Nanostructured Lipid Carriers and Polymeric Nanoparticles for Targeted Anticancer Drug Delivery: Mechanistic Insights into Tumor Microenvironment-Responsive Release Systems

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Abstract
The clinical management of solid malignancies remains constrained by the suboptimal therapeutic index of conventional chemotherapeutic agents, which arises from non-selective biodistribution, rapid systemic clearance, and the development of multidrug resistance. Pharmaceutical nanotechnology has engendered transformative platforms for addressing these limitations through the rational design of nanocarriers capable of tumor-selective drug deposition. This review provides a technical examination of two prominent nanocarrier classes—nanostructured lipid carriers (NLCs) and polymeric nanoparticles—with emphasis on their engineering principles and tumor microenvironment (TME)-responsive release mechanisms. NLCs, characterized by their imperfect crystalline matrix comprising blended solid and liquid lipids, offer enhanced drug loading capacity, prolonged stability, and compatibility with stimuli-responsive lipid excipients. Polymeric nanoparticles fabricated from biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), chitosan, and polyethylene glycol (PEG) derivatives enable precise control over release kinetics and surface functionalization for active targeting. The pathophysiological features of the TME—including acidic pH, redox imbalance, enzymatic overexpression, and hypoxic gradients—serve as endogenous triggers for site-specific drug liberation through mechanisms including acid-labile bond cleavage, redox-sensitive linker degradation, and enzyme-activated shedding of protective coatings. Multi-stimuli responsive platforms integrating dual sensing capabilities are advancing toward spatiotemporally controlled delivery. A comparative evaluation of NLCs and polymeric nanoparticles reveals distinct advantages in drug loading, stability, and translational potential. While challenges in manufacturing scalability and regulatory approval persist, these nanotechnology-enabled strategies hold substantial promise for improving oncological outcomes through precision delivery.

Keywords: Nanostructured Lipid Carriers, Polymeric Nanoparticles, Tumor Microenvironment, Stimuli-Responsive Release, Targeted Drug Delivery, Controlled Release Systems

1. Introduction

Cancer constitutes a leading cause of global mortality, with solid tumors representing the predominant clinical presentation. Despite significant advances in surgical resection and radiotherapy, systemic chemotherapy remains indispensable for managing disseminated disease and microme-tastatic deposits [1]. Conventional chemotherapeutic agents, however, exhibit pharmacokinetic profiles characterized by extensive volume of distribution, short plasma half-lives, and dose-limiting toxicities attributable to off-target effects on proliferating healthy tissues [2]. The narrow therapeutic window of these agents necessitates administration at suboptimal doses or treatment interruptions, compromising efficacy and fostering acquired drug resistance.
Nanotechnology-based drug delivery systems have emerged as a strategic approach to overcome these limitations through the

encapsulation of therapeutic agents within carriers engineered at the nanometer scale [3]. These systems exploit the unique pathophysiological features of solid tumors—particularly the enhanced permeability and retention (EPR) effect—to achieve preferential accumulation at malignant sites while sparing normal tissues [4]. Beyond passive targeting, surface functionalization with ligands recognizing tumor-associated receptors enables active targeting and receptor-mediated internalization.

The therapeutic efficacy of nanocarriers is critically dependent on their ability to release the encapsulated drug at the intended site of action. Premature release during systemic circulation diminishes tumor selectivity and may exacerbate toxicity, while insufficient release within the tumor compromises therapeutic effect [5]. This has motivated the development of stimuli-responsive nanocarriers that leverage the distinctive biochemical milieu of the TME as an endogenous trigger for site-specific drug liberation. The acidic pH, elevated glutathione (GSH) concentrations, overexpression of matrix metalloproteinases (MMPs), and hypoxic conditions characteristic of solid tumors provide a repertoire of signals that can be harnessed for controlled release [6].

This review provides a comprehensive analysis of NLCs and polymeric nanoparticles as platforms for TME-responsive anticancer drug delivery. The physicochemical properties, formulation strategies, and release mechanisms of each carrier class are examined in detail, with emphasis on their integration with stimuli-responsive elements. A comparative evaluation of these systems informs the rational selection of nanocarriers for specific therapeutic applications, while discussion of current challenges and future directions addresses the translational pathway toward clinical implementation.

2. Tumor Microenvironment as a Therapeutic Target

2.1. Pathophysiological Characteristics of Solid Tumors

The TME represents a complex, dynamic ecosystem comprising malignant cells, stromal fibroblasts, endothelial cells, immune infiltrates, and extracellular matrix (ECM) components, all existing under aberrant physiological conditions resulting from uncontrolled proliferation and inadequate vascularization [7]. This pathological milieu exhibits several distinctive features that differentiate it from normal tissues and provide opportunities for targeted intervention.

Acidic pH: Rapid tumor growth coupled with defective vascular networks creates regions of hypoxia that shift cellular metabolism toward glycolysis, producing lactic acid even under aerobic conditions—a phenomenon termed the Warburg effect [8]. Insufficient clearance of acidic metabolites by the compromised vasculature results in extracellular acidification, with pH values ranging from 6.5 to 6.9 in tumors compared to 7.4 in normal tissues. This pH gradient provides a robust trigger for acid-responsive drug release systems.

Redox Imbalance: The intracellular compartment of tumor cells maintains elevated concentrations of glutathione (GSH; 2–10 mM) relative to the extracellular milieu (2–20 μM), creating a sharp redox gradient [9]. This reducing environment is exploited by nanocarriers incorporating disulfide linkages that undergo cleavage upon cellular internalization, enabling cytosolic drug release.

Enzymatic Overexpression: Tumor progression and metastasis require degradation of ECM components, a process mediated by upregulated proteolytic enzymes. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are overexpressed in numerous malignancies and accumulate in the TME [10]. Other enzymes, including cathepsins and phospholipases, exhibit elevated activity and provide additional triggers for enzyme-responsive delivery systems.

Hypoxia: Inadequate oxygen delivery to rapidly expanding tumor masses creates hypoxic regions that promote angiogenesis, metabolic adaptation, and therapeutic resistance. Hypoxic conditions can be exploited through bioreductive prodrugs or oxygen-sensitive delivery systems [11].

2.2. Enhanced Permeability and Retention Effect

The EPR effect constitutes the foundational principle underlying passive tumor targeting of nanocarriers. Tumor vasculature, formed through rapid angiogenesis, exhibits structural abnormalities including wide fenestrations (200–800 nm), lack of smooth muscle layer, and impaired lymphatic drainage [12]. These features enable preferential extravasation and retention of nanoparticles within tumor interstitium, providing a passive targeting mechanism that increases drug accumulation at malignant sites by 10- to 50-fold compared to free drug administration.

2.3. Biological Barriers to Nanoparticle Delivery

Despite the advantages conferred by the EPR effect, successful nanocarrier-mediated drug delivery must overcome multiple biological barriers. Following intravenous administration, nanoparticles encounter opsonization by serum proteins and recognition by mononuclear phagocyte system (MPS) components, leading to rapid clearance [13]. Strategies employing hydrophilic polymer coatings—particularly PEGylation—reduce protein adsorption and prolong circulation half-life. Upon extravasation into tumor tissue, nanoparticles must penetrate through dense ECM and elevated interstitial fluid pressure to reach cancer cells distant from vasculature [14]. Additionally, efficient internalization requires interaction with the cell membrane, often facilitated by surface charge or targeting ligands. These sequential barriers necessitate sophisticated nanocarrier design incorporating multiple functionalities.

3. Nanostructured Lipid Carriers (NLCs)

3.1. Structural Composition and Formulation Strategies

Nanostructured lipid carriers represent second-generation lipid-based nanoparticles developed to address limitations of solid lipid nanoparticles (SLNs), particularly low drug loading capacity and drug expulsion during storage [15]. NLCs are composed of a binary mixture of solid lipids (e.g., glyceryl monostearate, cetyl palmitate) and liquid lipids (e.g., oleic acid, medium-chain triglycerides), which together form an imperfect crystalline matrix with increased space for drug accommodation.

Three principal structural models describe NLC architecture: the imperfect crystal type, where spatial incompatibilities between different lipids create lattice defects; the amorphous

type, where lipid mixing prevents crystallization entirely; and the multiple oil-in-solid-fat-in-water type, where liquid lipid nano-compartments are embedded within a solid lipid matrix [16]. These structural variations influence drug incorporation capacity and release kinetics. Formulation typically employs high-pressure homogenization, microemulsion techniques, or solvent emulsification-evaporation methods, with careful optimization of lipid ratios, surfactant selection, and processing parameters to achieve desired particle characteristics.

3.2. Drug Loading and Encapsulation Mechanisms

The heterogeneous matrix of NLCs accommodates both lipophilic and hydrophilic drugs through multiple mechanisms. Lipophilic agents partition into the lipid phase during nanoparticle formation, while hydrophilic drugs may be incorporated through double emulsion techniques or conjugation to lipid moieties [17]. Drug loading capacity in NLCs (typically 20–40% w/w) substantially exceeds that of SLNs due to the increased solubility of drugs in liquid lipids and the presence of imperfections that accommodate drug molecules. Encapsulation efficiency exceeding 80% is routinely achieved for lipophilic chemotherapeutics including paclitaxel, doxorubicin, and curcumin.

3.3. Controlled and Sustained Release Properties

Release kinetics from NLCs are governed by drug distribution within the lipid matrix, lipid composition, and particle size. Drugs localized in the lipid core exhibit sustained release profiles extending over days, while those enriched in the outer shell may show initial burst release [18]. Modulation of the solid-to-liquid lipid ratio enables tailoring of release rates, with higher liquid lipid content generally accelerating drug liberation. The solid matrix at body temperature provides a diffusion barrier that slows drug efflux, maintaining therapeutic concentrations at tumor sites while minimizing systemic exposure.

3.4. TME-Responsive Lipid-Based Systems

Recent advances in lipid chemistry have enabled incorporation of stimuli-responsive elements into NLC formulations. pH-sensitive NLCs employ ionizable lipids containing amine groups that undergo protonation in acidic environments, altering lipid organization and triggering drug release [19]. Alternatively, incorporation of acid-labile linkages between lipid components enables pH-dependent degradation. Redox-responsive NLCs incorporating disulfide bonds in lipid backbones or between lipid and drug facilitate GSH-triggered release intracellularly. Enzyme-responsive systems utilize lipid substrates cleavable by MMPs or phospholipases overexpressed in the TME, achieving site-specific drug liberation [20]. Table 1 summarizes formulation characteristics of representative NLC and polymeric nanoparticle systems.

3.5. Applications in Anticancer Therapy

Ligand-decorated NLCs targeting tumor-associated receptors have demonstrated enhanced therapeutic efficacy in preclinical models. Folate receptor-targeted NLCs loaded with paclitaxel showed improved cellular uptake and cytotoxicity in folate receptor-overexpressing cancer cells compared to non-targeted formulations [21]. Transferrin receptor-targeted NLCs have been developed for brain tumor delivery, exploiting transferrin receptor expression on the blood-brain barrier and glioma cells. Combination therapy approaches utilizing NLCs for co-delivery of chemotherapeutics and nucleic acids (siRNA, miRNA) are under active investigation for synergistic anticancer effects.

Table 1: Formulation Characteristics of Nanostructured Lipid Carriers and Polymeric Nanoparticles in Anticancer Drug Delivery

Nanocarrier Type	Key Materials	Drug Loading Mechanism	Release Mechanism	Example Anticancer Drugs
NLCs	Glyceryl monostearate, oleic acid, polysorbate 80	Matrix encapsulation in lipid imperfections	Diffusion-controlled, lipid matrix erosion	Paclitaxel, doxorubicin, camptothecin
pH-responsive NLCs	Ionizable lipids, PEGylated lipids	Hydrophobic interactions	pH-dependent protonation-induced destabilization	Cisplatin, 5-fluorouracil
Redox-responsive NLCs	Disulfide-containing lipids	Covalent conjugation or encapsulation	GSH-triggered disulfide cleavage	Docetaxel, methotrexate
Polymeric nanoparticles	PLGA, PLA	Polymer matrix encapsulation	Polymer hydrolysis, diffusion	Paclitaxel, docetaxel
PEGylated polymeric NPs	PLGA-PEG, PLA-PEG	Core encapsulation with stealth coating	Sustained diffusion, polymer degradation	Doxorubicin, cisplatin
Chitosan nanoparticles	Chitosan, tripolyphosphate	Ionic gelation, electrostatic complexation	pH-dependent swelling, enzymatic degradation	Gemcitabine, oxaliplatin

4. Polymeric Nanoparticles

4.1. Biodegradable Polymers in Nanocarrier Design

Polymeric nanoparticles offer distinct advantages for drug delivery, including versatility in polymer chemistry, tunable degradation kinetics, and compatibility with diverse drug molecules [22]. Biodegradable polymers circumvent concerns regarding chronic toxicity and obviate the need for surgical removal following drug depletion.

Poly(lactic-co-glycolic acid) (PLGA) represents the most extensively investigated polymer for nanomedicine applications due to its FDA approval, biocompatibility, and hydrolytic degradation to endogenous metabolites (lactic and glycolic acids). The degradation rate—and consequently drug release kinetics—can be modulated by varying the lactic-to-glycolic acid ratio and polymer molecular weight [23]. Poly (lactic acid) (PLA) exhibits slower degradation than PLGA and is suitable for longer-term delivery applications.

Chitosan, a cationic polysaccharide derived from chitin, offers mucoadhesive properties, biocompatibility, and pH-responsive behavior arising from its primary amine groups [24]. The protonation of these amines at acidic pH enhances polymer solubility and swelling, facilitating drug release in tumor environments. Chitosan nanoparticles are typically prepared through ionic gelation with polyanions such as tripolyphosphate, enabling mild formulation conditions suitable for sensitive biologics.

4.2. Surface Functionalization and Active Targeting

The nanoparticle surface constitutes the interface with biological systems, determining circulation half-life, biodistribution, and cellular interactions. PEGylation—the covalent attachment of polyethylene glycol chains—remains the predominant strategy for achieving stealth properties, reducing protein adsorption and MPS recognition [25]. The density and molecular weight of PEG coatings influence circulation time and should be optimized for each application.

Active targeting is achieved through conjugation of ligands recognizing receptors overexpressed on tumor cells or tumor vasculature. Antibodies, antibody fragments, peptides (e.g., RGD for integrin targeting), aptamers, and small molecules (e.g., folic acid, transferrin) have been successfully employed [26]. Targeting ligands facilitate receptor-mediated endocytosis, enhancing intracellular drug delivery and potentially overcoming efflux pump-mediated resistance. The optimal ligand density balances targeting efficiency with potential immunogenicity and manufacturing complexity.

4.3. Stimuli-Responsive Polymeric Systems

Polymeric nanoparticles are particularly amenable to stimuli-responsive design through incorporation of functional groups or linkages that respond to TME signals [27]. pH-responsive polymers containing ionizable groups (e.g., polyhistidine, poly(β-amino esters)) undergo conformational changes or solubility transitions upon protonation, triggering drug release. Alternatively, polymers incorporating acid-labile bonds (acetal, hydrazone, cis-aconityl) between polymer and drug or within the polymer backbone enable pH-dependent cleavage.

Redox-responsive systems employ disulfide linkages that remain stable in the oxidizing extracellular environment but undergo rapid cleavage in the reducing intracellular milieu [28]. Polymeric nanoparticles with disulfide-crosslinked cores or shell-shedding mechanisms demonstrate GSH-triggered drug release and enhanced cytotoxicity in cancer cells with elevated GSH levels.

Enzyme-responsive polymers are designed with peptide sequences cleavable by proteases overexpressed in the TME. MMP-cleavable peptides incorporated into PEG coatings enable de-shielding upon tumor accumulation, exposing previously concealed targeting ligands or facilitating cellular uptake [29].

4.4. Release Kinetics and Degradation-Controlled Delivery

Drug release from polymeric nanoparticles occurs through multiple mechanisms, including diffusion through the polymer matrix, polymer erosion, and polymer swelling [30]. In bulk-eroding polymers such as PLGA, water penetration into the matrix leads to uniform hydrolysis throughout the particle, while surface-eroding polymers degrade from the exterior inward. The release profile typically exhibits an initial burst release of surface-associated drug, followed by sustained release governed by diffusion and degradation processes. Mathematical modeling of release kinetics enables rational design of formulations matching desired therapeutic schedules.

4.5. Clinical and Translational Relevance

Polymeric nanoparticle formulations have achieved regulatory approval and entered clinical practice. Abraxane® (albumin-bound paclitaxel nanoparticles) exemplifies successful translation of protein-based nanoparticles for cancer therapy [31]. Genexol-PM, a polymeric micelle formulation of paclitaxel, has received approval in several countries. Numerous PLGA-based formulations are in various stages of clinical development, with encouraging results in early-phase trials.

5. Mechanisms of Tumor Microenvironment-Responsive Release

5.1. pH-Responsive Systems

The acidic TME provides a universal trigger for site-specific drug release applicable across diverse tumor types. pH-responsive nanocarriers exploit the pH gradient between extracellular tumor pH (6.5–6.9) and normal tissue pH (7.4) or the more acidic endolysosomal compartments (pH 4.5–6.0) following cellular uptake [32]. Three principal mechanisms underlie pH-responsive release:

Protonation-induced charge changes: Polymers containing ionizable groups (amines, carboxylic acids) undergo charge alterations upon pH change, disrupting electrostatic interactions or inducing conformational transitions. Poly(β-amino esters) protonate and solubilize at acidic pH, releasing encapsulated cargo.

Acid-labile bond cleavage: Linkages including hydrazone, acetal, and cis-aconityl bonds undergo hydrolysis under acidic conditions. Doxorubicin conjugated to polymeric carriers via hydrazone linkers demonstrates pH-dependent release and enhanced antitumor efficacy.

Conformational transitions: pH-sensitive peptides or polymers may undergo structural reorganization (e.g., coil-to-globule transitions) that destabilize nanocarrier architecture and promote drug release.

5.2. Enzyme-Triggered Release

Enzyme-responsive systems offer high specificity due to the differential expression of proteolytic enzymes in malignant versus normal tissues. MMP-2 and MMP-9, gelatinases involved in ECM remodeling and metastasis, are particularly attractive targets [33]. Nanoparticles can be designed with MMP-cleavable peptide sequences positioned in surface coatings or between polymer components. Cleavage by tumor-associated enzymes removes steric barriers, exposes targeting ligands, or directly liberates drug conjugates.

Cathepsin B, a cysteine protease upregulated in various cancers and active in lysosomal compartments, has been exploited for intracellular drug release. Peptide sequences cleavable by cathepsin B (e.g., Gly-Phe-Leu-Gly) incorporated into polymeric or lipid-based carriers enable lysosome-specific drug liberation following endocytic uptake.

5.3. Redox-Responsive Systems

The redox gradient between the oxidizing extracellular environment and reducing intracellular compartment provides a robust trigger for site-specific release. Disulfide bonds, stable in circulation but cleaved by intracellular GSH, are widely employed in redox-responsive nanocarriers [34]. These linkages can be incorporated into crosslinked polymer networks, between polymer and drug, or in lipid components of NLCs. Thiolytic cleavage of disulfide bonds leads to rapid nanocarrier destabilization and drug release upon cellular

internalization. The high GSH concentrations in many cancer cells (up to 4-fold higher than normal cells) confer additional tumor selectivity. Systems incorporating multiple disulfide crosslinks demonstrate minimal extracellular release and rapid intracellular drug liberation.

5.4. Hypoxia-Sensitive Carriers

Hypoxic regions within solid tumors, resulting from inadequate vascular perfusion, are associated with therapeutic resistance and metastatic potential. Hypoxia-responsive delivery systems exploit bioreductive enzymes overexpressed under low oxygen conditions [35]. Nitroaromatic compounds, azobenzene derivatives, and quinones undergo enzymatic reduction in hypoxic environments, triggering structural changes that facilitate drug release. Azobenzene-containing polymers, for example, undergo cleavage by azoreductases under hypoxic conditions, enabling selective drug liberation in poorly vascularized tumor regions.

5.5. Multi-Stimuli Responsive Platforms

The heterogeneity of the TME—both between tumors and within individual lesions—motivates the development of nanocarriers responsive to multiple triggers [36]. Dual pH/redox-responsive systems combine acid-labile and disulfide linkages to achieve release under conditions of either acidity or reducing environment. Triple-responsive platforms integrating pH, redox, and enzyme sensitivity provide robust activation across diverse tumor microenvironments.

Multi-stimuli responsive nanoparticles demonstrate enhanced selectivity and therapeutic efficacy compared to single-stimulus systems. The integration of multiple trigger mechanisms also addresses the challenge of tumor heterogeneity, ensuring drug release even in regions lacking one specific TME characteristic. Table 2 summarizes the design principles and therapeutic significance of major TME-responsive mechanisms.

Table 2: Tumor Microenvironment-Responsive Mechanisms in Nanotechnology-Based Drug Delivery

TME Trigger	Responsive Material Design	Mechanism of Drug Release	Therapeutic Significance
Acidic pH (6.5-6.9)	Ionizable polymers (polyhistidine), acid-labile linkers (hydrazone)	Protonation-induced destabilization, linker hydrolysis	Tumor-selective release, endosomal escape
Redox (GSH)	Disulfide-bonded crosslinks, disulfide-drug conjugates	Thiol-disulfide exchange, bond cleavage	Intracellular-specific release, overcomes efflux
MMP enzymes	MMP-cleavable peptides in coatings or linkers	Enzymatic cleavage, shedding of protective layers	Tumor-specific activation, enhanced penetration
Hypoxia	Nitroaromatic compounds, azobenzene derivatives	Bioreductive activation, structural rearrangement	Release in poorly vascularized regions
Multi-stimuli	Combined responsive elements (pH/redox, pH/enzyme)	Multiple trigger-dependent mechanisms	Overcomes tumor heterogeneity, robust activation

6. Comparative Evaluation of NLCs and Polymeric Nanoparticles

6.1. Drug Loading Efficiency and Capacity

NLCs generally exhibit superior drug loading capacity for lipophilic drugs compared to polymeric nanoparticles due to the solvent properties of liquid lipids and the imperfect crystalline matrix accommodating drug molecules. Loading capacities of 20–40% w/w are routinely achieved, substantially exceeding the 5–15% typical of PLGA nanoparticles [37]. Polymeric nanoparticles, however, offer greater versatility for hydrophilic drug encapsulation through double emulsion techniques or drug-polymer conjugation.

6.2. Stability and Storage

Both NLCs and polymeric nanoparticles demonstrate good colloidal stability when appropriately formulated, though the underlying mechanisms differ. NLC stability derives from surfactant-stabilized lipid interfaces, while polymeric nanoparticles rely on electrostatic or steric stabilization from surface coatings. PEGylated polymeric nanoparticles exhibit excellent stability in biological fluids and during storage. Lipid nanoparticles may be susceptible to polymorphic transitions affecting drug retention, though the imperfect matrix of NLCs minimizes this risk compared to SLNs.

6.3. Biocompatibility and Toxicity

Both carrier classes employ generally regarded as safe (GRAS) materials with established biocompatibility profiles. The degradation products of NLCs (lipid components) are physiological or readily metabolized, while PLGA degradation yields lactic and glycolic acids that enter endogenous metabolic pathways. Chitosan nanoparticles demonstrate excellent biocompatibility but may exhibit batch-to-batch variability due to natural polymer sourcing.

6.4. Targeting Capability

Surface functionalization for active targeting is well-established for both platforms. Polymeric nanoparticles offer greater chemical versatility for ligand conjugation through functional groups (carboxyl, amine, thiol) present on polymer chains or introduced during synthesis. NLCs can be functionalized through incorporation of PEG-lipid conjugates bearing terminal reactive groups or through post-formulation surface modification.

6.5. Clinical Translation Potential

Polymeric nanoparticles have achieved greater clinical penetration to date, with multiple FDA-approved formulations and numerous candidates in advanced clinical trials. The regulatory pathway for polymeric systems benefits from established precedent and well-characterized materials. NLCs, while extensively studied preclinically, have yielded fewer clinical candidates, though their favorable drug loading and scalability position them for increasing translational activity. Table 3 provides a comparative assessment of these platforms with clinical implications.

Table 3: Comparative Advantages and Limitations of Nanostructured Lipid Carriers and Polymeric Nanoparticles

Parameter	NLCs	Polymeric Nanoparticles	Clinical Implications
Drug loading capacity	High (20-40% for lipophilic drugs)	Moderate (5-15% typical)	NLCs preferred for poorly soluble chemotherapeutics
Physical stability	Good, minimal drug expulsion	Excellent with PEGylation	Both suitable for commercial formulation
Biocompatibility	Excellent (GRAS lipids)	Material-dependent (PLGA: excellent; others: variable)	PLGA and lipid systems have regulatory precedent
Targeting versatility	Moderate (surface modification possible)	High (multiple functional groups available)	Polymeric systems offer more targeting options
Scale-up feasibility	Good (homogenization methods established)	Moderate to good (method-dependent)	Both scalable with appropriate manufacturing
Clinical translation	Emerging (few approved products)	Established (multiple approvals)	Polymeric systems have clearer regulatory pathway

7. Challenges and Future Perspectives

7.1. Manufacturing Scale-up and Reproducibility

Translation of nanocarrier formulations from laboratory-scale to GMP manufacturing presents substantial challenges. Batch-to-batch reproducibility requires precise control over multiple parameters including particle size distribution, drug loading, and surface characteristics [38]. For NLCs, the high-pressure homogenization process is scalable but requires optimization of temperature cycles and homogenization parameters. Polymeric nanoparticle production by nanoprecipitation or emulsification-solvent evaporation faces challenges in achieving consistent particle properties at industrial scale. Quality-by-design approaches and process analytical technology implementation are essential for robust manufacturing.

7.2. Regulatory Considerations

Regulatory approval of nanomedicine products requires demonstration of safety, efficacy, and quality with particular attention to nanomaterial characterization. The complex, multi-component nature of stimuli-responsive nanocarriers presents challenges for establishing specification limits and stability-indicating methods [39]. Regulatory agencies have published guidance documents for nanomaterial-containing drug products, emphasizing the need for thorough physicochemical characterization and demonstration of product consistency.

7.3. Toxicity Concerns

While the materials comprising NLCs and polymeric nanoparticles are generally biocompatible, the nanoscale dimensions and surface properties may introduce unanticipated toxicity. Accumulation in mononuclear phagocyte system organs (liver, spleen) raises concerns regarding chronic toxicity, particularly for repeated-dose regimens. Stimuli-responsive elements—including pH-sensitive polymers and redox-labile linkages—must be evaluated for potential toxicity of degradation products. Comprehensive toxicological assessment incorporating both standard regulatory studies and nanomaterial-specific evaluations is required.

7.4. Personalized Nanomedicine

The heterogeneity of human tumors suggests that optimal nanocarrier design may vary among patients and even within individual tumors over time. Advances in tumor profiling and biomarker identification create opportunities for personalized nanomedicine approaches [40]. Selection of targeting ligands based on individual patient receptor expression, or choice of stimuli-responsive mechanism based on dominant TME characteristics of a particular tumor, could enhance therapeutic outcomes. Companion diagnostic approaches linking nanocarrier selection to tumor biomarkers represent a future direction for precision nanomedicine.

7.5. Future Design Strategies

Emerging directions in nanocarrier design include biomimetic approaches, where nanoparticles are coated with cell membranes derived from erythrocytes, immune cells, or cancer cells to achieve immune evasion and tumor targeting. Sequential or cascading release systems, where one trigger event enables subsequent responses, offer potential for multi-stage drug delivery. Integration of theranostic capabilities—combining therapy with real-time imaging—enables treatment monitoring and dose adjustment. These innovations, combined with continued optimization of TME-responsive mechanisms, will advance the clinical utility of nanocarrier-based cancer therapy.

8. Conclusion

Nanostructured lipid carriers and polymeric nanoparticles represent sophisticated platforms for targeted anticancer drug delivery, offering distinct advantages in drug loading, controlled release, and biocompatibility. The integration of TME-responsive elements—harnessing acidic pH, redox gradients, enzymatic activity, and hypoxic conditions—enables site-specific drug liberation that enhances therapeutic efficacy while minimizing systemic toxicity. Comparative evaluation reveals that NLCs excel in lipophilic drug loading and formulation simplicity, while polymeric nanoparticles offer greater chemical versatility and established clinical precedent. The selection between platforms should be guided by specific therapeutic requirements, drug physicochemical properties, and target tumor characteristics. Despite challenges in manufacturing scale-up, regulatory approval, and toxicity assessment, the continued evolution of these technologies—particularly through multi-stimuli responsive designs and personalized approaches—positions them as transformative modalities in oncological therapeutics. The translation of these innovations from preclinical development to clinical practice holds promise for improving outcomes for patients with solid malignancies.

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