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Mechanistic Design and Engineering of Nanocarrier Systems for Targeted Drug Delivery: Fabrication Strategies and Therapeutic Applications

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ABSTRACT: Despite significant advances in technology and medical sciences, and substantial investment in drug discovery by the pharmaceutical industry, the clinical success of therapeutic agents for cancer and chronic diseases remains limited. Poor aqueous solubility, low bioavailability, rapid systemic clearance, and restricted access to target tissues continue to compromise therapeutic outcomes. Nanocarrier-based drug delivery systems have emerged as rationally engineered platforms capable of overcoming these limitations through controlled release, enhanced tissue accumulation, and improved pharmacokinetic profiles. This review provides a critical overview of recent developments in the mechanistic design, fabrication strategies, and therapeutic relevance of polymeric, lipid-based, inorganic, and hybrid nanocarriers for spatially and temporally controlled drug delivery. Particular emphasis is placed on understanding structure–function relationships that govern drug encapsulation, stability, safety, biological interactions, barrier penetration, and target specificity, including strategies to overcome the tumour microenvironment and the blood–brain barrier. Fundamental fabrication approaches such as nanoprecipitation, double emulsion techniques, surface functionalization, and stimuli-responsive systems are discussed in relation to therapeutic performance. Translational considerations including scale-up feasibility, regulatory challenges, and safety assessment are also addressed. Although substantial preclinical progress has been achieved, further standardization and integration of quality-by-design principles are essential to enable reliable clinical translation and precision therapeutics.

1. INTRODUCTION

The development of new chemical entities (NCEs) and drug delivery systems continues to address major challenges associated with poor aqueous solubility, low bioavailability, and extensive first-pass metabolism. More than 90% of the drugs from the pre-clinical trials phase get rejected for the clinical settings due to the poor aqueous solubility, limited permeability, and suboptimal pharmacokinetic profiles, which leads to huge loss to the R&D sectors of pharmaceutical industries [1]. According to recent estimates, nearly 60–70% of newly identified drug candidates fall under Biopharmaceutics Classification System (BCS) Class II and 10-20% for BCS Class IV categories, characterized by poor aqueous solubility. These physicochemical limitations are the concessions for oral bioavailability, therapeutic efficacy, and clinical translation [2]. Lipowski was first introduced a patent for oral formulations by sustaining the drug release formulation using enteric coating polymers in 1951 [3]. The expiration

of pharmaceutical patents and subsequent approval of abbreviated new drug applications (ANDAs) have also encouraged interest in re-engineering conventional drugs into novel drug delivery systems (NDDS) [4]. In recent years, advances in nanomaterials and their application to therapeutic delivery have opened new opportunities for the development of advanced drug delivery systems. These nanocarriers are capable of modulating pharmacokinetics, enhancing bioavailability, and enabling site-specific drug accumulation [5].

In 1955 first polymer–drug conjugate was prepared by Jatzkewitz's in the form of nanoparticles, followed by this the first liposome was discovered that initiates the era of nanotechnology. In 1972, first protein-based microspheres developed by Scheffel and thereafter Peter Paul Speiser's research labs formed microcapsules in 1976 [3]. From their inception in the 1960s to the advanced breakthroughs of 2026, nanocarriers have evolved from basic lipid structures into highly intelligent, "programmable" delivery systems. The journey began with organic nanocarriers, led by liposomes and followed by polymeric micelles, dendrimers, and nanogels, all designed to improve the solubility and stability of drugs. This field reached a globa1 turning point with lipid nanoparticles (LNPs), which became the gold standard for mRNA delivery during the early 2020s [6]. Alongside these organic platforms, inorganic nanocarriers emerged, utilizing materials like mesoporous silica, silver (AgNPs), gold (AuNPs) nanoparticles, quantum dots (QDs) or semiconductor nanocrystals, and superparamagnetic iron oxide nanoparticles (SPIONs) to provide unique imaging and heat-triggering, drug targeting capabilities. In the current scenario, the focus has shifted toward biological and hybrid systems, including exosomes and cell-membrane- particles that "hide" from the immune system [7], [8], [9]. Modern medicine now researches to deliver DNA, RNA for the correction of the neurological disorders, in the year 2025 noble prize work of metal-organic frameworks (MOFs), building a diverse delivery system that allows for the precise, stimulus-responsive targeting of genetic material and protein therapies directly to diseased cells [10].

Conventional dosage forms such as tablets, capsules, solution and suspensions rely primarily on passive diffusion process and bulk pharmacokinetics; non target, drug accumulations, adverse action precipitations, in contract to the nanocarrier systems which works based on functional nano–bio interface, where their biological performance is dictated by dynamic interactions with physiological components and target-sites [11]. Building upon the initial interaction at the nano–bio interface, the transition from systemic circulation to cellular entry is governed by physicochemical forces and biological interactions. Nanocarrier that reaches the target site, get interact with biological membranes through the electrostatic forces, receptor-mediated binding, and hydrophobic interactions. These cell-cell membrane fusion mechanisms are highly sensitive to the nanoparticle's surface charge, which dictates initial membrane affinity, and its surface ligands, that provide the high-affinity "lock and key" precision necessary for receptor-specific drug targeting [12]. Parenteral administration of nanoparticles immediately encounters a complex biological milieu of plasma proteins (albumin, glycoproteins), lipids, and immune cells, leading to the rapid formation drug-target binding. Additionally, dynamic adsorption layer of drug-protein at in the blood stream effectively masks the nanoparticle's synthetic surface, providing it with a "biological identity" that significantly maps its circulation time, bio distribution, and immune clearance via the mononuclear phagocyte system. As body interacts with this acquired drug encapsulated biomolecules rather than the underlying material, nanocarrier functionality is governed not solely by its intrinsic chemical composition but also by emergent properties resulting from these complex nano–bio interactions [6], [13]. Consequently, optimizing therapeutic efficacy requires engineering the surface modifications, such as, conjugations, PEGylation, to minimize non-specific protein adsorption and maintain the integrity of the intended targeting mechanisms within the physiological environment. By deploying these surface characteristics, researchers can enhance the carrier's ability to bypass the cellular lipid bilayer, transforming the nanodevice from a passive dose-dependent transporter into an active agent capable of precise spatial localization [14].

The challenges of nanocarriers laying mainly on the selection of the biocompatible precursors, loading of drugs-encapsulations and specific cellular internalization pathways triggered by the particle's geometric and structural properties. Physicochemical properties of the nanocarriers such as particle size, surface charges, polydispersity, drug-polymer interactions serve as biological interface that steer the carrier toward distinct endocytic routes, including clathrin-mediated endocytosis for smaller particles or macropinocytosis and phagocytosis for larger or irregularly shaped aggregates [15]. Consequently, the engineering of controlled physicochemical factors remains the foundation of developing effective, next-generation nanomedicine platforms. This level of precision is necessary to move beyond the high variability often seen in early-stage nanocarriers, where minor deviations in zeta potential or ligand density could lead to drastic changes in biodistribution and immunogenicity [16]. This transition is very important for clinical usage, as it allows for the development of highly reproducible DDSs that can navigate the body's complex physiological barriers with high specificity, ultimately reducing off-target toxicity and improving patient outcomes. Furthermore, the structural architecture of nanocarriers determines drug loading mechanisms, whether through physical entrapment,

adsorption, covalent conjugation, or self-assembly and subsequently influences release behavior and kinetics mechanisms [17]. Hydrophobic drugs especially biopharmaceutical classification BCS class II and IV may be incorporated into lipid bilayers or polymeric matrices, whereas hydrophilic molecules BCS class I and III can be encapsulated within aqueous cores or chemically conjugated to polymeric backbones or core. Controlled release of the drug can be achieved through diffusion, matrix degradation, erosion, swelling, or stimuli-responsive mechanisms triggered by pH, redox gradients, enzymes, or temperature changes by using thermos responsive polymers [18].

Interdisciplinary nature of nanocarrier systems spots them at the merging of materials science, pharmaceutical engineering, and molecular biology. Materials science contributes to polymer synthesis, lipid engineering, and surface chemistry modification; pharmaceutical engineering enables scalable fabrication techniques such as nanoprecipitation, double emulsion, high-pressure homogenization, and microfluidics; while molecular biology provides insights into receptor targeting, intracellular trafficking, and disease-specific micro environmental conditions. Collectively, the ability to rationally design nanocarriers at both physicochemical and biological levels enables modulation of pharmacokinetics, prolongation of systemic circulation, reduction of adverse effects, and enhancement of site-specific drug accumulation [3], [4], [20]. However, achieving reproducible nano–bio interactions and predictable *in vivo* behavior remains a critical challenge, necessitating deeper mechanistic understanding and standardized characterization methodologies. Despite significant advancements, translational success for the clinical implications remains restricted due to challenges in scalability, reproducibility, toxicity assessments, and regulatory approval. Therefore, a mechanistic and engineering-oriented framework is essential for rational nanocarrier design [21-22].

This review aims to provide a comprehensive and critical evaluation of the mechanistic design principles governing nanocarrier systems for targeted drug delivery for precise delivery, with particular emphasis on the integration of materials engineering, fabrication technologies, and therapeutic applications.

Further, this work aims to bridge the gap between laboratory-scale innovation and clinical translation by offering a mechanistically grounded, engineering-oriented outline for the rational design of next-generation nanocarrier systems. This article provides strategic direction for researchers, formulation scientists, and regulatory professionals working toward precision-based therapeutic delivery platforms. However, despite decades of research, a mechanistically unified framework linking fabrication engineering parameters to the therapeutic performance remains insufficiently addressed in research scientific domains. This review addresses this gap

2. MECHANISTIC APPROACHES FOR TARGETED DRUG DELIVERY SYSTEMS

Targeted drug delivery systems (TDDS) using nanocarriers are governed by coordinated physicochemical and biological interactions that determine drug distribution, accumulation, cellular uptake, and intracellular release. However, conventional dosage forms depend primarily on passive diffusion and systemic pharmacokinetics, therefore, nanocarriers are engineered to navigate complex physiological cell membrane barriers and respond dynamically to pathological environments and disease targets. Their biological performance is influenced by numerous factors such as particle size, shape, surface charge, composition, and environmental responsiveness. A mechanistic understanding of these interrelated parameters is essential for rational drug design, DDS and clinical significance [23].

2.1 Passive targeting and pathophysiological exploitation

Passive targeting is primarily based on the natural mechanisms; structural and physiological abnormalities present in diseased tissues, particularly solid tumors. Development of DDS to shift from systemic circulation to tumor accumulation is strongly influenced by the unique and often hostile tumor microenvironment. Tumor vasculature is characterized by irregular endothelial architecture, defective cell-cycle, and enlarged fenestrations, which permit nanoparticles within an optimal size range typically (10–200 nm) to extravasate into the tumor interstitium. This phenomenon is widely attributed to the enhanced permeability and retention (EPR) effect as reported by Vagena. In addition to increased vascular permeability, compromised lymphatic drainage within tumors contributes to prolonged nanoparticle retention, thereby enhancing local drug concentration. However, once a nanocarrier extravasates from the leaky vasculature, it must navigate a dense extracellular matrix, elevated interstitial fluid pressure, and heterogeneous stromal architecture before reaching malignant cells. These physical barriers significantly influence intratumoral distribution and therapeutic penetration depth [22], [23].

At the cellular level, passive accumulation alone does not guarantee effective internalization and target site drug binding. Nanocarriers must interact with tumor cell membranes through electrostatic interactions or engage with overexpressed surface

receptors to initiate cytotoxic drug uptake. However, the physiological heterogeneity of solid tumors; including variations in receptor expression, hypoxic regions, and immune infiltration exhibits additional complexity. Therefore, while passive targeting facilitates preferential tumor accumulation, its efficiency is highly dependent on tumor biology and nanoparticle physicochemical design. Precise engineering of particle size, surface chemistry, and hydrophilicity is essential to maximize deposition while minimizing premature clearance and drug loss.

2.2 Active targeting and ligand–receptor mechanisms

Active targeting enhances specificity through surface functionalization of nanocarriers with ligands capable of binding selectively to overexpressed receptors on diseased cells. These ligands may include monoclonal antibodies, peptides, aptamers, folate derivatives, transferrin, or small-molecule receptor binders, labelled conjugates. Ligand receptor interaction of nanocarriers undergo receptor-mediated endocytosis, facilitating enhanced intracellular drug delivery and spatial drug effect. Spada in their study reported the surface modification of nanocarriers with anti- epidermal growth factor receptor (EGFR) ligands could be used to kill cancer cells in the form of active targeting [24].

The efficiency of active targeting depends on multiple mechanistic parameters, including ligand density, binding affinity, spatial orientation, and conjugation, binding bond stability. Excessive ligand loading may increase opsonization and immune recognition, whereas insufficient ligand density compromises targeting efficiency. Moreover, active targeting often functions synergistically with passive accumulation; without adequate tissue deposition, receptor-mediated uptake remains limited. Thus, surface engineering requires a delicate balance between targeting specificity and systemic stealth characteristics.

2.3 Stimuli-responsive targeting approaches

To overcome limitations associated with passive and active targeting, stimuli-responsive nanocarriers have been developed to enable target temporal control over drug release. These systems are also called as smart drug delivery systems (SDDSs) designed to respond to endogenous triggers such as acidic tumor pH, elevated intracellular glutathione concentrations, enzymatic overexpression, or hypoxic microenvironments. Exogenous stimuli including temperature, magnetic fields, ultrasound, and light irradiation may also be employed to activate drug release selectively at target sites, sometime by using magnets in case of magnetic responsive nanoparticles or SPIONs.

Review of Rana explains the stimuli-responsive systems could be smartly utilized in the future of translational medicines to get the maximum benefits by efficiently deploying nanocarriers for the effective treatment across a wide range of disorders [25]. Mechanistically, stimuli-responsive systems incorporate cleavable chemical linkers, redox-sensitive disulfide(s-s) bonds, thermosensitive polymers (Pluronic F-127), or photo responsive chromophore groups that undergo structural transformation upon exposure to specific triggers. This controlled destabilization ensures localized drug release while minimizing premature systemic leakage, thereby enhancing therapeutic precision and safety.

2.4 Nano–Bio interface and biomolecular core developments

Parenteral administration of nanocarriers immediately interact with plasma proteins and other biomolecules, leading to the formation of a dynamic biomolecular radiance. This surface-bound biological layer confers an acquired biological identity that governs subsequent immune recognition, biodistribution, and clearance mechanisms. The composition of this adsorption layer is influenced by nanoparticle surface chemistry, charge density, hydrophobicity, and shape, curvature. The biomolecular entity may mask targeting ligands and alter surface characteristics, thereby affecting receptor-mediated specificity. Zhu, exploration of the nanocarriers for intracellular delivery of protein drugs was widely reviewed to apply the nano sized carriers in biomedical field particularly for cancer treatment, gene editing and imaging utilized in the diagnostic studies [26].

Additionally, it plays a crucial role in complement activation and uptake by the mononuclear phagocyte system. Surface engineering strategies such as PEGylation, zwitterionic coatings, are therefore applied to regulate biomolecular adsorption and prolong systemic circulation for long duration action especially in chronic disease conditions. However, understanding and controlling nano–bio interactions remain critical for predictable *in vivo* behavior.

2.5 Cellular internalization and intracellular interactions

After drug accumulating at the target site, nanocarriers must transverse through lipoidal cell membranes to efficiently deliver loaded therapeutic for effective treatment. Internalization occurs through various endocytic pathways, including endocytosis

mediated uptake, macropinocytosis, and phagocytosis. Particle size, geometry, and surface chemistry influence the preferred uptake mechanism. Following endocytosis, nanocarriers are typically transported into endosomal and lysosomal compartments, where acidic environments may compromise drug stability. Successful intracellular delivery therefore often requires mechanisms for endosomal escape, such as the proton sponge effect, membrane-disruptive peptides, pH-sensitive destabilization, or lipid fusion strategies. Advanced nanocarriers may also incorporate organelle-targeting signals to direct therapeutic agents to specific subcellular locations, further enhancing efficacy [26], [27].

3. ENGINEERING AND FABRICATION STRATEGIES OF NANOCARRIERS

Therapeutics success of nanocarrier systems depends on fabrication technologies, as preparation processes determine particle size, surface charge, morphology, drug loading capacity, and release kinetics. Fabrication is therefore not merely a technical preparation step but a mechanistically governed design strategy that directly influences nano–bio interactions and therapeutic outcomes. The formation of nanocarriers is driven by physicochemical principles including solvent diffusion, interfacial tension modulation, polymer precipitation, electro hydrodynamic forces, crosslinking reactions, and colloidal stabilization dynamics. A comprehensive understanding of these mechanisms is essential to ensure reproducibility, scalability, and translational feasibility [28].

3.1 Nanoprecipitation: Diffusion-driven nucleation and stabilizations

Nanoprecipitation, also called as solvent displacement, is a widely employed bottom-up technique for preparing polymeric nanoparticles, particularly for hydrophobic BCS class II and IV drugs. The mechanism is governed by rapid solvent diffusion and super saturation-induced nucleation. In this process, a biodegradable polymer and drug are dissolved in a water-miscible organic solvent and subsequently introduced into an aqueous phase containing stabilizing agents (surfactants). Dispersion with the aqueous medium, the organic solvent rapidly diffuses outward, reducing polymer solubility and generating transient super saturation. This condition promotes spontaneous nucleation of nanoscale polymer aggregates [29].

Particle growth is controlled by diffusion kinetics and adsorption of stabilizers onto the forming particle surface, which prevent uncontrolled aggregation through steric or electrostatic repulsion. Thermodynamically, the system minimizes Gibbs free energy by reorganizing polymer chains into energetically favorable nanostructures. The final particle size and polydispersity are strongly influenced by engineering parameters such as polymer concentration, solvent-to-antisolvent ratio, injection speed, mixing intensity, and surfactant concentration. Rapid and homogeneous mixing favors uniform nucleation, producing particles with narrow polydispersity index. Nanoprecipitation is advantageous due to its simplicity, mild processing conditions, and scalability; however, its efficiency decreases for hydrophilic drugs due to their preferential diffusion into the aqueous phase.

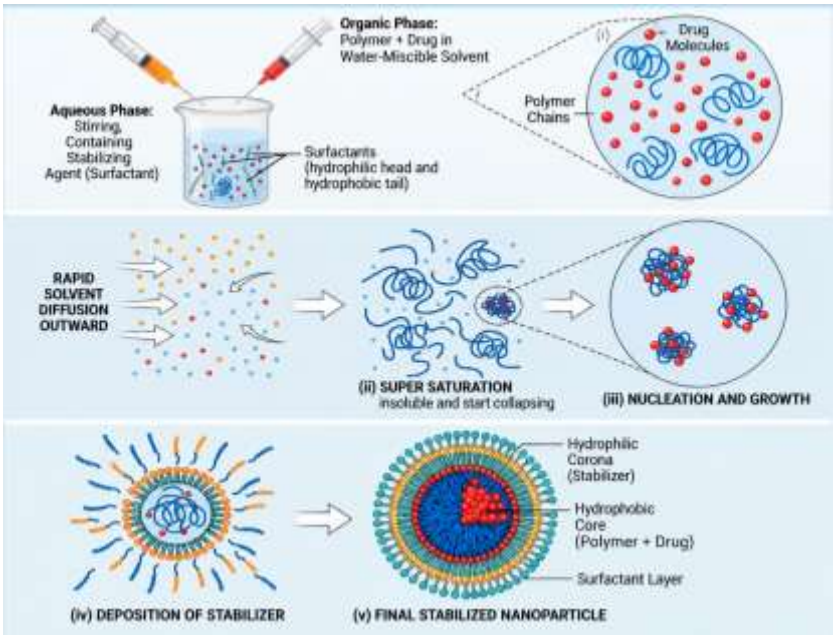


Figure 1. Nanoprecipitation Mechanism

3.2 Double emulsion solvent evaporation: interfacial engineering for hydrophilic drug loadings

The double emulsion solvent evaporation technique is specifically designed to encapsulate hydrophilic therapeutic molecules such as peptides, proteins, and nucleic acids. This method involves the sequential formation of a primary water-in-oil (W/O) emulsion followed by re-emulsification into a secondary aqueous phase, generating a W/O/W multiple emulsion system. Initially, the internal aqueous drug solution is dispersed within a polymer-containing organic phase under high shear or probe-sonication, forming aqueous droplets of nano size, stabilized within the organic matrix using stabilizers or combination of surfactants. This primary emulsion is then emulsified into an external aqueous phase containing surfactants, creating the double emulsion.

The mechanistic basis of this process lies in interfacial tension gradients and shear-induced droplet breakup dynamics. Organic solvent evaporation or diffusion into the aqueous phase, the polymer precipitates and solidifies around the internal aqueous droplets, entrapping the drug. Encapsulation efficiency is governed by osmotic pressure differences, drug partitioning between internal and external phases, solvent volatility, and stabilizer concentration. Precise engineering control over homogenization speed, sonication watt/time, phase volume ratios, and emulsifier selection is critical for achieving uniform particle nano size and minimizing drug leakage. Emerging microfluidic technologies have improved droplet uniformity and reproducibility, addressing scale-up limitations associated with conventional emulsification methods of aqueous titration [30].

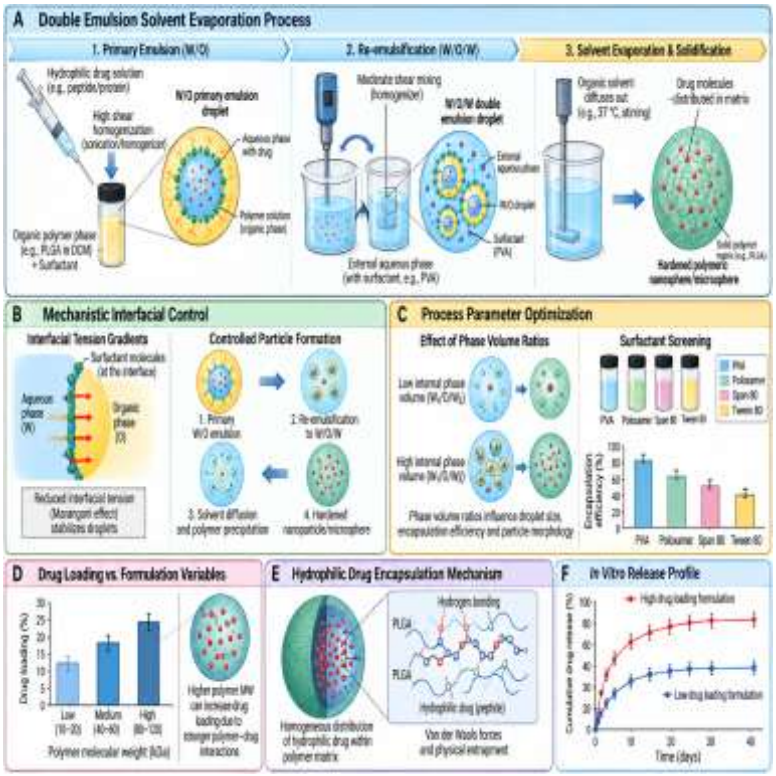


Figure 2. Double Emulsion (W/O/W) Mechanism

3.3 Crosslink cyclodextrin nanosponges: Network and porosity engineering

Besides ethyl cellulose nanosponges, cyclodextrin nanosponges (CNs) represent a unique class of cross-linked polymeric nanocarriers characterized by a three-dimensional porous architecture. Their formation is governed by covalent crosslinking reactions between hydroxyl groups of cyclodextrin molecules and bi-functional crosslinking agents such as diphenyl carbonate (DPC), carbonyldiimidazole (CBI), or epichlorohydrin. The reaction proceeds through nucleophilic substitution or condensation mechanisms, resulting in carbonate, ether, or ester linkages that form an interconnected polymeric network. Excess of cross linker can be removed using organic solvent by soxhlet extractions followed by aqueous washing multiple times.

The crosslinking density determines the structural and functional properties of the nanosponge, including pore size distribution, surface area, swelling capacity, and mechanical stability. Drug loading occurs via multiple mechanisms, including inclusion complex formation within the hydrophobic cavity of cyclodextrin units and adsorption within the porous network through hydrogen bonding or van der Waals interactions. Engineering control of molar ratios, reaction temperature, solvent system, and curing duration allows fine-tuning of network architecture and drug release kinetics. Higher crosslinking produces density typically results in smaller pore size and prolonged drug release, making nanosponges suitable for sustained and controlled delivery applications besides showing relatively higher entrapment efficiency due to the porousness compared to the nanoparticles [31]. Fatima & Anwer has successfully developed the nanosponges using the ethyl cellulose and polyvinyl alcohol as the stabilizer for assessed it against the MCF-7 cell lines and showed potential anticancer effect of ibrutinib in the breast cancer treatment [32].

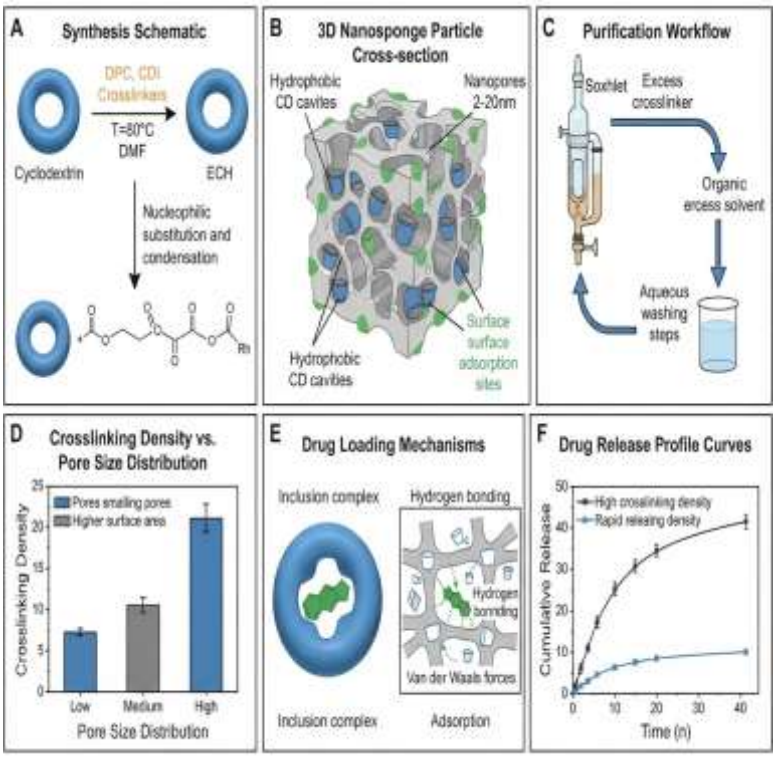


Figure 3. Cyclodextrin Nanosponge Crosslinking Chemistry

3.4 Electrospinning: Fiber formation and control

Besides the centrifugal spinning, electrospinning widely used in the research labs works on electro hydrodynamic technique that produces nano fibrous drug delivery systems (NFDDS) with exceptionally high surface area-to-volume ratios. The mechanism is governed by the interplay between electrostatic forces and surface tension at the polymer solution interface. When a high voltage is applied to a polymer solution. Once electrostatic forces exceed surface tension, a charged jet is ejected and undergoes elongation and whipping instabilities during its travel toward a grounded collector. Simultaneously, rapid solvent evaporation leads to the formation of solid nanofibers.

Fiber morphology and diameter are determined by solution viscosity, polymer concentration, electrical conductivity, applied voltage, flow rate, and tip-to-collector distance. Drug incorporation may occur via molecular dispersion within the polymer matrix or through core–shell architectures in coaxial electrospinning systems. The release profile from electrospun fibers is governed by polymer degradation rate, fiber porosity, drug-polymer compatibility, and diffusion pathways. This method enables the engineering of immediate, sustained, or stimuli-responsive drug delivery platforms, particularly suitable for transdermal, buccal, wound healing, and implantable applications. The technique has the advantages if ease of preparation, pilot-scale up

and low cost technology [33]. Alamer experimented on the sildenafil-glycyrrhizin-loaded nanofibers and showed the novel buccal delivery that elicits the quick action as needed for the erectile dysfunction conditions [34].

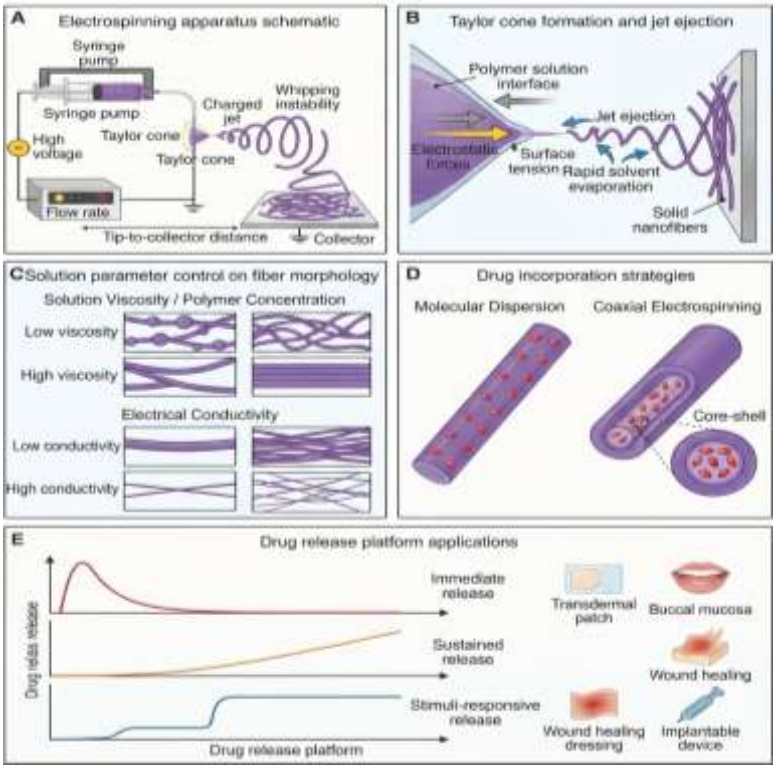


Figure 4. Electrospinning Fiber Formation

3.5 Nanoemulsion formation: Interfacial stabilization of colloidal dispersions

Unlike conventional emulsions, nanoemulsions are kinetically stable dispersions of immiscible liquids with droplet sizes typically below 200 nm. Their formation relies on high-energy input such as high-pressure homogenization or probe-ultrasonication, or on low-energy spontaneous emulsification techniques. The stability of nanoemulsions depends largely on the reduction of interfacial tension and the formation of a protective interfacial film by surfactants. Although nanoemulsions are thermodynamically metastable systems, kinetic stabilization mechanisms delay destabilization processes including flocculation, coalescence, and Ostwald ripening. Engineering factors such as surfactant concentration, hydrophilic-lipophilic balance, oil phase composition, and homogenization pressure critically influence droplet size and long-term stability. Mixtures of surfactants may be used to improve interfacial stabilization and maintain droplets within the nanometer size range. Nanoemulsions are particularly effective for enhancing the solubility and absorption of lipophilic drugs and may facilitate lymphatic uptake, thereby improving systemic bioavailability [35].

Collectively, these emulsification methods illustrate how the process and its parameters can directly affect the physicochemical properties of the nanocarriers, including their particle size, surface characteristics, internal structure, and release profile. These parameters then determine the nano–bio interactions, pharmacokinetics, biodistribution, and therapeutic efficacy. Thus, rational fabrication design is key to the development of targeted and stimuli-responsive delivery systems. Reproducibility and scalability are essential for these fabrication processes to be successful for clinical translation.

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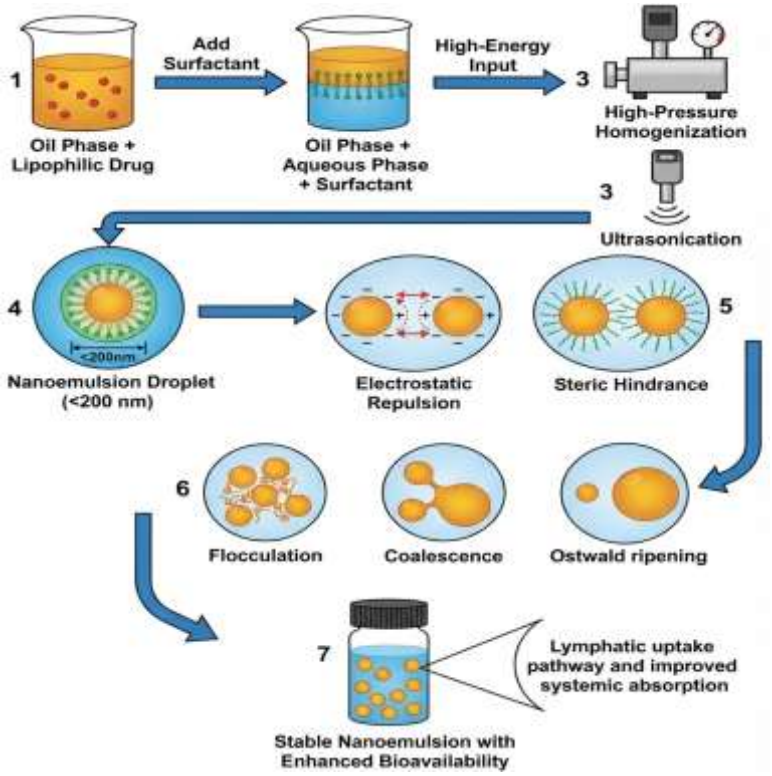


Figure 5. Nanoemulsion Stabilization Mechanism

4. Therapeutic implications of engineered nanocarrier

Engineered nanocarrier systems have demonstrated broad therapeutic applications in medical sciences; oncology, neurological disorders, and infectious diseases. The integration of fabrication strategies with mechanistic targeting principles has enabled the translation of physicochemical design into improved pharmacokinetic performance and therapeutic efficacy. To systematically summarize representative applications, recent literature is organized below according to nanocarrier platform and therapeutic focus.

Table 1. Engineered nanocarriers in oncology

Article Focus	Drug	Nanocarrier System	Engineering Strategy	Therapeutic Evaluation	Ref
PLGA nanoparticles for anticancer therapy	Doxorubicin	PLGA nanoparticles stabilized with bovine serum albumin	Nanoprecipitation	Particle size, release, cytotoxicity- MDA-MB-231 breast cancer cells	36
Polymer nanoparticles for anticancer activity	Doxorubicin	PLGA / PLGA-PEG	Solvent displacement / emulsion	Drug release, cell viability, uptake, ABCB1-expressing cell lines	37
Optimized targeted PLGA nanoparticles	Doxorubicin	PLGA	Single emulsion solvent evaporation	Size, entrapment efficiency, release	38
NIR-triggered cancer therapy	Doxorubicin	PLGA nanoparticles	Polymer synthesis + conjugation	Tumor size reduction, histology, *in vivo* response	39

Magnetic targeted therapy	Doxorubicin	Superparamagnetic iron oxide nanoparticles	Electrostatic drug loading	MTT assay, uptake, cell cycle analysis	40
Reduction-sensitive delivery	Paclitaxel	Dextran polymer conjugate nanoparticles	Polymer–drug conjugation + self-assembly	Drug release, cytotoxicity	41
Paclitaxel targeted lung cancer therapy	Paclitaxel palmitate	Cetuximab-conjugated PLGA NPs	Antibody conjugation (thioether bonds)	Efficacy of targeting	42
Aptamer-targeted prostate cancer	Doxorubicin	Aptamer-conjugated unimolecular micelles	Ligand conjugation + pH-sensitive release	Cellular uptake, apoptosis	43
HER2-targeted breast cancer	Doxorubicin	Grapefruit-derived nanovectors + HER2 aptamer	Aptamer conjugation	Tumor accumulation, *in vivo* efficacy	44
Folate-targeted breast cancer	Erlotinib	Folic acid-conjugated β-lactoglobulin NPs	Surface conjugation	Apoptosis induction	45
FA-conjugated thermoresponsive NPs	5-Fluorouracil	FA-PHEA-b-PNIPAAm nanoparticles	RAFT polymerization	Cytotoxicity, targeting	46
Conjugated gold nanoparticles	Doxorubicin	Gold nanoparticles + oligonucleotide	Gold conjugation	Apoptosis, colorectal cancer therapy	47
Cremophor-free anticancer delivery	Paclitaxel	Cyclodextrin nanosponge	Drug loading into nanosponge	*In vitro* anticancer activity	48

Table 2. Nanocarriers in anti-inflammatory and rheumatic disorders

Article Focus	**Drug**	**Nanocarrier**	**Engineering Strategy**	**Evaluation**	**Ref**
Site-retentive nanogel for arthritis	Methotrexate	β-cyclodextrin nanosponge + gel	Crosslinking + gel incorporation	*In vivo* inflammation model	49
COX-2 inhibitor topical gel	Lumiracoxib	Cyclodextrin nanosponge + gel	Drug-loaded nanosponge gel	Ex vivo permeation, cytotoxicity	50
Anti-inflammatory semisolid delivery	Diclofenac	β-CD nanosponge	Crosslinking + gel incorporation	Skin permeation	51
NSAID transdermal nanoemulsion	Diclofenac	Oil-in-water nanoemulsion	Phase inversion emulsification	Skin permeation	52

Table 3. Nanocarriers for oral bioavailability enhancement

Article Focus	Drug	Carrier System	Engineering Strategy	Evaluation	Ref
Oral atorvastatin enhancement	Atorvastatin	β-CD nanosponge (CDI crosslinked)	Crosslinking + drug complexation	Dissolution, PK study	53
Rosuvastatin bioavailability	Rosuvastatin	β-CD nanosponge (PDA crosslinked)	Crosslinking + lyophilization	*In vivo* oral PK	54
Griseofulvin dissolution enhancement	Griseofulvin	β-CD nanosponge (DPC crosslinked)	Ultrasonication crosslinking	Dissolution, bioavailability	55
Curcumin oral nanofibers	Curcumin	PVP nanofibers	Electrospinning	Dissolution enhancement	56
SNEDDS formulation	Cyclosporine	Lipid SNEDDS	Self-emulsification	Bioavailability	57
Ibuprofen nanoemulsion	Ibuprofen	Lipid nanoemulsion	Ultrasonication	Dissolution, PK	58
Vitamin D nanoemulsion	Vitamin D	Lipid nanoemulsion	Homogenization	Stability, release	59

Table 4. Nanocarriers in CNS and brain targeting

Article Focus	Drug	Nanocarrier	Engineering Strategy	Evaluation	Ref
Intranasal brain targeting	Rivastigmine	Lipid nanoemulsion	Spontaneous emulsification	BBB penetration, brain uptake	60
Intranasal direct transport	CNS actives	Nanoemulsion	Nose-to-brain	Rapid CNS delivery	61

Table 5. Nanocarriers in antimicrobial and peptide delivery

Article Focus	Drug	Nanocarrier	Engineering Strategy	Evaluation	Ref
Antibacterial wound dressing	Gentamicin	Chitosan nanofibers	Electrospinning	Antibacterial assay	62
Tetracycline antibacterial therapy	Tetracycline	PCL nanofibers	Electrospinning	Release kinetics	63
Clotrimazole antifungal nanoemulsion	Clotrimazole	Oil nanoemulsion	Ultrasonication	MIC test	64
Econazole topical hydrogel	Econazole nitrate	β-CD nanosponge + hydrogel	Melt method + gel formulation	Skin permeation	65
Insulin oral delivery	Insulin	CPP-modified PLGA nanoparticles	Peptide conjugation	*In vivo* glucose reduction	66
Colon-targeted insulin	Insulin	Tat-modified PLGA nanoparticles	Surface peptide modification	Caco-2 uptake, SPECT imaging	67
Peptide-grafted chitosan NPs	Insulin	Chitosan nanoparticles	Ionic gelation	*In vivo* efficacy	68
BMP-2 biomolecule delivery	BMP-2	PLGA nanoparticles	Double emulsion	Cell proliferation	69

Collectively, all these studies demonstrate that fabrication-driven control of nanoscale physicochemical properties directly influences therapeutic performance. The mechanistic integration of particle engineering, surface functionalization, and biological targeting reinforces the clinical relevance of nanocarrier systems across diverse disease models.

5. Translational and regulatory challenges of nanocarriers in clinical settings

5.1 Scale-Up and manufacturing reproducibility

Most significant recapitulation barriers in nanomedicine is the difficulty of scaling laboratory preparation methods into reproducible, industrial-scale manufacturing processes. Aforementioned fabrication techniques, such as nanoprecipitation, double emulsion, and electrospinning, are highly complex to process parameters including mixing rate, sonication-power/time, shear force, temperature, and solvent evaporation time and kinetics. Minor variations in these parameters can lead to substantial changes in particle size, polydispersity index (PDI), zeta potential, drug loading efficiency, and release kinetics profiles. Batch-to-batch variability poses a critical challenge for regulatory approval, as consistent physicochemical parameters are required by the international drug agencies to ensure predictable pharmacokinetics and therapeutic performance. Techniques such as microfluidic-assisted fabrication have been recently proposed to improve reproducibility and scalability [70], [71], [72].

5.2 Nano-Bio interactions and *in vivo* unpredictability

Nanocarriers are engineered with defined physicochemical attributes; however, their biological behavior following systemic administration may differ substantially from their intended design characteristics. Parenteral administration of nanoparticles interacts with bio components, dynamically with plasma proteins majorly albumin, lipoproteins, and immune components, resulting in the formation of an adsorbed biomolecular layer that alters surface characteristics and cellular recognition and targets-sites. This phenomenon can modify biodistribution, cellular uptake, clearance rates, drug delivery efficiency and targeting effectiveness. Nanocarriers optimized under controlled *in vitro* conditions may exhibit altered behavior *in vivo* due to immune recognition, opsonization, or rapid clearance by the mononuclear phagocyte system. Therefore, a deeper mechanistic understanding of nano–bio interactions is required to improve predictive modeling and translational reliability [73-77].

5.3 Toxicological and immunological concerns

The long-term safety of nanocarriers remains an important concern in nanomedicine development, particularly because standardized approaches for evaluating chronic toxicity and immunological effects remain limited. Although a wide variety of nanocarriers are prepared using naturally derived, biodegradable, or biocompatible polymers or lipids, but concerns remain unanswered regarding dose-dumping, chronic toxicity, and immunogenicity. Nanocarriers may induce oxidative stress, particularly in the liver and spleen. Additionally, surface modifications by certain polymers for intended enhance targeting may alter immunological recognition. Comprehensive safety-toxicological assessment, including pharmacokinetics, biodistribution studies, immunotoxicity evaluation, and chronic exposure analysis, is necessary to ensure clinical safety and patient compliance [78].

5.4 Regulatory classification and standardization

Regulatory evaluation to get the marketing approvals by international agencies for nanocarrier systems remains complex because of their diverse compositions, structures, biological interactions, and limited regulatory precedent. Current regulatory frameworks may not fully accommodate the complex and evolving characteristics of nanomedicines. Standardization of characterization techniques and evaluation processes is essential for regulatory acceptance. However, the lack of universally harmonized guidelines such as ICH for nanocarrier characterization creates variability in regulatory expectations across different regions including GCC [79].

5.5 Quality-by-Design and rational engineering for clinical set-up

To bridge the gap between laboratory innovation, formulation design and clinical significance, a systematic Quality-by-Design approach is essential for the safe usage of drug entity. QbD integrates risk assessment, design management, and process optimization to ensure consistent product quality with less defects and failures. In nanocarrier development, this involves defining critical material attributes (CMAs) and critical process parameters (CPPs) that influence critical quality attributes (CQAs), such as particle size, polydispersity index (PDI), surface charge, functionality, and drug release kinetics. Mechanistic understanding of nanoformulation fabrication processes enables rational design of scalable systems (commercial production)

with predictable *in vivo* performance. Advanced analytical tools, real-time monitoring technologies, and AI-integrated, computational modeling further support process control and optimization [80].

6. FUTURE PERSPECTIVES

Future advances in nanocarrier-based drug delivery are expected to shift toward intelligent, adaptive, and precision-engineered systems that synchronized with the materials science, cellular biology, and computational pharmacodynamics and pharmacokinetic modeling. Emerging platforms of these nanocarriers are increasingly designed to be stimuli-responsive, temporal –target based, capable of releasing therapeutic drug load in signaling with pH, antigen, cell-signal, redox gradients, enzymatic degradation, or external triggers such as temperature, magnetic field, thereby enhancing spatial and temporal control to the drug delivery. Personalized nanomedicine, supported by molecular diagnostics and biomarker profiling, will further allow customization of targeting ligands and drug release kinetics according to patient-specific disease conditions and genomic sequence.

7. CONCLUSION

Nanocarrier-based drug delivery systems represent a promising approach for improving the precision and efficiency of therapeutic delivery to target sites. The optimization and engineering the composition proportions, particle, globule - size, surface properties, and drug-release behavior of these nanocarriers, formulation scientist may reduce the demerits of associated with conventional dosage forms such as tablets and capsules, the issues of poor solubility, low bioavailability, inadequate penetration across biological barriers, and systemic toxicity, can be reduced. Their potential has been demonstrated in several therapeutic areas, particularly cancer, CNS disorders, infectious diseases, and the delivery of biological molecules. However, promising laboratory results do not always translate successfully into clinical practice. Challenges related to large-scale production, reproducibility, stability, long-term safety, and regulatory requirements continue to slow their development. Future research should therefore focus not only on designing increasingly sophisticated nanocarriers, but also on developing systems that are practical, reproducible, safe, and suitable for manufacturing at scale. A better understanding of how formulation characteristics influence biological performance, supported by standardized evaluation methods and quality-by-design approaches, could help bridge the gap between laboratory research and clinical translation. Such efforts may ultimately lead to more reliable and effective nanocarrier-based therapies tailored to specific therapeutic and personalized needs.

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AUTHOR CONTRIBUTIONS

Farhat Fatima: Conceptualization, Investigation.

Ahmed Al Saqr, Mohammed F. Aldawsari, Almutairy BK, Alsulays B: Methodology, Laboratory Analysis.

Ahmed Mohammed Mubeen: Data Curation, Formal Analysis.

Mohammed Muqtader Ahmed: Supervision, Writing—Review & Editing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

AI DISCLOSURE

Oreate AI (Oreate AI, AI Image) was used to generate the graphical abstract, as well as to illustrate the scientific concepts of each nanocarriers category formulation development process. Oreate AI was not used for manuscript writing, data collection and analysis, or interpretation of the study findings.

REFERENCES

[1] Kalepu, S., Nekkanti, V., 2015. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharmaceutica Sinica B 5(5), 442-453. doi:10.1016/j.apsb.2015.07.003

[2] Bhalani, D.V., Nutan, B., Kumar, A., Chandel, A.K.S., 2022. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines 10(9), 2055. doi:10.3390/biomedicines10092055

[3] Ezike, T.C., Okpala, U.S., Onoja, U.L., et al., 2023. Advances in drug delivery systems, challenges and future directions. Heliyon 9(6), e17488. doi:10.1016/j.heliyon.2023.e17488

[4] Wittayanukorn, S., Rosenberg, M., Schick, A., et al., 2020. Factors that have an Impact on Abbreviated New Drug Application (ANDA) Submissions. Therapeutic Innovation & Regulatory Science 54(6), 1372-1381. doi:10.1007/s43441-020-00163-x

[5] Parhi, R., Kaishap, P.P., Jena, G.K., 2023. Recent advances in nanomaterial-based drug delivery systems for melanoma therapy. ADMET & DMPK 12(1), 107-150. doi:10.5599/admet.2088

[6] Beach, M.A., Nayanathara, U., Gao, Y., et al., 2024. Polymeric nanoparticles for drug delivery. Chemical Reviews 124(9), 5505-5616. doi:10.1021/acs.chemrev.3c00705

[7] Rarokar, N., Yadav, S., Saoji, S., et al., 2024. Magnetic nanosystem a tool for targeted delivery and diagnostic application: Current challenges and recent advancement. International Journal of Pharmaceutics X 7, 100231. doi:10.1016/j.ijpx.2024.100231

[8] Unnikrishnan, G., Joy, A., Megha, M., Kolanthai, E., Senthilkumar, M., 2023. Exploration of inorganic nanoparticles for revolutionary drug delivery applications: a critical review. Discover Nano 18(1), 157. doi:10.1186/s11671-023-03943-0

[9] Del Castillo-Santaella, T., Ortega-Oller, I., Padial-Molina, M., et al., 2019. Formulation, colloidal characterization, and in vitro biological effect of BMP-2 loaded PLGA nanoparticles for bone regeneration. Pharmaceutics 11(8), 388. doi:10.3390/pharmaceutics11080388

[10] Ruan, H., Chen, Y., Qian, J., et al., 2026. Advances in metal–organic framework-based drug delivery system in cuproptosis-mediated cancer therapy. European Journal of Pharmaceutics and Biopharmaceutics 222, 115021. doi:10.1016/j.ejpb.2026.115021

[11] Harun-Or-Rashid, Md., Aktar, Most.N., Hossain, Md.S., et al., 2023. Recent advances in micro- and Nano-Drug delivery systems based on natural and synthetic biomaterials. Polymers 15(23), 4563. doi:10.3390/polym15234563

[12] Hillaireau, H., Couvreur, P., 2009. Nanocarriers' entry into the cell: relevance to drug delivery. Cellular and Molecular Life Sciences 66(17), 2873-2896. doi:10.1007/s00018-009-0053-z

[13] Wang, H., Wu, X., Wang, J., Wang, X., Lu, Y., 2025. In vitro and in vivo correlation of injectable lipid-based nanomedicines: From dissolution to protein coronas. Materials Today Bio 35, 102393. doi:10.1016/j.mtbio.2025.102393

[14] Shah, R.M., Kaur, I.P., Jadhav, S.R., 2025. The surface-first paradigm: Engineering nanocarriers for infection-responsive drug delivery. Advances in Colloid and Interface Science 349, 103761. doi:10.1016/j.cis.2025.103761

[15] Zhang, W., Taheri-Ledari, R., Ganjali, F., et al., 2022. Effects of morphology and size of nanoscale drug carriers on cellular uptake and internalization process: a review. RSC Advances 13(1), 80-114. doi:10.1039/d2ra06888e

[16] Zhao, L., Liu, X., Deng, X., 2025. AI-engineered multifunctional nanoplatforms: synergistically bridging precision diagnosis and intelligent therapy in next-generation oncology. Journal of Nanobiotechnology 24(1), 73. doi:10.1186/s12951-025-03947-1

[17] Lee, Y.J., Kim, M.S., 2025. Advances in drug-loaded microspheres for targeted, controlled, and sustained drug delivery: Potential, applications, and future directions. Biomedicine & Pharmacotherapy 189, 118244. doi:10.1016/j.biopha.2025.118244

[18] Samineni, R., Chimakurthy, J., Konidala, S., 2021. Emerging Role of Biopharmaceutical Classification and Biopharmaceutical Drug Disposition System in Dosage form Development: A Systematic Review. Turkish Journal of Pharmaceutical Sciences 19(6), 706-713. doi:10.4274/tjps.galenos.2021.73554

[19] Guo, Z., Zhang, Y., Zhao, M., et al., 2025. Intelligent transdermal nanoparticles as synergizing advanced delivery systems for precision therapeutics. Materials Today Bio 34, 102220. doi:10.1016/j.mtbio.2025.102220

[20] Kim, M., Shin, M., Zhao, Y., Ghosh, M., Son, Y., 2024. Transformative impact of nanocarrier-mediated drug delivery: Overcoming biological barriers and expanding therapeutic horizons. Small Science 4(11), 2400280. doi:10.1002/smsc.202400280

[21] Desai, N., Rana, D., Patel, M., Bajwa, N., Prasad, R., Vora, L.K., 2025. Nanoparticle Therapeutics in Clinical perspective: Classification, marketed products, and regulatory landscape. Small 21(29), e2502315. doi:10.1002/smll.202502315

[22] Vagena, I.A., Malapani, C., Gatou, M.A., Lagopati, N., Pavlatou, E.A., 2025. Enhancement of EPR effect for passive tumor targeting: Current status and future perspectives. Applied Sciences 15(6), 3189. doi:10.3390/app15063189

[23] Song, B., Wang, X., Qin, L., Hussain, S., Liang, W., 2024. Brain gliomas: Diagnostic and therapeutic issues and the prospects of drug-targeted nano-delivery technology. Pharmacological Research 206, 107308. doi:10.1016/j.phrs.2024.107308

[24] Spada, A., Gerber-Lemaire, S., 2025. Surface Functionalization of Nanocarriers with Anti-EGFR Ligands for Cancer Active Targeting. Nanomaterials 15(3), 158. doi:10.3390/nano15030158

[25] Rana, A., Adhikary, M., Singh, P.K., Das, B.C., Bhatnagar, S., 2023. "Smart" drug delivery: A window to future of translational medicine. Frontiers in Chemistry 10, 1095598. doi:10.3389/fchem.2022.1095598

[26] Zhu, C., Mu, J., Liang, L., 2024. Nanocarriers for intracellular delivery of proteins in biomedical applications: strategies and recent advances. Journal of Nanobiotechnology 22(1), 688. doi:10.1186/s12951-024-02969-5

[27] Mazumdar, S., Chitkara, D., Mittal, A., 2021. Exploration and insights into the cellular internalization and intracellular fate of amphiphilic polymeric nanocarriers. Acta Pharmaceutica Sinica B 11(4), 903-924. doi:10.1016/j.apsb.2021.02.019

[28] Pattnaik, S., Swain, K., 2025. Techniques in the characterization of lipid-based nanotherapeutics: state of the art, challenges, and future direction. Discover Pharmaceutical Sciences 1(1). doi:10.1007/s44395-025-00021-5

[29] Tao, J., Chow, S.F., Zheng, Y., 2018. Application of flash nanoprecipitation to fabricate poorly water-soluble drug nanoparticles. Acta Pharmaceutica Sinica B 9(1), 4-18. doi:10.1016/j.apsb.2018.11.001

[30] Boudoukhani, M., Yahoum, M.M., Ezzroug, K., et al., 2024. Formulation and Characterization of Double Emulsions W/O/W Stabilized by Two Natural Polymers with Two Manufacturing Processes (Comparative Study). ChemEngineering 8(2), 34. doi:10.3390/chemengineering8020034

[31] Pyrak, B., Rogacka-Pyrak, K., Gubica, T., Szeleszczuk Ł, 2024. Exploring Cyclodextrin-Based Nanosponges as Drug delivery systems: Understanding the physicochemical factors influencing drug loading and release kinetics. International Journal of Molecular Sciences 25(6), 3527. doi:10.3390/ijms25063527

[32] Fatima, F., Anwer, M.d.K., 2023. Development and Characterization of Ibrutinib-Loaded Ethylcellulose-Based Nanosponges: Cytotoxicity Assay against MCF-7 Cell Lines. Applied Sciences 13(8), 4984. doi:10.3390/app13084984

[33] Lian, S., Lamprou, D., Zhao, M., 2023. Electrospinning technologies for the delivery of Biopharmaceuticals: Current status and future trends. International Journal of Pharmaceutics 651, 123641. doi:10.1016/j.ijpharm.2023.123641

[34] Alamer, A.A., Alshehri, A.A., Aodah, A.H., et al., 2024. Development and evaluation of sildenafil/glycyrrhizin-loaded nanofibers as a potential novel buccal delivery system for erectile dysfunction. Saudi Pharmaceutical Journal 32(5), 102038. doi:10.1016/j.jsps.2024.102038

[35] Li, J., Fang, Z., Tang, H., et al., 2025. Continuous preparation of 50 nm emulsions of soybean oil using a novel temperature-controllable ultrasonic tandem emulsifying unit. Food and Bioproducts Processing 153, 350-361. doi:10.1016/j.fbp.2025.07.010

[36] Betancourt, T., Brown, B., Brannon-Peppas, L., 2007. Doxorubicin-Loaded PLGA nanoparticles by Nanoprecipitation: preparation, characterization and in vitro evaluation. Nanomedicine 2(2), 219-232. doi:10.2217/17435889.2.2.219

[37] Pieper, S., Onafuye, H., Mulac, D., et al., 2019. Incorporation of doxorubicin in different polymer nanoparticles and their anticancer activity. Beilstein Journal of Nanotechnology 10, 2062-2072. doi:10.3762/bjnano.10.201

[38] Shaikh, M.V., Kala, M., Nivsarkar, M., 2017. Formulation and optimization of doxorubicin loaded polymeric nanoparticles using Box-Behnken design: ex-vivo stability and in-vitro activity. European Journal of Pharmaceutical Sciences 100, 262-272. doi:10.1016/j.ejps.2017.01.026

[39] Khan, T.Z., Newaj, S.M., Rahman, A., et al., 2023. NIR-light-triggered delivery of doxorubicin-loaded PLGA nanoparticles for synergistic cancer therapy on DMBA/TPA induced tumor-bearing mice. Materials Advances 4(21), 5175-5183. doi:10.1039/d3ma00375b

[40] Tomankova, K., Polakova, K., Pizova, K., et al., 2015. In vitro cytotoxicity analysis of doxorubicin-loaded/superparamagnetic iron oxide colloidal nanoassemblies on MCF7 and NIH3T3 cell lines. International Journal of Nanomedicine 10, 949. doi:10.2147/ijn.s72590

[41] Kanwal, S., Naveed, M., Arshad, A., et al., 2021. Reduction-Sensitive Dextran–Paclitaxel Polymer–Drug Conjugate: Synthesis, Self-Assembly into Nanoparticles, and In Vitro Anticancer Efficacy. Bioconjugate Chemistry 32(12), 2516-2529. doi:10.1021/acs.bioconjchem.1c00492

[42] Karra, N., Nassar, T., Ripin, A.N., Schwob, O., Borlak, J., Benita, S., 2013. Antibody Conjugated PLGA nanoparticles for targeted delivery of paclitaxel palmitate: Efficacy and biofate in a lung cancer mouse model. Small 9(24), 4221-4236. doi:10.1002/smll.201301417

[43] Xu, W., Siddiqui, I.A., Nihal, M., et al., 2013. Aptamer-conjugated and doxorubicin-loaded unimolecular micelles for targeted therapy of prostate cancer. Biomaterials 34(21), 5244-5253. doi:10.1016/j.biomaterials.2013.03.006

[44] Tang, Z., Jun, Y., Lv, Y., et al., 2019. Aptamer-conjugated and doxorubicin-loaded grapefruit-derived nanovectors for targeted therapy against HER2+ breast cancer. Journal of Drug Targeting 28(2), 186-194. doi:10.1080/1061186x.2019.1624970

[45] Mangla, B., Pathan, T., Kumar, P., Aggarwal, G., 2025. Development and in vivo biodistribution of folate-targeted nanolipid system for erlotinib in breast cancer treatment. Nanomedicine 20(13), 1525-1536. doi:10.1080/17435889.2025.2508135

[46] Milewska, S., Siemiaszko, G., Wilczewska, A.Z., et al., 2023. Folic-Acid-Conjugated thermoresponsive polymeric particles for targeted delivery of 5-Fluorouracil to CRC cells. International Journal of Molecular Sciences 24(2), 1364. doi:10.3390/ijms24021364

[47] Lee, C.S., Kim, H., Yu, J., et al., 2017. Doxorubicin-loaded oligonucleotide conjugated gold nanoparticles: A promising in vivo drug delivery system for colorectal cancer therapy. European Journal of Medicinal Chemistry 142, 416-423. doi:10.1016/j.ejmech.2017.08.063

[48] Mognetti, B., Barberis, A., Marino, S., et al., 2012. In vitro enhancement of anticancer activity of paclitaxel by a Cremophor free cyclodextrin-based nanosponge formulation. Journal of Inclusion Phenomena and Macrocyclic Chemistry 74(1-4), 201-210. doi:10.1007/s10847-011-0101-9

[49] Kadian, V., Rao, R., 2024. Enhancing anti-inflammatory effect of brucine nanohydrogel using rosemary oil: a promising strategy for dermal delivery in arthritic inflammation. 3 Biotech 14(6), 157. doi:10.1007/s13205-024-03997-6

[50] Hani, U., Paramshetti, S., Angolkar, M., et al., 2024. Cyclodextrin-Nanosponge-Loaded Cyclo-Oxygenase-2 Inhibitor-Based Topical Gel for Treatment of Psoriatic Arthritis: Formulation Design, Development, and In vitro Evaluations. Pharmaceuticals 17(12), 1598. doi:10.3390/ph17121598

[51] Pratap, R., Lankalapalli, S., 2024. DEVELOPMENT AND EVALUATION OF CYCLODEXTRIN NANOSPONGES-BASED TOPICAL FORMULATION OF TAZAROTENE. International Journal of Applied Pharmaceutics 16(6), 90-97. doi:10.22159/ijap.2024v16i6.51926

[52] Md, S., Alhakamy, N.A., Aldawsari, H.M., et al., 2020. Improved Analgesic and Anti-Inflammatory Effect of Diclofenac sodium by Topical Nanoemulgel: Formulation Development—In VitroandIn VivoStudies. Journal of Chemistry 2020, 1-10. doi:10.1155/2020/4071818

[53] Arora, A., Aggarwal, G., Singh, T.G., Singh, M., Arora, G., Nagpal, M., 2019. Inclusion complexes of atorvastatin calcium–sulfobutyl ether β cyclodextrin with enhanced hypolipidemic activity. Journal of Applied Pharmaceutical Science 9(11), 60-68. doi:10.7324/japs.2019.91108

[54] Gabr, M.M., Mortada, S.M., Sallam, M.A., 2017. Carboxylate cross-linked cyclodextrin: A nanoporous scaffold for enhancement of rosuvastatin oral bioavailability. European Journal of Pharmaceutical Sciences 111, 1-12. doi:10.1016/j.ejps.2017.09.026

[55] Omar, S.M., Ibrahim, F., Ismail, A., 2020. Formulation and evaluation of cyclodextrin-based nanosponges of griseofulvin as pediatric oral liquid dosage form for enhancing bioavailability and masking bitter taste. Saudi Pharmaceutical Journal 28(3), 349-361. doi:10.1016/j.jsps.2020.01.016

[56] Manatunga, D.C., Jayasinghe, J.A.B., Sandaruwan, C., De Silva, R.M., De Silva, K.M.N., 2022. Enhancement of Release and Solubility of Curcumin from Electrospun PEO–EC–PVP Tripolymer-Based Nanofibers: A Study on the Effect of Hydrogenated Castor Oil. ACS Omega 7(42), 37264-37278. doi:10.1021/acsomega.2c03495

[57] Qi, J., Wu, W., Wang, K., et al., 2014. Enhancement of oral bioavailability of cyclosporine A: comparison of various nanoscale drug-delivery systems. International Journal of Nanomedicine 9, 4991. doi:10.2147/ijn.s72560

[58] Anuar, N., Sabri, A.H., Effendi, T.J.B., Hamid, K.A., 2020. Development and characterisation of ibuprofen-loaded nanoemulsion with enhanced oral bioavailability. Heliyon 6(7), e04570. doi:10.1016/j.heliyon.2020.e04570

[59] Khalid, A., Arshad, M.U., Imran, A., Khalid, S.H., Shah, M.A., 2023. Development, stabilization, and characterization of nanoemulsion of vitamin D3-enriched canola oil. Frontiers in Nutrition 10, 1205200. doi:10.3389/fnut.2023.1205200

[60] Bahadur, S., Pardhi, D.M., Rautio, J., Rosenholm, J.M., Pathak, K., 2020. Intranasal nanoemulsions for direct Nose-to-Brain delivery of actives for CNS disorders. Pharmaceutics 12(12), 1230. doi:10.3390/pharmaceutics12121230

[61] Senanayake, D., Yapa, P., Dabare, S., Munaweera, I., 2025. Precision targeting of the CNS: recent progress in brain-directed nanodrug delivery. RSC Advances 15(32), 25910-25928. doi:10.1039/d5ra03578c

[62] Monteiro, N., Martins, M., Martins, A., et al., 2015. Antibacterial activity of chitosan nanofiber meshes with liposomes immobilized releasing gentamicin. Acta Biomaterialia 18, 196-205. doi:10.1016/j.actbio.2015.02.018

[63] Bottino, M.C., Münchow, E.A., Albuquerque, M.T.P., et al., 2016. Tetracycline-incorporated polymer nanofibers as a potential dental implant surface modifier. Journal of Biomedical Materials Research Part B Applied Biomaterials 105(7), 2085-2092. doi:10.1002/jbm.b.33743

[64] Smoleński, M., Muschert, S., Haznar-Garbacz, D., Małolepsza-Jarmołowska, K., 2023. Nanoemulsion Loaded with Clotrimazole Based on Rapeseed Oil for Potential Vaginal Application—Development, Initial Assessment, and Pilot Release Studies. Pharmaceutics 15(5), 1437. doi:10.3390/pharmaceutics15051437

[65] Srivastava, S., Mahor, A., Singh, G., et al., 2021. Formulation Development, in vitro and in vivo evaluation of topical hydrogel formulation of econazole Nitrate-Loaded B-Cyclodextrin nanosponges. Journal of Pharmaceutical Sciences 110(11), 3702-3714. doi:10.1016/j.xphs.2021.07.008

[66] Zheng, Y., Fang, X., Gao, J., 2026. Re-engineering insulin for oral delivery: structural modifications, advanced formulation strategies, and future directions. Drug Delivery 33(1), 2624192. doi:10.1080/10717544.2026.2624192

[67] Guo, F., Zhang, M., Gao, Y., et al., 2015. Modified nanoparticles with cell-penetrating peptide and amphipathic chitosan derivative for enhanced oral colon absorption of insulin: preparation and evaluation. Drug Delivery 23(6), 2003-2014. doi:10.3109/10717544.2015.1048489

[68] Barbari, G.R., Dorkoosh, F., Amini, M., et al., 2018. Synthesis and characterization of a novel peptide-grafted Cs and evaluation of its nanoparticles for the oral delivery of insulin, in vitro, and in vivo study. International Journal of Nanomedicine 13, 5127-5138. doi:10.2147/ijn.s161240

[69] Ortega-Oller, I., Del Castillo-Santaella, T., Padial-Molina, M., Galindo-Moreno, P., Jódar-Reyes, A.B., Peula-García, J.M., 2017. Dual delivery nanosystem for biomolecules. Formulation, characterization, and in vitro release. Colloids and Surfaces B Biointerfaces 159, 586-595. doi:10.1016/j.colsurfb.2017.08.027

[70] Costa, C., Padrela, L., 2025. Progress on drug nanoparticle manufacturing: exploring the adaptability of batch bottom-up approaches to continuous manufacturing. Journal of Drug Delivery Science and Technology 111, 107120. doi:10.1016/j.jddst.2025.107120

[71] Paliwal, R., Babu, R.J., Palakurthi, S., 2014. Nanomedicine Scale-up Technologies: Feasibilities and challenges. AAPS PharmSciTech 15(6), 1527-1534. doi:10.1208/s12249-014-0177-9

[72] Hachhach, M., Bayou, S., Kasmi, A.E., et al., 2025. Towards Sustainable Scaling-Up of Nanomaterials Fabrication: Current situation, challenges, and Future Perspectives. Eng—Advances in Engineering 6(7), 149. doi:10.3390/eng6070149

[73] Chennamsetty, S., Keerikkadu, M., Shetty, A., Bangera, P.D., Tippavajhala, V.K., Rathnanand, M., 2025. Biohybrid nanocarriers for targeted drug delivery by integrating biological interfaces with synthetic platforms for site-specific therapeutics. International Journal of Pharmaceutics 687, 126400. doi:10.1016/j.ijpharm.2025.126400

[74] Ilić, T., Đoković, J.B., Nikolić, I., et al., 2023. Parenteral Lipid-Based Nanoparticles for CNS Disorders: Integrating Various Facets of Preclinical Evaluation towards More Effective Clinical Translation. Pharmaceutics 15(2), 443. doi:10.3390/pharmaceutics15020443

[75] Boushehri M, a., 2025. S. Long circulating nanocarriers: achievements and shortcomings of biomimetic approaches. International Journal of Pharmaceutics 689, 126488. doi:10.1016/j.ijpharm.2025.126488

[76] Breznica, P., Koliqi, R., Daka, A., 2020. A review of the current understanding of nanoparticles protein corona composition. Medicine and Pharmacy Reports 93(4), 342-350. doi:10.15386/mpr-1756

[77] Petrovic, S., Bita, B., Barbinta-Patrascu, M.E., 2024. Nanoformulations in Pharmaceutical and Biomedical Applications: Green Perspectives. International Journal of Molecular Sciences 25(11), 5842. doi:10.3390/ijms25115842

[78] Sairam, A.B., Sanmugam, A., Pushparaj, A., et al., 2023. Toxicity of polymeric nanodrugs as drug carriers. ACS Chemical Health & Safety 30(5), 236-250. doi:10.1021/acs.chas.3c00008

[79] Rodríguez-Gómez, F.D., Monferrer, D., Penon, O., Rivera-Gil, P., 2025. Regulatory pathways and guidelines for nanotechnology-enabled health products: a comparative review of EU and US frameworks. Frontiers in Medicine 12, 1544393. doi:10.3389/fmed.2025.1544393

[80] Buya, A.B., Mahlangu, P., Witika, B.A., 2024. From lab to industrial development of lipid nanocarriers using quality by design approach. International Journal of Pharmaceutics X 8, 100266. doi:10.1016/j.ijpx.2024.100266