nonspecific tissue exposure and cumulative cardiotoxicity [15]. PEGylated liposomal encapsulation changed this profile without changing the drug

molecule itself [16]. A rigid cholesterol-containing membrane limits premature leakage, ammonium sulfate gradient loading stabilizes intraliposomal drug retention, and PEG chains delay mononuclear phagocyte system clearance [17]. Together, these features prolong circulation, reduce free-drug exposure, and increase the opportunity for tumor accumulation. Doxil therefore became a landmark because it showed that carrier architecture can create a new clinical behavior for an old cytotoxic drug [18]. It also showed the limits of this strategy, because long circulation does not guarantee uniform tumor penetration, efficient intracellular release, or freedom from PEG-associated immune responses [19].

LNPs represent the strongest form of carrier dependence. RNA is large, anionic, enzymatically unstable, immunostimulatory, and poorly membrane-permeable [20]. Ionizable LNPs address these barriers by condensing RNA during formulation, reducing excessive surface charge in circulation, and promoting endosomal escape after cellular uptake [21]. This design enabled systemic siRNA therapy [22] and later mRNA vaccines [23], where the carrier protects the transcript and allows host cells to produce the encoded protein. In this sense, LNPs did not merely improve RNA therapeutics, reaching the clinical approval [24].

In this review, we use these three clinically validated platforms to examine why some nanomedicines reach patients while most remain preclinical. Nanoemulsions show how carriers solve pharmaceutical usability. Doxil shows how carriers reshape exposure and toxicity. LNPs show how carriers enable intracellular therapies that are otherwise not clinically feasible. Together, they reveal a central rule of translation: a nanocarrier succeeds when its function is inseparable from the therapeutic need. Building on this framework, we discuss the key barriers that must be addressed for the next generation of nanomedicine, including biological identity [25], tissue transport [26], intracellular release, and reproducible manufacturing [27].

CLINICAL TRANSLATION AND APPLICATIONS OF NANOMEDICINE

The clinical translation of nanomedicine is best understood by asking what problem the carrier solved in patients. Nanoemulsions solved pharmaceutical usability. Doxil redesigned the exposure and toxicity profile of chemotherapy [28]. Lipid nanoparticles enabled intracellular delivery of RNA. These three platforms therefore represent different stages of carrier dependence in medicine, from making difficult agents administrable, to improving the pharmacology of an existing drug, to creating a clinically viable genetic medicine platform.

Nanoemulsions: formulation rescue and routine clinical use

Nanoemulsions are among the most mature nanomedicine platforms due to their earliest clinical successes addressed practical formulation barriers rather than targeting. Their oil-in-water structure allows hydrophobic compounds, lipids, or locally irritating agents to be dispersed in aqueous formulations using physiologically tolerated oils and emulsifiers [9]. This feature made nanoemulsions suitable for parenteral nutrition [29], anesthesia [11], ophthalmology [30], immunosuppression [8], blood pressure control [31], antiemetic therapy [32], and vaccine adjuvant [33]. The clinical evolution and applications of nanoemulsions are summarized in Fig. 1.

Intralipid established one of the earliest clinical routes for nanoemulsions by providing calories and essential fatty acids to patients who cannot receive sufficient oral or enteral nutrition [10]. Its soybean oil, phospholipid, glycerin, and aqueous composition explain why it could enter routine clinical use: it used metabolizable and physiologically tolerated components to solve an essential medical need [34]. Propofol emulsions later extended this principle to anesthesia [9]. Propofol is highly lipophilic and unsuitable for simple aqueous injection,

whereas emulsion formulation enabled intravenous administration and helped make propofol a core drug in modern operating rooms and intensive care [11].

Cyclosporine formulations further show how nanoemulsions can solve absorption and local delivery barriers [35]. Neoral improved oral cyclosporine exposure compared with earlier formulations, reducing the absorption variability that complicated transplant immunosuppression [36]. Restasis used cyclosporine ophthalmic emulsion to deliver a hydrophobic immunomodulator to the ocular surface for chronic dry eye disease [12]. Later products expanded nanoemulsions into acute care and supportive oncology. Cleviprex enabled titratable intravenous delivery of clevidipine for rapid blood pressure control [31], while aprepitant injectable emulsion provided an intravenous option for chemotherapy-induced nausea and vomiting [32,37]. In nutritional medicine, SMOFlipid advanced lipid-emulsion design by combining soybean oil, medium-chain triglycerides, olive oil, and fish oil [29,38,39].

Nanoemulsions are also clinically important as vaccine adjuvant systems. MF59, a squalene-based oil-in-water emulsion used in influenza vaccines, enhances immune responses in older adults [13,33]. This application extends nanoemulsions beyond solubilization and nutrition into immune modulation. Overall, nanoemulsions reached the clinic because they made difficult agents usable, tolerable, scalable, and compatible with accepted routes of administration. Their strongest clinical evidence lies in formulation rescue, parenteral nutrition, anesthesia, local delivery, supportive care, and adjuvant, rather than precise disease-site targeting [40].

Doxil: pharmacokinetic redesign of chemotherapy

Doxil represents a different translational model due to its purpose was not simply to formulate doxorubicin, but to change how doxorubicin behaves in the body [41]. Con-

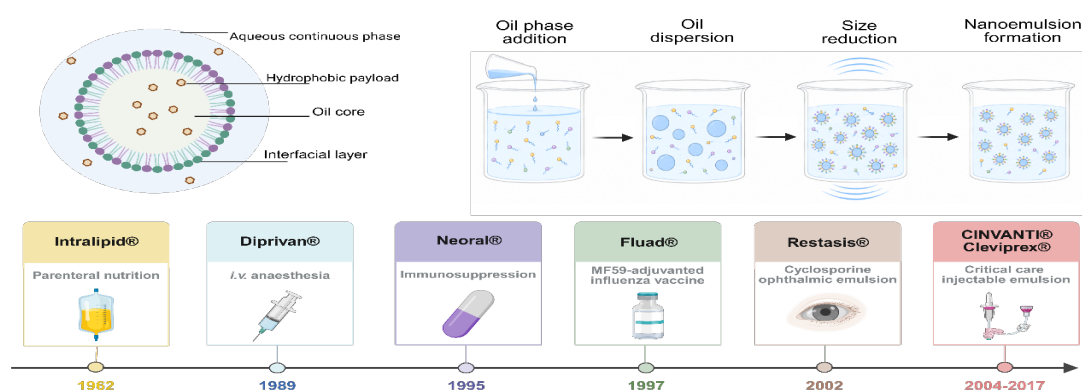


Figure 1. Clinical translation and working principle of nanoemulsions. (a) Structure of an oil-in-water nanoemulsion, displaying the aqueous continuous phase, interfacial surfactant layer, central oil core, and encapsulated hydrophobic payload. (B) Stepwise preparation workflow of nanoemulsions via high-energy emulsification. (C) Timeline of representative marketed nanoemulsion products, covering diverse therapeutic fields: Intralipid for parenteral nutrition (1962) [34]; Diprivan propofol injectable emulsion for intravenous anesthesia (1989) [9]; Neoral oral cyclosporine microemulsion for immunosuppression (1995) [35], Flud MF59 nanoemulsion-adjuvanted influenza vaccine (1997) [33], Restasis cyclosporine ophthalmic nanoemulsion for ocular disorders (2002) [12], Cleviprex (blood pressure control) [31] and CINVANTI (antiemetic therapy) [37] injectable nanoemulsions for critical care applications (2004–2017).

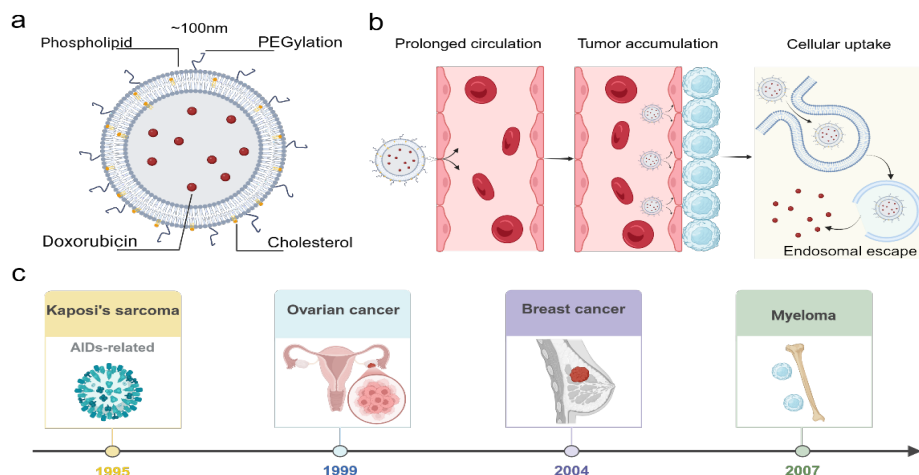


Figure 2. Clinical translation and mechanism of Doxil.(a) Structure and composition of Doxil. (b) In vivo fate and mechanism of action of Doxil. (c) Timeline of Doxil clinical development and indication expansion. Doxil was approved for AIDS-related Kaposi's sarcoma (1995) [43], followed by ovarian cancer (1999) [53], metastatic breast cancer (2004) [54], and multiple myeloma (2007) [55].

tional doxorubicin is highly effective against cancer, yet its use is limited by nonspecific tissue exposure and cumulative cardiotoxicity [42]. Doxil, approved in 1995 for AIDS-related Kaposi's sarcoma [43], and widely recognized as the first FDA-approved nanodrug [44] and a landmark example of how carrier engineering can improve the clinical profile of an established cytotoxic agent. The clinical timeline, composition, and in vivo mechanism of Doxil are shown in Fig. 2.

The translational success of Doxil came from matching carrier architecture to the main failure modes of free doxorubicin [45]. PEGylated liposomes reduce rapid clearance by the mononuclear phagocyte system and prolong systemic circulation [46]. Remote loading through an ammonium sulfate gradient enables high and stable doxorubicin encapsulation [47]. A cholesterol-containing, high-transition-temperature lipid bilayer limits premature leakage and preserves the drug in the liposomal core during circulation. These features convert doxorubicin from a rapidly distributing small molecule into a long-circulating nanoparticle-associated drug reservoir [48].

This pharmacokinetic redesign changed the therapeutic window. Prolonged circulation increases the probability of tumor exposure, especially in vascular tumors such as Kaposi's sarcoma, where leaky neovasculature and inflammatory lesions favor nanoparticle extravasation [49]. Stable liposomal retention also reduces free doxorubicin exposure in healthy tissues, which helps explain the reduced cardiotoxic burden relative to conventional doxorubicin [50]. The key clinical lesson is that Doxil succeeded due to its decoupled antitumor drug exposure from immediate systemic toxicity [42].

Doxil also created the conceptual foundation for later cancer nanomedicines [51]. It validated PEGylation, remote loading, liposomal stability, and passive tumor accumulation as clinically relevant design principles. It also clarified why oncology nanomedicine remains difficult. Prolonged circulation increases tumor access, but it does not guarantee homogeneous tumor penetration, efficient cellular uptake, or synchro-

nized intracellular drug release. Thus, Doxil is both a success in clinical pharmacology and a reference model for understanding the limits of first-generation tumor-targeted nanomedicine [52].

Lipid nanoparticles: clinical enablement of RNA therapeutics

LNPs represent the most carrier-dependent form of clinical translation among the three platforms discussed here. Small-molecule drugs and chemotherapeutics may be improved by nanocarriers, but RNA therapeutics generally cannot function as free molecules [56]. RNA is large, anionic, enzymatically unstable, immunostimulatory, and unable to efficiently cross cell membranes [57]. LNPs became clinically decisive because they solved the linked problems of RNA protection, encapsulation, systemic tolerability, cellular uptake, and endosomal escape [58]. The evolution from early lipid transfection systems to clinically approved LNP-RNA medicines is summarized in Fig. 3.

The development path from cationic liposomes to modern LNPs was driven by the need to balance nucleic acid binding with in vivo safety. Early cationic lipids such as DOTMA improved nucleic acid complexation and transfection [59], but permanently charged systems were associated with toxicity and rapid clearance [60]. The field therefore moved toward ionizable lipids, which become positively charged under acidic formulation conditions to package RNA [61], while remaining less charged at physiological pH to improve tolerability in circulation [62]. After cellular uptake, protonation in acidic endosomes promotes interaction with anionic endosomal lipids, membrane disruption, and cytosolic RNA release [63].

This design principle matured through systems such as Stabilized Plasmid-Lipid Particles (SPLP) [64], Stabilized Antisense-Lipid Particles (SALP) [65], Stable Nucleic Acid Lipid Particles (SNALP) [66], and later LNP formulations optimized around ionizable lipid structure and apparent pKa. A

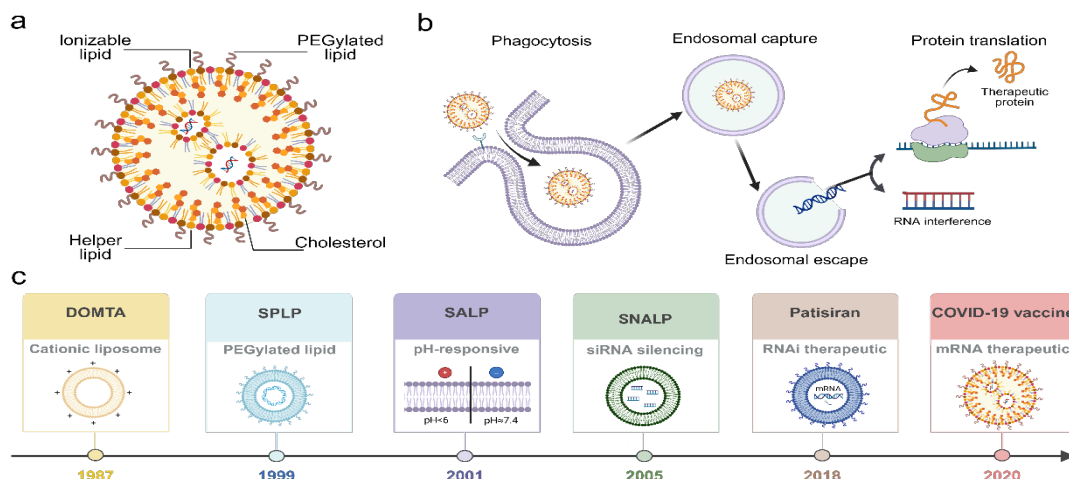


Figure 3. Clinical translation and working mechanism of lipid nanoparticles.

(a) Structural diagram of LNPs composed of ionizable lipid, helper lipid, cholesterol and PEGylated lipid. (b) Schematic process of LNP-mediated nucleic acid delivery: phagocytosis, endosomal capture, endosomal escape, followed by mRNA translation or siRNA-induced RNA interference. (c) Timeline of classic lipid delivery systems and clinical products: DOMTA cationic liposome [77], SPLP [64], SALP [65], SNALP [66], patisiran [78], and LNP COVID-19 mRNA vaccine [79].

major clinical breakthrough was patisiran, an siRNA formulated in LNPs for hereditary transthyretin-mediated amyloidosis [67]. Its approval demonstrated that systemic RNA interference could be achieved in humans through a nanoparticle delivery system, especially for liver-directed targets.

The same carrier logic later enabled mRNA vaccines. In this setting, LNPs protect mRNA after administration, facilitate cellular uptake, and allow host cells to translate the encoded antigen [68]. The global deployment of LNP-based COVID-19 vaccines showed that LNP-mRNA technology could be manufactured and distributed at clinical scale under urgent demand. This success changed the status of nanomedicine [69]. LNPs were no longer viewed only as delivery vehicles for niche genetic drugs, but as a deployable platform for programmable medicine.

Today, LNPs are being extended beyond COVID-19 vaccines and liver-directed siRNA toward broader applications [70,71], including infectious disease vaccines [72], cancer vaccines [73], protein replacement [74], genome editing [75], and immunotherapy [76]. Their clinical impact comes from a simple but powerful principle: the carrier is inseparable from the therapeutic mechanism. For RNA medicines, delivery is not a supporting technology, it is part of the drug itself.

Overall, nanoemulsions, Doxil and LNPs show three distinct routes by which nanomedicine has crossed into clinical practice. Nanoemulsions made difficult agents administrable. Doxil redesigned the exposure and toxicity profile of chemotherapy. LNPs enabled RNA therapeutics by solving intracellular delivery. These successes provide the clinical foundation for the next question: why do so many other nanomedicines fail to translate despite strong preclinical performance?

TRANSLATIONAL BARRIERS AND IMPROVE-

MENT STRATEGIES

The clinical success of nanoemulsions, Doxil and LNPs does not mean that nanomedicine translation has become straightforward. Instead, these platforms show a recurring pattern. The same design features that make a nanocarrier clinically useful can also create new barriers during storage, manufacturing, dosing, biodistribution, immune exposure, and intracellular release. Nanoemulsions are limited mainly by colloidal stability [80], lipid burden [10,34], drug loading [31,80], and scale-up [12]. Doxil is limited by tumor transport [81], immune recognition [82], and the balance between systemic stability and drug release [83]. LNPs are limited by tissue tropism [84], endosomal escape [85], repeat dosing [86], immunogenicity [87], and storage stability [88].

Nanoemulsions: stability, safety, and targeting beyond formulation rescue

The strongest clinical advantage of nanoemulsions is also their first translational weakness. They are colloidal systems rather than fixed molecular entities. During long-term storage, droplets may aggregate, coalesce, undergo Ostwald ripening, or separate into different phases [80]. These changes can increase particle size, reduce uniformity, cause drug precipitation, and disrupt surface modifications such as targeting ligands [80]. Sterilization, freeze-drying, and large-scale homogenization can further damage the emulsion structure, making batch-to-batch consistency difficult to maintain [5,31,89]. For therapeutic nanoemulsions, this instability is not only a formulation issue [5,8,31]. It directly affects dose accuracy, safety, biodistribution, and regulatory acceptance.

A second barrier is lipid-related safety after repeated or high-dose administration. Many therapeutic nanoemulsions contain substantial oil phases and surfactants [8,38]. After intravenous injection, these components are processed mainly

through lipid metabolism and reticuloendothelial uptake, which can increase hepatic lipid burden, inflammatory responses, and coagulation-related risks in vulnerable patients [10,34]. This is particularly relevant for cancer patients, patients with liver dysfunction, premature infants, and individuals with abnormal lipid metabolism [10,34]. Some surfactants can also cause infusion-site irritation or hypersensitivity reactions [8,38]. Therefore, the clinical use of therapeutic nanoemulsions requires not only drug efficacy, but also careful control of oil composition, surfactant selection, lipid clearance, and cumulative dosing.

A third limitation is the gap between formulation success and disease targeting. Nanoemulsions can improve solubility and local retention, but systemic delivery to tumors, liver disease, brain disorders, or infected tissues remains much harder to control [90-93]. Passive accumulation through vascular leakage is variable, while active targeting by surface ligands often loses efficiency after protein adsorption in blood [89-95]. In addition, the upper limit of drug loading can be low for some payloads, especially when the drug has weak compatibility with the oil phase or partitions rapidly into surrounding biological fluids. These problems reduce the ability of nanoemulsions to deliver sufficient drug concentrations to diseased tissues [31,80].

Future improvement should therefore focus on three directions. First, formulation stability can be improved through optimized oil composition, mixed surfactant systems, interfacial film strengthening, antioxidant protection, and lyophilization strategies that preserve droplet structure [6,80,96]. Second, safety can be improved by using metabolically tolerated oils, reducing irritant surfactants, and designing lipid compositions that avoid excessive hepatic burden [38,39,97]. Third, therapeutic precision can be enhanced by moving beyond simple ligand decoration toward disease-responsive release, biomimetic interfaces, and better prediction of the protein corona formed on nanoemulsion droplets in human fluids [89,98,99]. These strategies will determine whether nanoemulsions can expand from mature supportive formulations into more advanced disease-modifying therapies.

Doxil: the limits of passive tumor delivery

Doxil remains a landmark in oncology nanomedicine because it reduced the systemic toxicity of doxorubicin through liposomal encapsulation and prolonged circulation [100]. However, its clinical trajectory also shows the limits of first-generation passive targeting. The central assumption behind Doxil is that long-circulating nanoparticles can accumulate in tumors through the enhanced permeability and retention effect [101]. This mechanism works best in tumors with leaky vasculature and poor lymphatic drainage, such as Kaposi's sarcoma [102]. In many other solid tumors, the same mechanism is far less predictable [103].

The main reason is that human tumors are biologically heterogeneous. Vascular density, endothelial permeability, blood perfusion, stromal content, immune infiltration, and interstitial fluid pressure differ across tumor types, across patients, and even across lesions within the same patient [104]. Dense extracellular matrix and high interstitial pressure can prevent nanoparticles from moving beyond perivascular regions [105]. As a result, liposomes may reach the tumor margin or vascular niche without distributing uniformly through

the tumor mass [106]. This explains why tumor accumulation does not necessarily translate into deep penetration, broad tumor-cell exposure, or proportional therapeutic benefit.

Doxil also illustrates an immunological paradox. PEGylation prolongs circulation by reducing early protein adsorption and mononuclear phagocyte system clearance, but repeated exposure can generate anti-PEG antibodies and accelerate clearance of later doses [107]. PEGylated liposomes may also trigger complement activation-related pseudoallergy, causing infusion reactions that range from mild symptoms to severe cardiopulmonary responses [108]. These effects show that "stealth" is not a permanent biological state [109]. It is a temporary interface that can be reshaped by immune recognition, complement activation, and prior exposure history.

A third limitation is the trade-off between stability and release. The rigid liposomal membrane and remote loading strategy help retain doxorubicin during circulation, which is essential for reducing systemic toxicity [110]. However, excessive stability can delay intracellular drug release after uptake. This creates a mismatch between nanoparticle accumulation and pharmacologically active drug availability. Doxil can also cause hand-foot syndrome, likely related to long circulation and leakage in mechanically stressed peripheral tissues [111]. Together, these issues show that improving circulation is not enough. A successful cancer nanomedicine must also overcome tumor transport barriers and release its payload at the right place and time [112].

Future strategies should therefore shift from passive accumulation alone to barrier-aware tumor delivery. These may include patient stratification based on tumor vascular permeability, imaging-guided prediction of nanoparticle accumulation, modulation of tumor stroma or interstitial pressure, stimuli-responsive liposomes, non-PEG stealth alternatives, and formulations that better balance blood stability with intracellular release [113]. Doxil should not be viewed only as a finished success story. It should be used as a reference model for designing the next generation of tumor nanomedicines [114].

Lipid nanoparticles: tissue tropism, repeat dosing, and RNA delivery beyond the liver

LNPs solved the central problem of RNA medicine by enabling RNA encapsulation, protection, cellular uptake, and cytosolic release [115]. Their clinical success in liver-directed siRNA therapy and mRNA vaccination is clear [69]. However, broader application is still limited by tissue selectivity. After intravenous administration, many LNPs adsorb apolipoprotein E and are preferentially taken up by hepatocytes through lipoprotein-related pathways [116]. This liver tropism is useful for hepatic gene silencing, but it limits delivery to the brain, heart, lung, bone marrow, immune cells, and solid tumors [117]. Extrahepatic targeting remains one of the most important barriers for next-generation LNP medicines.

Another limitation is intracellular delivery efficiency [118]. For siRNA and mRNA, cytosolic delivery is sufficient, but only a small fraction of internalized RNA typically escapes from endosomes. Most cargo is degraded in endo-lysosomal compartments. For DNA-based delivery, the problem is even more difficult because DNA must reach the nucleus for transcription [119]. This is especially challenging in non-dividing cells, where the nuclear envelope remains in-

tact. Therefore, LNPs are highly effective for some RNA applications, but their performance is much less universal across nucleic acid types, tissues, and disease settings.

Safety and repeat dosing are also major concerns. Ionizable lipids reduce the toxicity associated with permanently cationic lipids [120], but lipid components and their metabolites can still accumulate in tissues and cause inflammatory or hepatic stress [121], depending on structure, dose, route, and dosing frequency. PEG-lipids improve colloidal stability and control particle size during formulation [122], but they can also contribute to anti-PEG antibody production [123], accelerated blood clearance, and hypersensitivity reactions after repeated administration. These problems are especially important for chronic diseases that require long-term dosing, where immune memory may reduce efficacy and increase risk.

Storage and manufacturing add another layer of difficulty. LNPs are complex colloidal systems containing ionizable lipid, helper phospholipid, cholesterol, PEG-lipid, and nucleic acid cargo [124]. Particle size, encapsulation efficiency, lipid ratio, RNA integrity, residual solvent, and mixing conditions all affect product quality [125]. LNP-mRNA products can also suffer from RNA degradation, particle aggregation, and leakage during storage [126], which explains the need for careful cold-chain management in many formulations. Although manufacturing has advanced rapidly, reproducible large-scale production remains a key requirement for expanding LNP therapies beyond emergency vaccine deployment.

Future LNP development should focus on four connected goals. First, extrahepatic delivery must be improved through selective organ targeting, ligand engineering, lipid structure optimization, and better control of protein corona formation [84,127]. Second, endosomal escape must be increased without increasing membrane toxicity [128]. Third, repeat dosing should be made safer by developing biodegradable ionizable lipids [129], PEG alternatives, and immune-silent surface chemistries. Fourth, formulation stability must be improved through more robust lipid design, lyoprotectants, dry-powder or thermostable formulations, and scalable microfluidic or impingement-mixing processes [130,131]. These improvements will decide whether LNPs can move from liver-directed and vaccine applications toward broader chronic and precision therapies.

The barriers described above are different in detail, but they point to one common problem. Nanomedicine translation often fails when carrier design is optimized in formulation space but not in biological space. In each case, preclinical performance is not enough unless the carrier behavior remains predictable across manufacturing, storage, administration, patient biology, and disease microenvironment [132]. The next stage of translational nanomedicine should therefore move from empirical optimization to mechanism-guided design. This requires integrating colloidal stability, protein corona formation, immune recognition, tissue transport, intracellular trafficking, and scalable manufacturing into the same development framework [133]. Future clinical success will depend less on making increasingly complex nanoparticles and more on understanding which carrier function is necessary for a specific patient population.

CONCLUSION

Clinical nanomedicine succeeds when the carrier solves a problem that the therapeutic agent cannot solve by itself. Nanoemulsions made poorly soluble or irritating agents clinically usable, Doxil showed that liposomal engineering can improve the pharmacokinetics and toxicity profile of a cytotoxic drug, and LNPs enabled RNA therapeutics by protecting nucleic acids and delivering them into cells. These examples also show that translation remains constrained by biology, including colloidal instability, immune recognition, heterogeneous tissue delivery, limited intracellular release, repeat-dose responses, and manufacturing complexity. Future progress will depend on moving from empirical formulation toward predictive translation, where carrier design is matched to the payload, disease, route of administration, and patient population.

NOTE

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

X.Y., S.L., and Y.S. contributed equally to this work, wrote the original draft, revised and edited the manuscript, and prepared the figures and illustrations. H.Y. edited and reviewed. D.B. conceptualized, reviewed and edited the manuscript.

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