Materials Chemistry Horizons

REVIEW

Engineering Lipid Nanocarriers for Wound Healing: From Microenvironment Modulation to Translational Nanomedicine

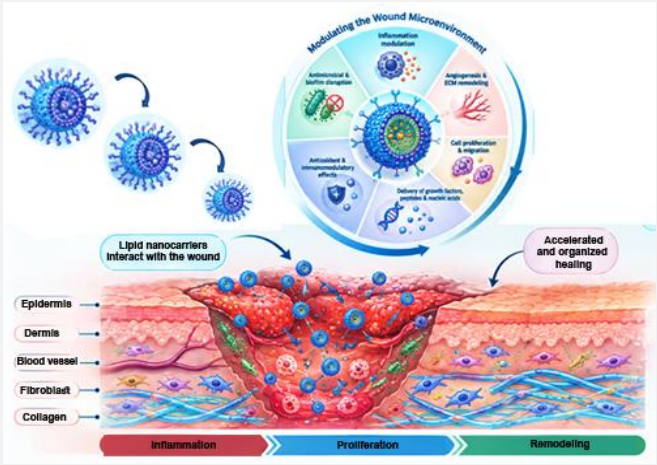
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ABSTRACT

Choronic wounds remain a major clinical challenge because persistent inflammation, infection, oxidative stress, and impaired tissue regeneration can disrupt the normal healing process. Lipid-based nanocarriers offer a versatile strategy for addressing these barriers by improving the delivery, stability, and local activity of therapeutic cargo within the wound microenvironment. This review critically examines the engineering of major lipid-based platforms, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, lipid/polymer hybrids, cubosomes, hexosomes, and exosome-mimetic vesicles, with emphasis on how their composition and structural features influence therapeutic performance. It discusses their roles in regulating inflammation, controlling microbial infections and biofilms, reducing oxidative stress, promoting angiogenesis, and supporting extracellular matrix remodeling. Recent applications in antimicrobial, gene, growth-factor, and regenerative therapies for diabetic, burn, and pressure wounds are highlighted, together with their integration into advanced topical formulations and wound dressings. Particular attention is given to biocompatibility, safety, preclinical evaluation, and the barriers that currently limit clinical translation. Finally, emerging opportunities in smart wound dressings, biosensing, personalized therapy, and AI-guided nanocarrier design are discussed. By connecting nanocarrier engineering with the biological complexity of wound repair, this review identifies key design considerations and future directions for developing more effective and clinically translatable lipid-based wound-healing platforms.



Keywords: Lipid-based nanocarriers, wound healing, wound microenvironment, targeted drug delivery, regenerative nanomedicine

1. Introduction

Skin makes up roughly 15-16% of total body weight, and its response to injury follows a fairly conserved sequence: hemostasis first, then inflammation, proliferation, and finally tissue remodeling [1,2]. Disruption is not rare, though. Bacterial infection alone accounts for a good share of it wounds stall, and complications can spread far beyond where the injury first occurred [3]. Twelve weeks tends to be the cutoff clinicians use; past that point, a wound stops being called acute and gets filed under chronic instead [2]. Two forces are driving up the number of such cases: populations are aging, and chronic disease is becoming more widespread, while acute traumatic wounds, by comparison, are being seen less often [2]. Chronic wounds impose a burden that is difficult to convey in numbers alone. In the United States, over 6 million people live with wounds that refuse to heal, and treatment costs there exceed 10 billion USD annually [2]. Costs look different elsewhere, but they are far from trivial; one study places the national burden in a separate setting at roughly 664 million USD [4].

Diabetes carries particular weight among the conditions that predispose patients to these wounds. Sustained high blood glucose slowly damages the very cells tissue repair relies on [1,2] Repair stalls as a result healing drags, and infection finds an opening it would rarely have otherwise. Left in that environment, bacteria rarely stay put as isolated invaders. Given time, they organize themselves into biofilms colonies wrapped in a matrix of their own making, one that shields them from what would normally clear them out [2,3,5] This creates a double barrier for treatment.

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None of the standard options dressings, negative-pressure therapy, topical antibiotics, skin grafts, flap surgery [2], escapes without some drawback. Take dressings: they cannot respond to what's happening in the wound, they just sit there, which is exactly why they falter when fluid levels tip too far one way or the other [2]. Surgery is not without cost either healthy tissue can be damaged along the way, and scarring is a common result [2]. Even antibiotics, relied on so heavily, rarely clear a biofilm completely; used repeatedly, they can push bacterial resistance in the wrong direction [2,3,5]. Taken together, these shortfalls make a strong case for delivery systems built with more intelligence than what currently exists.

That gap is largely what pulled nanobiotechnology into the spotlight as a research field [2]. It started narrow simple constructs meant for short-term healing but has since grown into something much broader, covering drug and gene delivery, antimicrobial platforms, and protection for therapeutic agents that would otherwise degrade too quickly. A lot of that growth traces back to a better grasp of how chronic wounds actually behave over time. Carried through these systems, agents such as antioxidants, nucleic acids, and antimicrobial peptides hold up better and reach their targets with more consistency [2,5].

Nanocarriers do this delivery work at the nanoscale, and they come in several structural forms organic, lipid-based, inorganic, hybrid (**Figure 1**) [6,7]. Behind all of them sits roughly the same idea: get drugs through the body more effectively than older formulations ever managed. But it is in the details that nanocarriers earn their reputation. Stability, solubility, bioavailability all tend to improve, and release itself becomes something that can be controlled and directed rather than left to chance [2,8]. Set against older materials, they cross biological barriers with less friction, concentrate more drug where it's actually needed, and leave fewer side effects in their wake [8,9].

Lipid-based versions draw particular interest, and for good reason: biocompatibility runs high, toxicity stays low, and the materials break down naturally in the body [10]. Loading capacity tends to be strong, release patterns hold steady, and scaling production up is more straightforward than with many alternatives [11]. Under this umbrella sit several distinct forms liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid drug conjugates (LDCs) [7,11]. SLNs came first chronologically; NLCs were developed afterward, specifically to work around certain limitations SLNs carried [11]. What emerges from all this is not one single advantage but several working in concert greater drug stability, longer circulation in the body, improved cellular uptake, and delivery that can actually be targeted [9]. Among the nanomaterials available, lipid-based systems in particular liposomes, nanoemulsions have drawn sustained research attention.

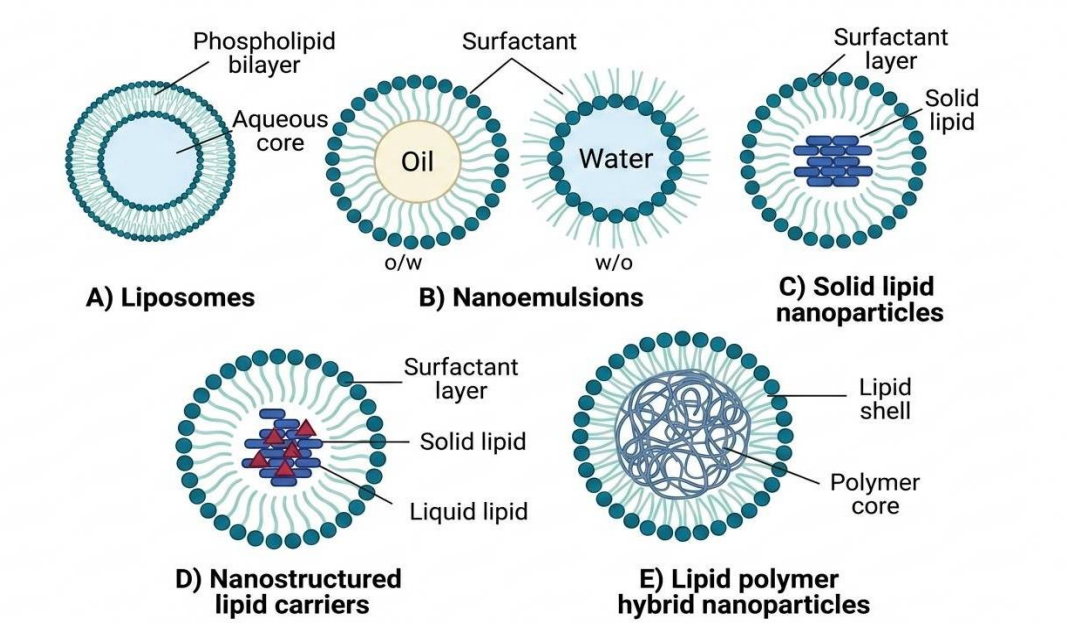


Figure 1. Schematic representation of major lipid-based nanocarriers used for drug delivery, including (**A**) Liposomes, (**B**) nanoemulsions; (**C**) solid lipid nanoparticles (SLNs); (**D**) nanostructured lipid carriers (NLCs); and (**E**) lipid–polymer hybrid nanoparticles (LPHNs). Abbreviations: O/W, oil-in-water; W/O, water-in-oil; SLNs, solid lipid nanoparticles; NLCs, nanostuctured lipid carriers; LPHNs, lipid–polymer hybrid nanoparticles [12].

2. Fundamentals of lipid-based nanocarriers

2.1. Structural characteristics of lipid nanoplatforms

Lipid nanoplatforms are not a single uniform system. There are several formats in use: liposomes, SLNs, NLCs, nanoemulsions, and lipid–polymer hybrid nanoparticles. They can look similar at first sight. But inside, the structures are different. This difference is not minor. It changes how particles behave in biological systems, especially stability and drug transport [12].

In vivo behavior follows structure. This becomes obvious when comparing systems side by side.

Liposomes represent the basic form these carriers take: phospholipid bilayers folding into a closed vesicle, an aqueous core sitting at its center. Two compartments, then, within one particle: hydrophilic drugs settle into the aqueous core, lipophilic ones lodge in the lipid bilayer itself [13,14]. Size is far from fixed, ranging from 20 up to 1000 nm and the difference is not trivial. Vesicles at or below 100 nm circulate longer in blood, slipping past immune detection more readily than larger ones do [12]. Instability remains a persistent problem, though. Drugs leak out. Clearance from the body can happen fast [15,16]. Simple structure, but not always stable in practice

SLNs change this design. No bilayer here. Only a solid lipid core. Most particles fall around 50–100 nm, depending on preparation [12]. The solid matrix protects the drug better. That part works well. But there is a trade-off. The internal crystal structure is highly ordered, and this reduces how much drug can be loaded. Sometimes drug is pushed out during storage. So, stability increases, but loading capacity drops.

NLCs modify this limitation. Solid and liquid lipids are combined. The structure becomes less ordered. This small change has a clear effect. More drug can be loaded, and leakage during storage is reduced [12]. Nanoemulsions are different again. They are dispersed droplets in another phase, usually oil-in-water or water-in-oil. Sizes are typically 50–500 nm [12]. Preparation is relatively easy. But stability depends strongly on formulation conditions. Small changes in composition can affect performance. Particle size influences almost everything. Stability, circulation time, and cellular uptake all depend on it. Below 100 nm, particles usually enter cells more efficiently and stay longer in blood. Larger ones behave differently. Higher drug capacity, but faster clearance in many cases [12]. DLS is commonly used to measure size. It is quick. But shape information is limited. Surface charge is another key factor. Zeta potential is used to describe it. When values are strongly positive or negative, particles repel each other. Aggregation decreases. Stability improves. When values are close to zero, aggregation becomes more likely [12]. The

trend is simple and consistent across systems. Morphology is examined using TEM, SEM, or AFM. These techniques show real shape and surface details. Smooth particles interact less with plasma proteins. This reduces immune recognition and can extend circulation time. Rough surfaces behave differently. They increase biological interactions and may change distribution in the body [12]. Surface modification also plays a role. PEG or targeting ligands can shift how particles are recognized and processed in vivo [12]. LPHNPs are a more complex structure. A polymer core, often PLGA, is covered by a lipid layer. Core–shell design. The polymer gives mechanical strength. The lipid part improves compatibility with biological systems. Result is a more stable platform, with wider flexibility for drug delivery use [17].

2.2. Lipid composition, stability, and biocompatibility

Lipid-based nanoplatforms are generally well tolerated in biological environments. In many reports, irritation is low or not observed. This is mainly related to their basic composition. They are built from physiological lipids or materials already accepted for pharmaceutical use. In practice, this makes their translation easier than many synthetic systems. Some of these lipids are also classified as GRAS for topical and oral administration, which further supports their safety profile [18].

A simple structural element in these systems is phospholipids. PC, PE, PS, and PG are common examples [11].Their role is not only to form a shell. The headgroup chemistry changes how the whole structure organizes. Even small differences in polarity or charge can shift the final architecture of the carrier.

But physical stability is not always ideal. Problems like aggregation may appear during storage. Lipid crystallinity is also not completely fixed and can change with time. These are not minor variations. These factors can shift how the system behaves under real conditions [16]. Stability, for this reason, tends to get treated as a core formulation parameter not an afterthought tacked on at the end.

In many designs, a mixed lipid system is used instead of a single solid lipid. Solid and liquid lipids are combined. This changes the packing of lipid chains. The crystal becomes less ordered. Rigidity falls off, and oddly long-term structural stability tends to hold up better because of it [13,19] A flawed crystal, apparently, can outlast a flawless one. Stability also hinges on processing. Freeze-drying is the standard route, but cryoprotectants trehalose, sucrose, mannitol, glucose go in first, before lyophilization begins, keeping particles from sticking together as they freeze and dry. Spray drying is another method. It can also preserve particle structure if conditions are well controlled [16,20].

2.3. Drug loading, release kinetics, and targeting strategies

How lipid nanocarriers arrange themselves in space ends up dictating what cargo they can hold and how that cargo eventually gets released. NLCs, for one, outperform their first-generation solid-lipid predecessors on both counts drug loading capacity and encapsulation efficiency come out markedly higher [13,14]. The reason traces back to structure itself: fluid lipid segments and the imperfections they introduce open up molecular voids, spaces that can accommodate far greater concentrations of active ingredient than a more ordered matrix would allow[16,19,21].

Tuning the ratio of liquid to solid lipid offers a way to control this disorder directly, and with it, a way to fine-tune encapsulation parameters with real precision [21]. Lipid-polymer hybrids put this principle into practice. Once a surface lipid layer is added DOTAP is one such example it works as a physical barrier, keeping hydrophilic drugs like vancomycin trapped inside the polymeric core instead of letting them slip out during fabrication. Higher encapsulation and loading efficiencies follow directly from this containment [17]. Push the formulation further and the numbers climb higher still: antimicrobial peptides adsorbed onto surfaces have reached 34-62% in reported studies, while reverse-micelle configurations have driven encapsulation up to 98% [22].

Location within the matrix, in the end, is what separates one encapsulation model from another whether the drug sits in a homogeneous matrix, concentrates in an enriched shell, or occupies an enriched core [20]. As illustrated in **Figure 2**, lipid-based nanocarriers can accommodate therapeutic cargo through distinct loading configurations, with subsequent release governed by drug localization within the lipid matrix and its physicochemical properties. Which model applies matters enormously for release behavior. NLCs typically release their payload in two distinct phases an initial burst, driven by drug molecules sitting near the particle surface, followed by a slower, more sustained release as whatever remains diffuses gradually out of the core [21,23].

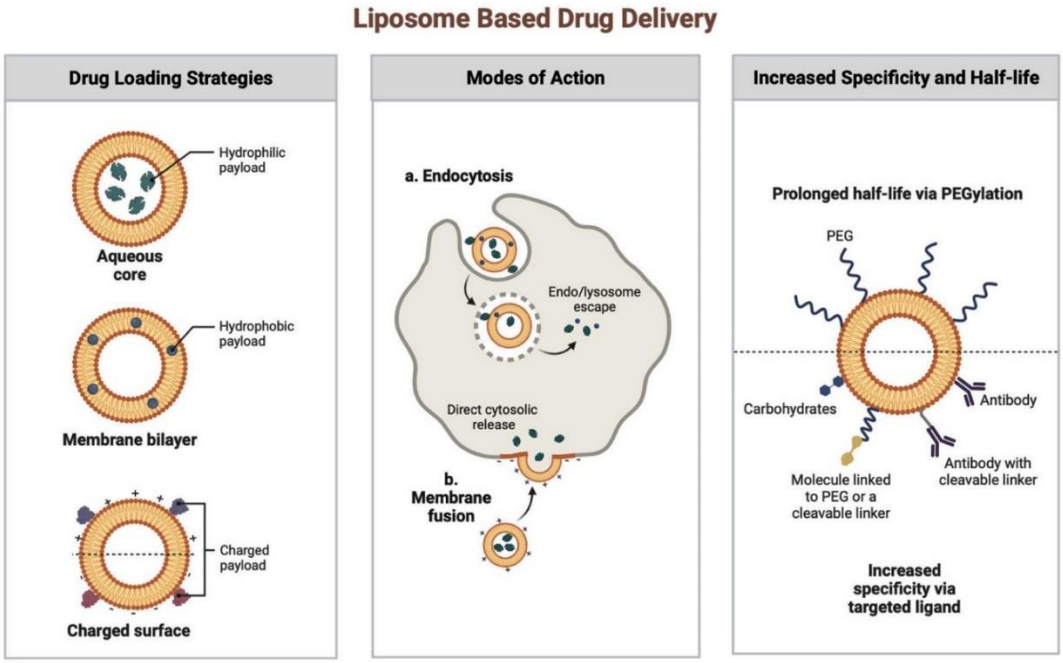


Figure 2. Schematic overview of lipid-based drug delivery systems, highlighting drug loading, cellular uptake, endosomal escape, membrane fusion, and surface functionalization for enhanced targeting. Drug release is governed by drug partitioning, lipid-matrix degradation, formulation composition, and environmental stimuli, enabling sustained or stimulus-responsive therapeutic delivery. In wound healing, passive lipid–skin interactions enhance hydration, barrier modulation, drug penetration, and local retention, while active targeting strategies improve site-specific therapeutic delivery and minimize systemic exposure.[25].

In addition to passive targeting, lipid nanocarriers can be designed to achieve active targeting. This is usually done by attaching specific ligands to the particle surface. The goal is to increase interaction with selected cells or tissues. Hyaluronic acid is a common example. It can bind to CD44 receptors, which are often expressed at higher levels in inflamed tissues and some pathological conditions. Cell-penetrating peptides such as TAT are another option. These peptides promote membrane translocation and help the carrier enter cells more efficiently [16]. Following their application to the wound site, lipid nanocarriers may cross the skin barrier through intercellular, transcellular, and transfollicular routes, facilitating drug deposition within the epidermis and dermis (**Figure 3**). The relative contribution of these pathways depends on carrier composition, surface characteristics, particle size, and interactions with the skin microenvironment.

This approach has attracted interest in chronic wound treatment. One reason is the high prevalence of persistent infections and bacterial biofilms in these wounds. Biofilms are organized microbial communities are enclosed within an extracellular polymeric substance (EPS) matrix. This matrix protects the microorganisms and significantly limits the penetration and effectiveness of antibiotics [26]. Because of this protection, infections are often difficult to eradicate. Recent studies have therefore explored surface-engineered lipid nanocarriers as a way to improve biofilm disruption and enhance antimicrobial delivery within the wound environment.

The interaction between nanocarriers and biofilms typically follows a stepwise pathway that includes movement toward the biofilm, adhesion to the EPS layer, and eventual penetration into its deeper regions [26]. Since the EPS matrix generally carries a negative charge, lipid nanocarriers can be optimized with cationic components such as DOTAP to enhance electrostatic attraction and binding to the biofilm surface [17]. This improved interaction not only increases retention at the interface but also supports deeper penetration into the matrix, enabling the carriers to protect their antimicrobial cargo from enzymatic degradation and deliver therapeutically relevant concentrations directly to the embedded bacterial cells [17,22,26].

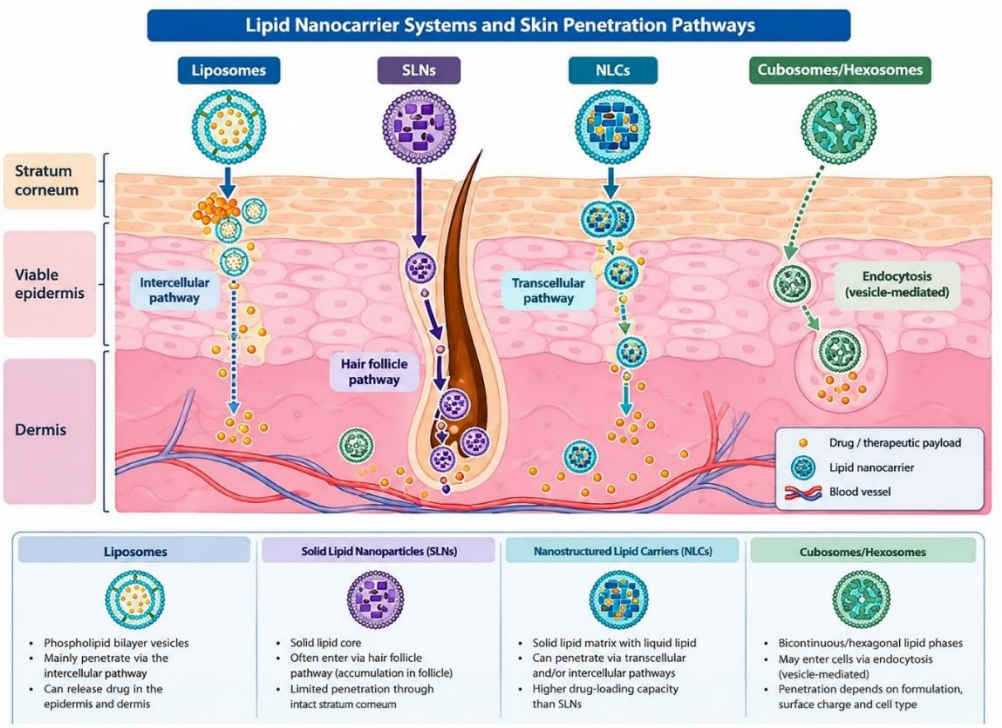


Figure 3. Schematic representation of the skin penetration routes (intercellular, transcellular, and transfollicular) used by lipid-based nanocarriers, including liposomes, transfersomes, ethosomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), to deliver drugs into the epidermis and dermis during wound healing. Abbreviations: SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers.

3. Types of lipids nanocarriers in wound healing

In this section, lipid nanocarriers used for wound healing are grouped according to their structural features and level of complexity, from conventional vesicular systems to more advanced biomimetic platforms.

3.1. Liposomes

Their biocompatibility is part of what makes liposomes such a mainstay in wound-healing drug delivery, but it's the controlled release at the injury site that really matters clinically local drug concentration rises while the rest of the body sees far less exposure [14,27]. Chronic and infected wounds benefit most from this, since sustained activity is exactly what's needed to keep inflammation down and healing moving forward over an extended period [26,28]. There's a protective dimension too. Enzymes and other unstable elements in the wound environment would otherwise break drugs down quickly, but liposomes shield against this, letting the drug stay active longer and work more effectively right where it's needed [28]. That extended activity feeds directly into inflammation control and tissue repair as healing progresses [27,28].

Skin penetration is where liposomes offer something distinct interaction with keratin and the lipids of the stratum corneum improves both drug retention and transdermal delivery [27]. Deeper skin layers become more accessible as a result, and drug accumulation in the wound area increases along with it. For topical and transdermal treatments, where the skin barrier is usually the main obstacle to absorption, this matters quite a bit [27,28]. How a liposome performs comes down largely to its structural design. Some are built to respond to biological conditions directly; others rely on ligand-mediated targeting to reach the intended site either way, this adaptability lets them suit a range of wound environments and treatment demands [14,27].

Not everything works in their favor, though. Instability, a limited half-life, encapsulation inefficiency these remain real problems [27]. Loading active molecules can shift stability further still. Take antimicrobial peptides as an example: their interaction with the lipid membrane tends to throw off its organization, and the carrier can end up

structurally weaker for it. Cholesterol is the usual fix wedged between lipid chains, it cuts down membrane fluidity, and the bilayer ends up packed tighter and mechanically stronger as a result [23]. What emerges, on balance, is a carrier that manages to combine drug protection, controlled release, and improved delivery to damaged tissue all at once flexible enough that liposomes have earned a central place among modern approaches to wound healing [14,27].

3.2. Solid lipid nanoparticles (SLNs)

SLNs stay solid at body temperature, which means their lipid core resists drug leakage. But solidity brings constraints: the tightly packed interior squeezes out space for drug loading, and rigidity robs the particle of any flexibility [14,22]. NLCs came into development precisely to overcome these limitations, and they do prove more stable during [29,30]. For wound healing, though, SLNs remain the standard option.

Much of their usefulness traces back to that solid architecture. Drugs stay shielded from damage, stability holds, and release can be tuned more precisely all of which translates into better local delivery once the carrier reaches the wound site [30]. Delivered locally, SLNs keep drugs concentrated in damaged tissue rather than letting them circulate widely, and that longer local residence means less drug reaching the rest of the body. Chronic and infected wounds cases that demand treatment over an extended stretch stand to gain the most from this. Reduced inflammation and infection follow, which in turn gives tissue repair more room to proceed during healing [30,31].

SLNs excel at safeguarding compounds from threat sources that would otherwise destroy them. Light damages them. Moisture does too. Enzymes break them down. Oxidation eats away at their structure [30].What sets SLNs apart from cruder approaches, though, is that they mount this defense without freezing the cargo inside; controlled release proceeds normally. When researchers paired curcumin and chamomile oil with SLNs, healing improved visibly, evidence that the protective envelope actually works in practice.

Limitations persist, even so. Drug loading capacity can run low, and lipid crystallization sometimes pushes the drug back out rather than holding it in place. Long-term storage brings its own risk, with physical stability tending to decline over time a real constraint once these systems move toward practical, real-world use [32].

3.3. Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs) are composed of a mixture of solid and liquid lipids, Compared with SLNs, NLCs generally provide higher drug loading and improved storage stability [16,21]. forming an imperfect lipid matrix with increased space for drug incorporation. This structural feature results in improved drug loading capacity and enhanced physical stability [33].

Formulation and manufacturing hurdles, however, have not disappeared. Solvent emulsification-evaporation, a technique still widely used, tends to leave organic solvent residues behind in the final product a real concern once that product reaches a patient. High-energy alternatives carry their own baggage: high-pressure homogenization demands tight control over processing conditions, and it typically consumes large quantities of water and surfactant, cutting into overall formulation efficiency. Push the lipid concentration higher and homogenization efficiency drops, often leaving behind dispersions so diluted that lipid content becomes negligible. Even when NLCs succeed in ferrying drugs across biological barriers the blood-brain barrier among them efflux transporters can still pull accumulated drug back out of cells, chipping away at therapeutic benefit. Scale-up, formulation optimization, consistent in vivo behavior: these remain the sticking points that keep NLCs, for all their edge over solid lipid nanoparticles, from wider clinical use [20].

Wound healing presents a different set of demands, but NLCs answer them reasonably well. Many compounds used therapeutically in this context are chemically fragile. Essential oils illustrate the problem clearly, breaking down readily under light, heat, or oxygen exposure. Once loaded into NLCs, though, these compounds degrade more slowly and release over an extended period once applied to the wound site[34]. Chronic wound treatment hinges on getting drugs through the skin barrier efficiently, and this is precisely where NLCs earn their keep improving local delivery by easing that penetration. The combined effects of these properties increase drug retention at the treatment site, which can improve the management of infected and chronic wounds. Owing to their high drug loading capacity, sustained drug release, enhanced stability, and efficient local drug delivery, NLCs have emerged as promising lipid-based carriers for wound healing [26].

3.4. Lipid–polymer hybrid systems

What sets polymer lipid hybrid nanoparticles, or PLHNPs, apart is the pairing of polymeric and lipid components on a single platform an attempt to capture what liposomes and polymeric nanoparticles each do well, without inheriting problems like poor stability, short circulation time, and drugs leaking out too early [35]. Holding the assembly together are hydrophobic interactions, van der Waals forces, and electrostatic attraction between the two components [35,36]. It's precisely in difficult delivery scenarios wound healing among them that these carriers tend to earn their keep [37–39].

A core shell arrangement is the usual structural pattern. Two components work together here. A lipid shell wraps around the polymer core, holding it stable and cutting down on premature drug loss, while the core itself sits at the structure's center, doing the actual work of carrying the drug and controlling how it's released [35,37,40]. Different structural configurations of lipid–polymer hybrid nanoparticles have been developed by varying the organization and distribution of their lipid and polymer components, as illustrated in **Figure 4.** That outer layer earns its place beyond mere protection, too it shapes how the particle interacts with biological systems, pushing its behavior closer to that of a natural membrane [37].

Preparation of these systems usually falls into one of two camps, nanoprecipitation or emulsification. The underlying mechanism doesn't change much between them: lipids and polymers, brought together in water, assemble themselves into nanoparticles. What does change, and change quite a bit, is the outcome, particle size, how stable the system stays, the pattern of drug release, and that outcome comes down to details easy to overlook: how much lipid relative to polymer goes in, what conditions the preparation is carried out under [35,37,40]. Against this backdrop, PLHNPs stand apart from conventional liposomes or polymeric nanoparticles used alone, offering something those single-component systems don't. Combine polymer strength with lipid biocompatibility, and the resulting carrier turns out mechanically sturdier while still allowing finer control over release. Not a small advantage: they can hold hydrophilic and hydrophobic drugs at the same time, and plasma stability, circulation time, biodegradability, and biocompatibility tend to improve together with more favorable release profiles [37].

Where PLHNPs really show promise in wound care is local delivery to damaged tissue useful given their antimicrobial and anti-inflammatory potential in wounds that are infected or slow to heal [38,39]. Release tends to unfold gradually, keeping the drug active over longer stretches [37]. Practical benefits follow from that: dosing less often, adherence to treatment potentially improving, and since delivery stays localized, systemic toxicity risk drops as well [37].

Still, the picture remains incomplete. As a fairly recent addition to the field, PLHNPs come with limited in vivo data, and most of what's known so far comes from laboratory or in vitro conditions leaving real gaps that more preclinical work will need to fill [37]. Their behavior once inside a living biological system isn't fully mapped out, and predicting how they'll perform in complex, real-world environments remain an open question [37].

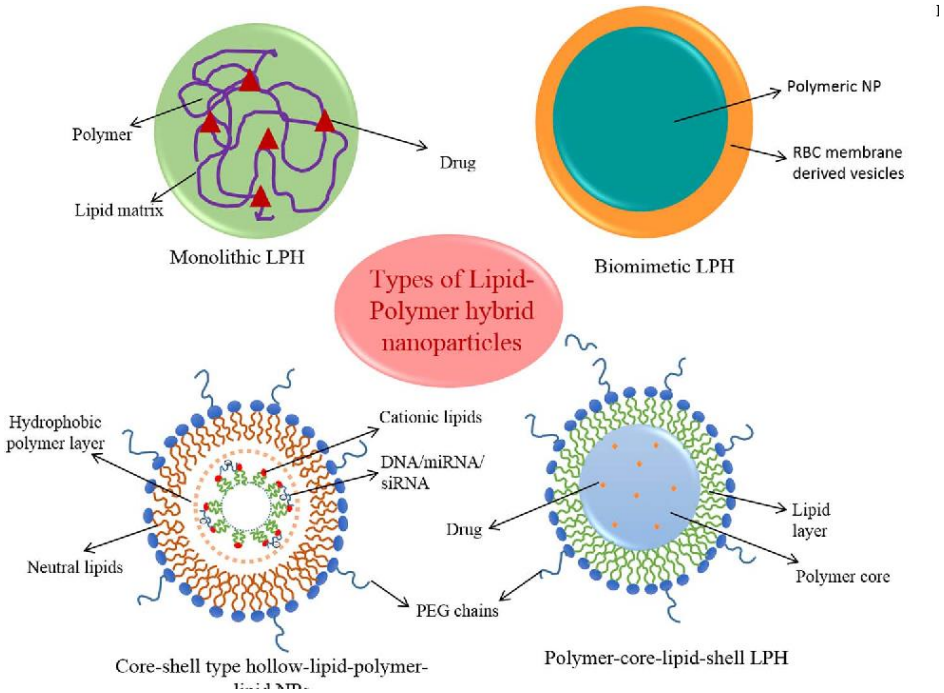


Figure 4. Types of lipid-polymer hybrid nanoparticles. The diagrams illustrate the structural organization of the polymer, lipid, and drug components, as well as the potential incorporation of nucleic acids and polyethylene glycol (PEG) chains. Abbreviations: LPHs, lipid–polymer hybrid nanoparticles; NP, nanoparticle; RBC, red blood cell; DNA, deoxyribonucleic acid; miRNA, microRNA; siRNA, small interfering RNA; PEG, polyethylene glycol [41].

3.5. Cubosomes and hexosomes

Self-assembly of lipids in water gives rise to cubosomes nanoparticles built around a continuous liquid crystalline structure where bilayers and water channels sit side by side [42,43]. That internal geometry is versatile enough to carry hydrophilic, hydrophobic, and amphiphilic drugs alike, without much regard for the drug's own solubility profile [42,44]. Hexosomes share this nonlamellar architecture, and together the two systems have earned a reputation as effective carriers, particularly for compounds that struggle with aqueous solubility [45]. Stabilizers turn out to be indispensable here without them, these structures wouldn't hold together and their presence also supports high drug loading and controlled release[45].

Flexibility across administration routes counts as a real strength: oral, topical, subcutaneous delivery all work reasonably well. Intravenous use is another story, though, since stability and compatibility issues in blood limit how far this route can be pushed [45]. In vivo behavior remains something of an open question too biodistribution, interaction with biological fluids none of it is fully mapped out yet [45]. Antimicrobial peptide-loaded cubosomes add another layer of uncertainty: some studies have found no real improvement over free peptides in antimicrobial activity, which hints that performance may depend heavily on which agent gets encapsulated [46].

Hexosomes, distinguished by a hexagonal internal arrangement, have simply received less research attention than cubosomes. Where comparisons exist, cubosomes tend to come out ahead better stability, stronger in vivo performance [46] though this doesn't rule hexosomes out; which system fits better still depends on the specific application. Chronic wound treatment stands to benefit from both, on balance. Drug stability improves, release can be controlled, and antimicrobial therapy gains support reasons enough to consider cubosomes and hexosomes genuinely promising carriers in this space.

3.6. Exosome-mimetic lipid vesicles

Lipid Vesicles Membrane -bound and wrapped in a lipid bilayer, extracellular vesicles (EVs) are secreted naturally by a wide range of cell types, functioning as key players in how cells communicate with one another. Exosomes typically 40 to 150 nm across make up one particular subtype, acting as carriers for proteins, lipids, and nucleic acids

that shuttle biological signals between cells and, in doing so, contribute to a range of processes, tissue repair chief among them [7]. Their origin in natural membranes gives them good biocompatibility and a low immune profile, qualities that make exosomes attractive candidates for drug delivery [48].

Exosomes derived from mesenchymal stem cells have drawn considerable attention in regenerative medicine, wound treatment being a particularly active area. Cell growth, cell migration, new blood vessel formation, immune regulation, tissue repair these vesicles touch all of it during healing [49,50]. Set against stem cell therapy directly, they come out ahead on safety, carrying lower risk of immune rejection and tumor formation[50].

Natural exosomes are not without real problems, though. Yield tends to run low, and achieving a uniform, stable product is genuinely difficult batch-to-batch variation gets in the way, and scaling production up is no simple task. Targeting remains weak, biodistribution in the body still poorly understood, and cargo loading efficiency leaves something to be desired. All of this together limits clinical translation, made harder still by the added complexity of meeting GMP requirements [51].

What emerged from these limitations is a class of vesicles built specifically to imitate exosomes structurally, EMVs. Getting there means forcing cells through filters, pore size shrinking at each pass, a process called extrusion, and what comes out is nanosized, with membrane composition and structure that closely resemble the natural version [52,53]. Compared with natural extraction, this route delivers far higher yield and lends itself much more readily to large-scale production [53,54].

What EMVs retain from their natural counterparts matters just as much as what's gained in production efficiency. The lipid bilayer stays intact, and proteins and RNA from parent cells still get carried along [55]. Biological compatibility remains strong as a result, immune response stays low, and a membrane so similar to the natural version helps the vesicles avoid immune recognition while holding up better once inside the body.

Taken as a whole, exosome-mimetic lipid vesicles look like genuinely promising biomimetic carrier’s natural exosome function paired with production that's actually scalable. Their biocompatibility and regenerative potential position them well for wound healing, though the work isn't finished: production methods still need refining, and safety along with clinical performance remain to be firmly established through further study [51,55].

The main characteristics, advantages, and limitations of some vesicular, particulate and hybrid lipid nanocarriers used in wound healing applications are summarized in **Tables 1** and **2**.

Table 1. Structural and formulation characteristics of vesicular lipid nanocarriers for wound healing.

Carrier type	Structure	Drug loading	Release profile	Stability	Biofilm-related potential	Key advantage	Main limitation	References
Liposomes	Phospholipid bilayer with an aqueous core	Carry hydrophilic and lipophilic drugs	Tunable; may provide sustained release	Prone to oxidation, aggregation, and drug leakage	May improve local antimicrobial delivery	Versatile drug encapsulation and biocompatibility	Leakage and limited storage stability	[56,57]
Cubosomes	Nanoparticles with a cubic liquid-crystalline structure	Accommodate drugs with different solubilities	Sustained or tunable release	Require suitable stabilizers	May improve local drug delivery; biofilm penetration requires validation	Versatile drug loading and high interfacial area	Complex formulation and limited clinical evidence	[58]
Hexosomes	Nanoparticles with a hexagonal liquid-crystalline structure	Accommodate drugs in lipid and interfacial domains	Depends on lipid composition and drug properties	Formulation-dependent	Potential for local antimicrobial delivery; direct evidence is limited	Distinct structure for tailoring drug release	Less studied and limited wound-healing evidence	[59]
Extracellular vesicles (EVs), including exosomes	Cell-derived lipid vesicles containing proteins and nucleic acids	Naturally carry biomolecules; additional loading depends on the method	Depends on cargo and cellular uptake	Varies with source, isolation, and storage	May influence wound-associated cells and biofilm-related processes	Biomolecule delivery and potential tissue-repair activity	Isolation, batch consistency, safety, and scale-up challenges	[60,61]

Table 2. Comparative performance and translational limitations of particulate and hybrid lipid nanocarriers for wound healing.

Carrier type	Structure	Drug loading	Release profile	Stability	Biofilm-related potential	Key advantage	Main limitation	References
Solid lipid nanoparticles (SLNs)	Solid lipid matrix stabilized by surfactants	May be limited by the ordered lipid matrix	Sustained release or initial burst	Crystallization may cause drug expulsion	May improve local antimicrobial retention; penetration requires testing	Drug protection and prolonged local retention	Limited loading and possible drug expulsion	[23, 62]
Nanostructured lipid carriers (NLCs)	Matrix of solid and liquid lipids	Often higher than SLNs due to a less ordered matrix	Tunable, potentially sustained release	May reduce drug expulsion; storage stability varies	May improve local antimicrobial availability; biofilm penetration requires validation	Greater loading flexibility than SLNs	Possible leakage, lipid oxidation, and scale-up challenges	[63,64,65]
Polymer–lipid hybrid nanoparticles (PLHNPs)	Polymer core combined with a lipid layer	Drugs can be incorporated into the core, lipid layer, or both	Controlled by polymer, lipid, and drug properties	Depends on composition and formulation	Surface modification may improve biofilm interactions; penetration needs validation	Combines polymeric structure with lipid functionality	Complex production and limited translational evidence	[37,66]

4. Mechanisms of action in wound repair

Wound healing is a dynamic process that is tightly controlled and it includes inflammatory, proliferative, and remodeling stages. Lipid-based nanocarriers help in wound repair through different but connected biological actions. These systems are not only used for drug delivery, but they also interact with the wound environment. As a result, they can improve drug availability at the site, regulate local conditions, and affect cell activities that are important for tissue regeneration.

4.1. Modulation of inflammatory response

Much of the anti-inflammatory promise nanoparticle systems hold for chronic wounds comes down to pharmacokinetics: once inside the body, circulation improves and delivery to inflamed tissue becomes noticeably sharper [67]. That's the basis on which anti-inflammatory nanocarriers have come to be seen as a workable route to reining in the abnormal immune activity that keeps stubborn wounds from closing [67]. NLRP3 is a different story. Inflammasome pathways are well mapped out in inflammation generally, but the picture gets blurry once the focus narrows to skin repair specifically. Some evidence gestures toward NLRP3's involvement, yet much of what happens downstream remains unsettled. Whether it links up with PGE2 signaling, or shapes how macrophages and fibroblasts communicate, remains unproven in vivo, and that gap is reason enough to hold claims about its precise role in wound repair somewhat loosely [68].

Chronic wounds are defined, in large part, by getting stuck in the inflammatory phase, the handoff to the next stage of healing just doesn't happen on schedule. Neutrophils and macrophages overstay their welcome, cytokines remain elevated, oxidative stress keeps building, and TNF-α, IL-1β, and MCP-1 turn up repeatedly at high levels, while NF-κB signaling stays switched on well past when it would normally shut off [69,70].Diabetes compounds the problem further: immune cells function less effectively, and oxidative stress in the wound climbs even higher [69].

Much of these dynamic centers on macrophages. Normal repair depends on their shift from the pro-inflammatory M1 phenotype toward the reparative M2 state, a transition that's more or less non-negotiable for healing to proceed properly. That shift stalls in chronic wounds, though; macrophages remain locked largely in M1, still churning out inflammatory mediators [70]. High glucose, oxidative stress, prolonged exposure to inflammatory signals, all of it feeds the imbalance, and aging or metabolic disease makes things worse still, since immune cells under those conditions may already be leaning inflammatory before a wound even forms [70].

Neutrophil extracellular traps (NETs) have been implicated in the persistent inflammatory response associated with impaired wound healing. Although NETs contribute to antimicrobial defense, their excessive accumulation may also promote tissue damage and prolong inflammation. In a study of human and rat diabetic wounds, increased NET formation was associated with NLRP3 inflammasome activation and IL-1β release in macrophages, suggesting a potential mechanistic link between persistent NET accumulation and inflammatory dysregulation in diabetic wounds [71]. However, these findings should not be interpreted as evidence that NET-mediated NLRP3 activation is a universal mechanism in all chronic wounds. The extent to which this pathway contributes to impaired healing may depend on the wound environment and underlying pathology [71].

Experimental findings from diabetic wound models suggest that NETs may promote NLRP3 inflammasome activation through at least two proposed mechanisms. One involves TLR4/TLR9-mediated NF-κB signaling, which may increase the expression of NLRP3 and pro-IL-1β. The other involves reactive oxygen species (ROS) and thioredoxin-interacting protein (TXNIP), which may facilitate NLRP3 inflammasome activation [72]. Although these findings provide mechanistic insight into NET-associated inflammation in diabetic wounds, further research is needed to establish the contribution and relative importance of these pathways across different chronic wound conditions.

In experimental diabetic wound models, DNase I-mediated NET degradation has been reported to reduce NLRP3 inflammasome activation and inflammatory responses, while improving wound-healing outcomes [72]. These findings support the potential of NET-targeting strategies, although their efficacy and safety in human chronic wounds require further investigation. Lipid-based nanocarriers may offer formulation-dependent advantages, including improved drug stability and localized delivery; however, the extent to which these properties translate into better inflammatory control and wound healing depends on the carrier composition, therapeutic payload, and experimental context [67]. Other

strategies converge on the same goal from different angles, blocking TNF-α or IL-1β, activating PPAR-γ, deploying antioxidants, all of them nudging macrophages toward a more reparative phenotype [70].

Inflammation in chronic wounds doesn't trace back to any single factor, immune imbalance, NET activity, oxidative stress, and cytokine overproduction all act in concert. Lipid-based nanocarriers may provide a platform for modulating multiple aspects of the chronic wound microenvironment, particularly when designed to deliver agents targeting complementary inflammatory pathways. However, whether these combined effects translate into improved healing outcomes must be established for each formulation through appropriate preclinical and clinical studies.

4.2. Antimicrobial and biofilm-disrupting activities

Why chronic wound infections resist treatment so persistently traces back, in large part, to bacteria's capacity for forming biofilms at the wound site. Organized into microbial communities, they end up wrapped in a self-produced extracellular polymeric substance built from polysaccharides, proteins, and extracellular DNA [72]. Antimicrobial agents struggle to get through this matrix, immune cells even more so, and bacteria sheltered inside survive conditions that would otherwise finish them off, feeding infections that won't resolve and healing that stalls indefinitely[26,73].

Multidrug resistance layers another problem on top. Staphylococcus aureus, MRSA, Pseudomonas aeruginosa, familiar names, all capable of standing up to multiple antibiotic classes at once. Biofilms make things worse still, blocking drug penetration and giving bacteria somewhere to hide from whatever treatment arrives [73]. What's needed, then, is a system doing two jobs simultaneously: killing bacteria while taking the biofilm apart.

This is exactly why lipid-based nanocarriers have become such a major research focus. Small size, generous surface area, adaptable design, together these features sharpen antimicrobial drug delivery, shield the drugs from breaking down prematurely, and allow slow release right at the infection site [72,73]. Their small size also lets them interact more closely with bacterial membranes, and moving through parts of the biofilm itself raises drug accumulation in infected tissue, potentially cutting both the dose needed and the odds that resistance develops [72].

Nanostructured lipid carriers bring something beyond delivery, too: antibacterial activity in their own right, evident against both Gram-positive and Gram-negative species across several studies, translating into a lower microbial burden in infected wound tissue.

Some lipid platforms push further, disrupting biofilms directly. LCNPs, lyotropic liquid crystalline nanoparticles, illustrate this well; their non-lamellar internal architecture lets antibiotics travel alongside agents built specifically to tear biofilms apart [26]. Action starts at the bacterial surface, electrostatic and hydrophobic forces pulling the particle in and triggering membrane engagement, drug release following shortly

after. Loading more than one agent at once opens up the possibility of hitting bacteria and biofilm matrix simultaneously [26]. Within these systems, biofilm breakdown tends to run through two mechanisms, quorum sensing inhibitors on one side, EPS-degrading enzymes on the other. Bacterial communication is what QSIs go after directly, interfering with acyl-homoserine lactones and their receptors, and as that breaks down, virulence drops along with the pace of biofilm formation. Enzymes take a different route: glycoside hydrolases break down polysaccharides, DNase I degrades extracellular DNA, and the biofilm that results are weaker, more porous, its bacteria exposed and easier for antibiotics to finish off [26]. LCNP structure protects the enzymes themselves as well, a large interfacial area limiting degradation from environmental exposure or protease activity. Against Pseudomonas aeruginosa biofilms in experimental testing, particles loaded with PslG enzyme and tobramycin outperformed free drug, and in animal models the antimicrobial and antibiofilm activity ran roughly tenfold higher [26]. There's something to this combination, pairing an antibiotic with an agent that dismantles biofilm, within one system, that appears to genuinely shift treatment outcomes.

Other routes reach toward the same end. Solid lipid nanoparticles carrying silver sulfadiazine gave stronger antibacterial action, longer release at the wound site, and lower toxicity toward skin cells [32,73]. A different combination shows up elsewhere, antimicrobial peptides paired with other agents, and together the two manage stronger antibacterial effects than either would achieve alone [32].

Natural antimicrobial compounds, essential oils among them, have found carriers too, in liposomes and NLCs. Their activity holds up better this way, delivery into infected tissue improves, and effectiveness shows against biofilm-forming organisms like Pseudomonas aeruginosa, Klebsiella pneumoniae, and Listeria monocytogenes [32].

4.3. Enhancement of angiogenesis and ECM remodeling

Repair hinges, first and foremost, on blood actually reaching the wound. When that supply falls short, healing either slows or stops altogether, and chronic wounds offer a clear illustration angiogenesis there tends to run blunted or considerably delayed, leaving cells short on the oxygen and nutrients they need to keep moving forward [74].

At its core, angiogenesis is simple enough: existing vessels branch into new ones. What sets the process off is a shift in conditions, hypoxia especially, which endothelial cells detect before anything else happens. Once activated, they use proteases to break down the basement membrane, then migrate into the extracellular matrix, proliferate, and begin assembling tube-like structures. These immature vessels gradually connect with one another, and out of that piecemeal process, something resembling a functional network takes shape [74].

None of this happens against a static backdrop, either. The ECM itself keeps changing throughout, VEGF and FGF directing endothelial migration and growth while MMPs break matrix components apart to open room for movement. Desynchronize these two processes, and repair falters visibly[74].

Further into the process, healing takes on a different character. Fibroblasts differentiate under the combined pull of mechanical stress and cytokine signaling, and a fraction of them go on to become myofibroblasts the cells actually responsible for pulling the wound closed. Collagen shifts too as this unfolds. Type III dominates in the early phase, then gradually cedes ground to the sturdier type I as healing moves forward. Vessel density, elevated during the proliferative phase, thins out afterward, leaving behind tissue that's finally stable and properly organized [75].

Angiogenic molecules rarely perform well when delivered on their own biological environments break them down quickly, and much of their activity is lost almost immediately. Nanocarriers change this equation: molecules stay protected, release becomes controllable, and retention at the wound improves considerably. This logic underlies much of the nanoparticle work aimed at pushing neovascularization and healing further.

A handful of growth factors, it turns out, regulate angiogenesis and ECM remodeling together the two processes are not governed separately. PDGF, TGF-β1, and FGF shape how fibroblasts move and how keratinocytes re-epithelialize; downstream, this feeds fibroblast-to-myofibroblast differentiation, which in turn drives contraction [28]. SDF-1 works differently. Signaling through CXCR4 and CXCR7, it activates the PI3K/Akt and MAPK/ERK pathways, and both migration and survival at the wound site gain strength as a result. Delivered through gene liposome systems, SDF-1α has shown clear improvement in healing and regeneration outcomes [28].

PDGF's main job is recruitment, pulling mesenchymal, epithelial, and endothelial cells toward the wound and ramping up production of collagen and other ECM components at the same time. It doesn't often work alone. Paired with VEGF, it coordinates several repair processes simultaneously [76], a finding borne out in vivo, where platelet lysate-enriched biomembranes drove granulation tissue formation and stronger collagen deposition, translating directly into faster skin regeneration [76].

Copper-based nanomaterials reach into both processes as well. Collagen-related molecule production rises under copper's influence, integrins governing cell–matrix interaction get regulated, and MMP activity shifts stimulated at low concentrations, though higher levels can instead raise fibroblast expression, both outcomes ultimately supporting ECM turnover [75]. Angiogenesis responds to copper too, through elevated VEGF secretion and stronger HIF-1α activity, which together switch on genes tied to vascular regeneration[75]. Copper sulfide nanoparticles specifically have been linked to higher VEGF levels and greater collagen deposition one platform managing to support vessel formation and ECM reconstruction at once [75].

Hybrid approaches take healing from yet another angle. Combine liposomes with silk fibroin hydrogels, and cell proliferation along with angiogenesis outpaces what liposomes alone achieve, wounds closing faster as a result [28]. Hydrogels and scaffolds work more simply keeping the wound moist, giving cells room to attach and migrate. Not sophisticated, exactly, but genuinely functional [30]. Niosome-based hydrogels land in similar territory, lifting fibroblast activity and collagen deposition in ways that feed ECM rebuilding [30]. Exosome-mimetic vesicles mark still another direction worth noting. Neovascularization gets direct support from these particles, new vascular structures forming in chronic wounds as a result [55], reason enough to view them as a strong candidate for improving vascular regeneration going forward.

4.4. Promotion of cellular proliferation and migration

Rarely does a single defect explain why a chronic wound stalls. Several things typically go wrong at once: growth factors fall short of what repair demands, immune cells stop behaving predictably, and the coordination underlying tissue regeneration weakens dragging the entire process down [69]. Layer hyperglycemia on top, and the picture darkens further. AGEs build up gradually, disturbing fibroblasts, keratinocytes, and the immune cells that would otherwise keep repair moving in the right direction [69].

The wound environment ends up trapped in inflammation for far longer than it should be. Movement toward the proliferative phase slows, at times nearly stopping altogether. Fibroblasts fail to migrate efficiently into the wound bed; keratinocytes take longer than expected to cover the surface and none of these traces back to one mechanism. Continuous inflammatory signaling combined with oxidative stress comes closer to the actual explanation [69]. Macrophages add to the difficulty too, failing to shift toward M2 the way they should, which leaves the inflammatory phase unresolved when it ought to be winding down [69].

Some ground can still be recovered, though, when drug delivery is optimized. Lipid-based nanocarriers tend to be the tool of choice here less because they fix the underlying biology, more because they alter how signals reach cells in the first place. Liposomal miR-132 offers a clear example: intracellular levels rise within wound tissue, and faster re-epithelialization tends to follow [69]. Something comparable turns up with PEGylated liposomes carrying LL-37: keratinocytes take up far more of the peptide this way than they do the free form, hinting at a tighter, more localized interaction at the wound surface [46]. As these delivery platforms become more refined, their grip on cellular behavior tightens too. Nanostructured lipid carriers loaded with LL-37 improve wound closure and epithelial regeneration both, extending well past simple antimicrobial effect [44]. A comparable pattern shows up with solid lipid nanoparticles carrying LL-37 and serpin A1 together: release proceeds slowly, cell toxicity drops, and fibroblasts along with keratinocytes end up working within a noticeably more stable environment [46].

Once peptides or growth factors arrive by way of nanoparticle carriers, the effect on cell migration becomes clearly measurable. In a preclinical study using a splinted mouse full-thickness excisional wound model, PLGA nanoparticles loaded with LL-37 accelerated wound healing compared with PLGA nanoparticles or free LL-37 alone. Increasing the dose of PLGA–LL-37 nanoparticles improved wound closure up to a plateau, whereas increasing the dose of free LL-37 did not produce a significant dose-dependent improvement under the conditions tested [77]. Pair growth factors with antimicrobial peptides, and fibroblast migration rises within the first 24 hours. That early window carries real weight, since it shapes how tissue repair unfolds from that point forward [46] to drug transport in the end. What these systems really accomplish is getting cells to behave more coherently fibroblasts more active, keratinocytes migrating faster, re-epithelialization showing up earlier than it would otherwise [69].

4.5. Controlled delivery of growth factors, peptides, and nucleic acids

Antimicrobial peptides get a lot more useful once wrapped in lipid nanoparticles, and this pairing has become a major focus of current research. Protection and controlled delivery together translate into stronger therapeutic effect with fewer side effects [23].

Unencapsulated AMPs run into trouble on several fronts at once: enzymatic degradation, poor stability once inside a biological environment, and, at higher doses, rising toxicity. Lipid carriers push back against exactly these weaknesses. By keeping the peptide's structure intact, they extend its activity, improve bioavailability, and let it penetrate deeper into skin tissue than the free form ever manages [23]. Biocompatibility matters here too. Built from lipids the body tolerates well, LNPs keep unwanted side effects to a minimum, and controlled release adds a further layer of safety by spreading drug delivery out more slowly and steadily [23]. Nanostructured lipid carriers bring their own set of advantages within this broader category. Skin hydration holds up better under their use, water loss from the surface drops, and drugs consequently move through the outer skin barrier more efficiently, reaching layers they might not otherwise penetrate [33,78]. Release from NLCs tends to stretch out rather than happen all at once gradual delivery instead of a single burst. Adding bioactive oils to the formulation improves stability further and makes the release profile more predictable overall [33,78].

What makes lipid-based carriers genuinely useful in wound settings comes down to persistence: drugs stay at the application site longer, move more readily across biological barriers, and sustain local activity for extended periods

[26]. Cubosomes deliver comparable benefits through a different route. In the moist environment typical of wounds, they limit drug degradation and keep therapeutic agents stable, while their nanoscale architecture supports controlled release and sharpens the efficiency of local delivery [42,44].

LL-37 is one antimicrobial peptide that's been carried this way, gaining protection from enzymatic breakdown and improved stability in biological environments as a result [42]. There's a further mechanism worth noting: Certain cubosome formulations have demonstrated cellular uptake in experimental systems, with the extent and mechanism of internalization depending on factors such as lipid composition, surface characteristics, and cell type. However, cellular uptake should not be equated with universal or direct cytosolic delivery, and further evidence is required before cubosomes can be considered mechanistically equivalent to naturally occurring exosomes [79,80].

Other lipid-based nanocarriers and hybrid polymer systems follow similar logic for controlled delivery in wound healing. A persistent obstacle in this field is how quickly factors and signaling molecules break down in the wound environment when applied Load a drug into these systems and it gains a kind of protection: enzymes have a harder time breaking it down, and release stretches out over time rather than happening all at once. The result is activity within the wound that lasts far longer than free application could ever sustain [30,81]. Fewer applications become necessary as a result, and drug levels stay more stable throughout treatment both factors that support better healing outcomes [30,81]. Hybrid lipid–polymer systems add still more to this picture. Drug loading capacity increases, physical stability of the formulation improves, and the resulting environment ends up resembling the extracellular matrix closely enough to support genuine cell interaction and tissue repair [30].

4.6. Antioxidant and immunomodulatory mechanisms

Chronic wounds hinge substantially on oxidative stress. ROS at normal levels are essential for cell signaling, but push them too high and cells start getting damaged, inflammatory pathways like NF-κB switch on, and cytokine production persists longer than it should [69]. Elevated ROS also throws immune balance off and keeps inflammation from resolving properly, feeding into delayed healing and wounds that simply won't close [82]. Prussian blue nanoparticles rank among the better-known antioxidant platforms addressing this problem. What makes them notable is a kind of multi-enzyme mimicry catalase, superoxide dismutase, peroxidase all rolled into one particle, letting them handle multiple ROS types in damaged tissue with real efficiency [48]. Keratinocytes, fibroblasts, and endothelial cells gain protection under oxidative stress as a result, and NRF2/HO-1 signaling part of the cell's own defense machinery can be restored in the process [48].

On their own, though, nanoparticles rarely stay stable within a wound environment for long. Loading PBNPs into thermosensitive hydrogels solves this reasonably well, slowing release and extending antioxidant activity at the wound site. Diabetic wound models treated this way showed reduced ROS along with lower inflammatory cytokines IL-6, TNF-α among them [48]. The benefit wasn't confined to inflammation alone, either: angiogenesis improved too, CD31-positive vessels increased, and wound closure sped up in vivo as a consequence [48].

At the heart of chronic wound immunomodulation sits macrophage behavior, and the pivotal event is a shift away from the pro-inflammatory M1 state toward the reparative M2 phenotype this is ultimately what resolves inflammation and gets repair underway [83]. Several factors can steer that shift at once. Biomaterial design counts among them, and surface properties in particular carry real weight: hydrophilicity, roughness, stiffness all shape which phenotype ends up dominant. Hydrophilic surfaces with moderate roughness tend to favor M2, whereas hydrophobic or overly stiff environments keep macrophages locked into inflammation [83]. Biomimetic hydrogels built around ECM components hyaluronic acid, collagen offer a different route entirely, delivering signals close enough to the body's own that anti-inflammatory macrophage activity gets a further push [83]. Trace elements like strontium and silicon work alongside external stimuli such as photodynamic or magnetic systems, adding still more avenues for reprogramming macrophages and driving regenerative response [83]. After macrophages polarize toward M2, they start releasing mediators IGF-1 and VEGF among them that act directly on fibroblasts and endothelial cells, tying immune modulation to angiogenesis and matrix remodeling in a chain that's fairly easy to trace [84]. What follows reads almost like a cascade: endothelial CD31 expression climbs, fibroblasts lay down more type I collagen, and these in vitro shifts track with outcomes seen in vivo stronger angiogenic activity, a better-organized matrix, and wounds that close faster [84].

5. Biomedical applications

5.1. Delivery of antibiotics, antimicrobial peptides, and antiseptics

The EPS layer is largely why biofilms make antibiotic treatment so hard drug diffusion slows, and much less of the drug ever reaches the bacteria hiding inside. Infections drag on as a result, sometimes turning chronic [26]. Bacteria within biofilms aren't equivalent to free-floating cells either, which adds yet another layer of resistance on top [26]. Lipid-based nanocarriers have drawn considerable research attention for this reason. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, liquid crystalline formulations all fall under this umbrella. What they share is protection against enzymatic degradation, stability preservation, and gradual release, which keeps the drug active longer at the infection site and improves its ability to move into the biofilm itself [26]. These systems also bring something valuable through membrane interaction. Being amphiphilic lets them associate readily with lipid bilayers fusion happens sometimes, simple surface adsorption other times. Whichever route it takes, drug accumulation near bacterial cells goes up, occasionally reaching inside them [2]. Some evidence points to the interaction itself destabilizing bacterial membranes, though how much depends heavily on the formulation in question [2].

Many of these delivery systems carry antimicrobial peptides along with them short, positively charged molecules that work mainly by disrupting bacterial membranes until the membrane potential collapses and the cell dies [85]. Their affinity for lipid bilayers is high. Selectivity, though, is a separate matter. Whether a peptide exists as a single monomer or clusters into aggregates can change its behavior quite a bit [85].

Membrane damage is easy to stop at, but it's only part of the story. Some peptides get past the membrane entirely and end up inside the bacterial cell, where they interfere with DNA, RNA, or protein synthesis a second mechanism that probably slows down resistance development [85]. This dual action doesn't apply across the board, though. Some peptides show both behaviors, some don't, and it really depends on which peptide you're looking at.

Antiseptics enter the picture too, particularly where chronic wounds demand rapid microbial reduction. Several studies paired antiseptics with proteases and EDTA specifically to break down Staphylococcus aureus and Pseudomonas aeruginosa biofilms [86]. EDTA works by stripping away the divalent ion’s calcium, magnesium that hold the EPS network together, weakening its structure and letting antiseptics penetrate more effectively, often at reduced doses [86]. In this field, combination therapy has become close to a default strategy. Bacteria die more effectively when multiple agents act together, and this also permits lower doses with reduced overall toxicity [2]. There's a complication, though biofilm bacteria tolerate antibiotic concentrations that would overwhelm planktonic cells, sometimes by orders of magnitude [2].

Lipid nanocarriers fit naturally into this combination strategy, as they can be integrated with other therapeutic components to enable coordinated antimicrobial delivery and stimulus-responsive release. [2,26]. For example, PEG-based hydrogels incorporating gold nanorods and IK8-loaded liposomes have been explored to achieve NIR-triggered peptide release, providing spatiotemporal control over antimicrobial delivery (**Figure 5**). The lipids themselves can shift how drugs partition into bacterial membranes, too, which may sharpen activity against both planktonic bacteria and those embedded within biofilms [2].

Intracellular delivery counts as a further advantage. Fusion with membranes, or entry through uptake pathways, raises drug concentration near or within bacterial cells [2], while partially sidestepping resistance mechanisms enzymatic degradation, reduced permeability that tend to run stronger inside biofilms [2].

None of this makes lipid-based carriers flawless, even so. Stability, penetration, combination delivery, direct membrane interaction real strengths, all of them but clinical translation remains limited, and more thorough in vivo validation is still needed before consistent real-world application becomes realistic [2,26,87].

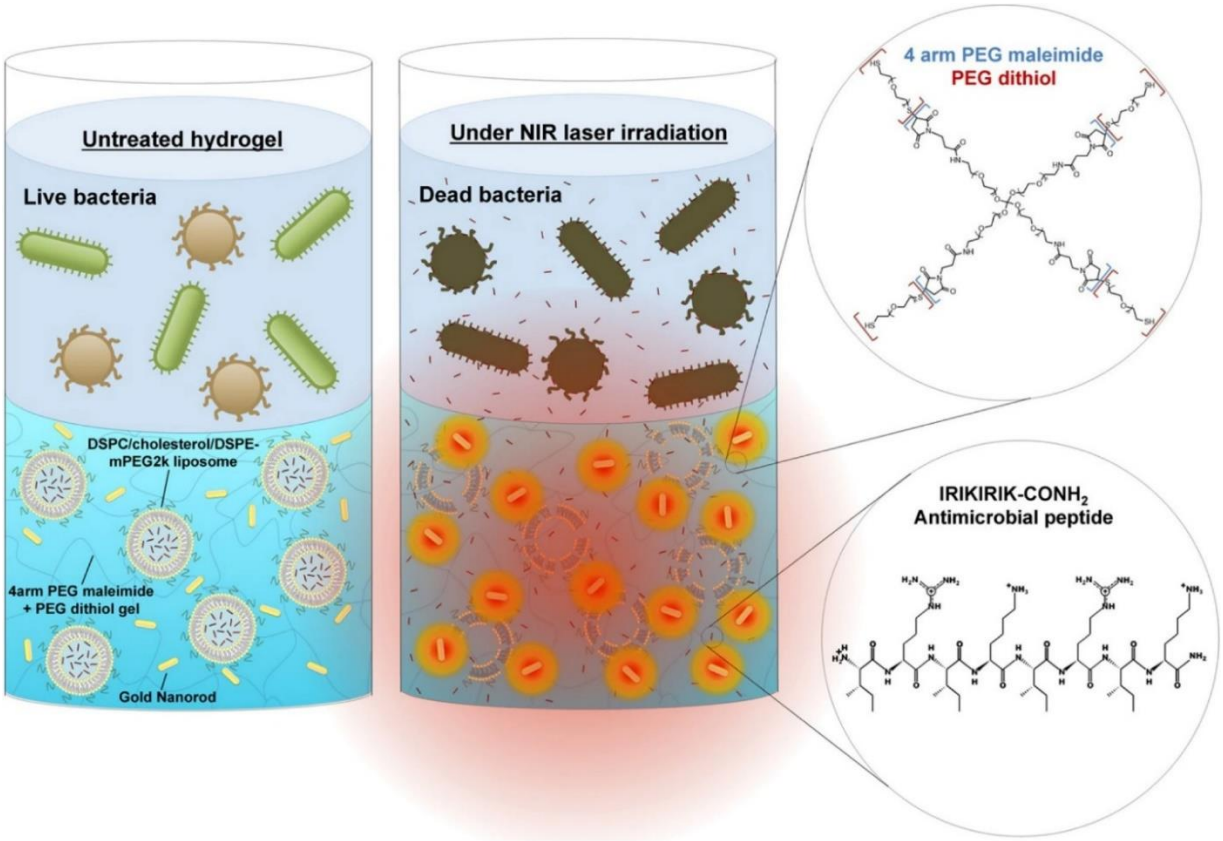


Figure 5. Schematic illustration of a PEG-based hydrogel incorporating gold nanorods and liposomes loaded with the antimicrobial peptide IK8, highlighting NIR-triggered peptide release and its potential role in localized antimicrobial therapy. Abbreviations: IK8, IRIKIRIK-$CONH_2$, PEG, poly(ethylene glycol) [88].

5.2. Gene and siRNA delivery in chronic wound therapy

What defines many chronic wounds is a prolonged inflammatory state that simply won't resolve the immune system fails to return to balance, and cytokines keep getting released well past when they should stop [89]. This ongoing activity throws off the normal sequence of healing: cell migration slows, repair-related cells fail to proliferate adequately, and extracellular matrix remodeling gets disturbed alongside everything else [89]. Together, these effects make proper wound closure genuinely difficult, and persistent inflammation is often singled out as a key driver behind wounds that heal slowly or not at all [89].

RNA interference tackles this problem right at the molecular source. Small non-coding RNAs drive this mechanism. They bind specific mRNA sequences and switch off their expression a regulatory step that happens naturally after transcription [90]. siRNA does most of the heavy lifting here, steering the target mRNA toward degradation and shutting down protein synthesis from that gene. The RISC complex carries out the actual work. Once siRNA enters a cell, Argonaute protein takes hold of it and directs it toward the matching mRNA sequence. Base pairing lines up correctly, cleavage follows, and the gene falls silent [90]. Chronic wounds stand to benefit from exactly this pathway downregulating genes linked to inflammation, and to the broader pathways behind abnormal tissue repair [90].

Real barriers stand in the way of direct siRNA application, though, despite its therapeutic promise. Physiological conditions are hostile to it nucleases degrade it rapidly. Its negative charge doesn't help either, limiting how efficiently it crosses cell membranes [90]. Even once internalized, siRNA can end up trapped in endosomal compartments, unable to reach the cytoplasm where RISC actually functions [90]. Functional efficiency suffers considerably as a result, and some kind of delivery system becomes essential.

Chronic wound research has poured considerable attention into lipid-based nanocarriers precisely because they offer a way around these obstacles. Enzymatic breakdown within the wound environment gets blocked, cellular uptake

improves, and the odds of successful intracellular delivery rise as a result [89]. Once the carrier reaches its target site, siRNA can be released into the cytoplasm, where gene silencing takes place [89].

Targeting inflammatory mediators with real precision is where more advanced lipid nanoparticle platforms have made their mark. Stable nucleic acid lipid nanoparticles carrying HMGB1-siRNA make a good example, engineered to suppress inflammation and abnormal remodeling by going after HMGB1 directly [91]. When specific ligands get attached to these systems, interaction with target cells improves further still, and both uptake and intracellular delivery benefit as a result [91]. Knocking down HMGB1 this way calms inflammatory signaling in the wound area. Cytokine output falls. Immune cells calm down noticeably [91]. The data back this up: TNF-α levels fall, and fewer immune cells make their way into the damaged tissue [91]. A wound does not close just because of this, but the local environment shifts toward something repair can actually work with.

Beyond HMGB1, other targets get similar attention as siRNA candidates in chronic wounds TNF-α, and MMPs, the enzymes that degrade matrix [89,90]. Silencing these calms excess inflammation, brings ECM turnover closer to balance, and gives angiogenesis an indirect boost [90]. The pattern across experimental wound models is fairly consistent. Lipid nanoparticle-delivered siRNA lowers inflammation, speeds up re-epithelialization, strengthens angiogenesis, and heals wounds faster than untreated controls do [90].

5.3. Growth factor and stem-cell–derived cargo delivery

Combined growth factor treatments tend to outperform single-factor approaches, at least in terms of healing outcomes [92]. which tracks well enough once you recognize that repair depends on multiple biological signals acting in concert rather than any single molecule carrying the process alone. bFGF, PDGF, VEGF, TGF-β: chronic wounds routinely show these running below normal levels [92], and such shortfalls can disrupt different stages of healing, slowing tissue repair as a whole. Growth factors have drawn considerable attention as regenerative cargo for local treatment precisely because their reach extends past any one cellular function. Cell migration, growth, differentiation all central to regeneration respond to their presence [92].

A different regenerative avenue altogether comes from the MSC secretome. Mesenchymal stem cells release it as a genuinely complex mixture cytokines, growth factors, lipids, extracellular vesicles, exosomes, mRNAs, and assorted signaling molecules, all bundled together [93]. Set against therapies built around a handful of selected factors, what distinguishes the secretome is its capacity to engage several repair pathways at once. VEGF, PDGF, EGF, FGF, HGF, IGF-1, TGF-β, SDF-1 these regenerative molecules turn up within it, each feeding into a different facet of tissue repair [93]. Preclinical models back this up with real evidence: diabetic and burn wounds treated with MSC-derived secretome achieved stronger re-epithelialization and closed faster than untreated comparisons did [93].

Within the secretome, though, not every component contributes equally. Among regenerative drivers, exosomes stand out in particular [94]. Proteins, lipids, nucleic acids these nanosized vesicles carry all of it between cells, shaping cellular responses as healing unfolds. Chronic wounds benefit especially from the anti-inflammatory side of this, given that inflammation which fails to resolve is what typically stalls healing. MSC-derived exosomes counter this stall directly. When macrophages shift toward M2, the M1 population the pro-inflammatory one goes down [94]. TNF-α and IL-1β decline too. IL-10 climbs [94]. What is left is a wound in much better shape to regenerate.

Direct effects on repair-relevant cells matter too. Fibroblasts and keratinocytes exposed to MSC-derived exosomes show increased migration and proliferation, responses that feed into more effective tissue reconstruction. Several wound models treated with exosomes showed improved re-epithelialization, better-organized tissue, and faster healing overall [94]. Growth factors, secretome-derived products, and exosomes don't share identical mechanisms each engages a somewhat different part of the healing process but this very difference is what makes them complementary, and what has made them attractive candidates for incorporation into lipid-based nanocarrier systems used in chronic wound therapy[92,94].

5.4. Lipid nanocarriers in diabetic, burn, and pressure ulcer healing

Diabetic ulcers, burn wounds, pressure ulcers lipid-based nanocarriers have been evaluated across all of these [32]. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers represent the main types, each carrying distinct formulation characteristics [69].

NLCs edge out SLNs in sophistication, largely because mixing solid and liquid lipids produces a less ordered matrix a structural quirk that turns out useful, permitting higher drug loading and more controllable release [69]. Liposomal systems find their niche too, particularly for bioactive compounds in wounds that are chronic or infected [69]. Compared with non-encapsulated drugs, lipid nanocarriers generally improve both wound closure and tissue regeneration across the experimental models tested [32]. Burn and diabetic wound studies similarly report accelerated wound closure and improved tissue regeneration in treated groups [32]. These therapeutic effects are closely associated with coordinated regulation of inflammation, apoptosis, angiogenesis, re-epithelialization, and extracellular matrix remodeling during wound repair **(Figure 6).** Pressure ulcer models have also demonstrated improved healing efficiency following treatment with lipid-based systems [32]. Preclinical findings are encouraging overall, although clinical translation remains limited [30].

One specific example: simvastatin-loaded NLCs, tested in pressure ulcer models, were built to improve the drug's water solubility and skin penetration [95]. The formulation aimed specifically at boosting skin deposition while sustaining release at the wound site [95]. Release itself proceeded slowly roughly 87% of the simvastatin released over 48 hours and this extended profile largely explains why local activity persisted as long as it did [95].

Animal testing found simvastatin-loaded NLC gel outperforming both conventional gel and drug-free NLCs in healing [95]. Even the drug-free NLCs offered some improvement, likely a byproduct of their occlusive effect on the wound surface rather than any pharmacological action. Inflammation dropped across treated groups, but re-epithelialization and dermal regeneration advanced furthest specifically in the drug-loaded NLC group, a pattern histology confirmed epidermal and dermal layers stayed more intact than in controls. Sustained release, higher local drug concentration, longer residence on the wound bed these together account for the improvement observed [95].

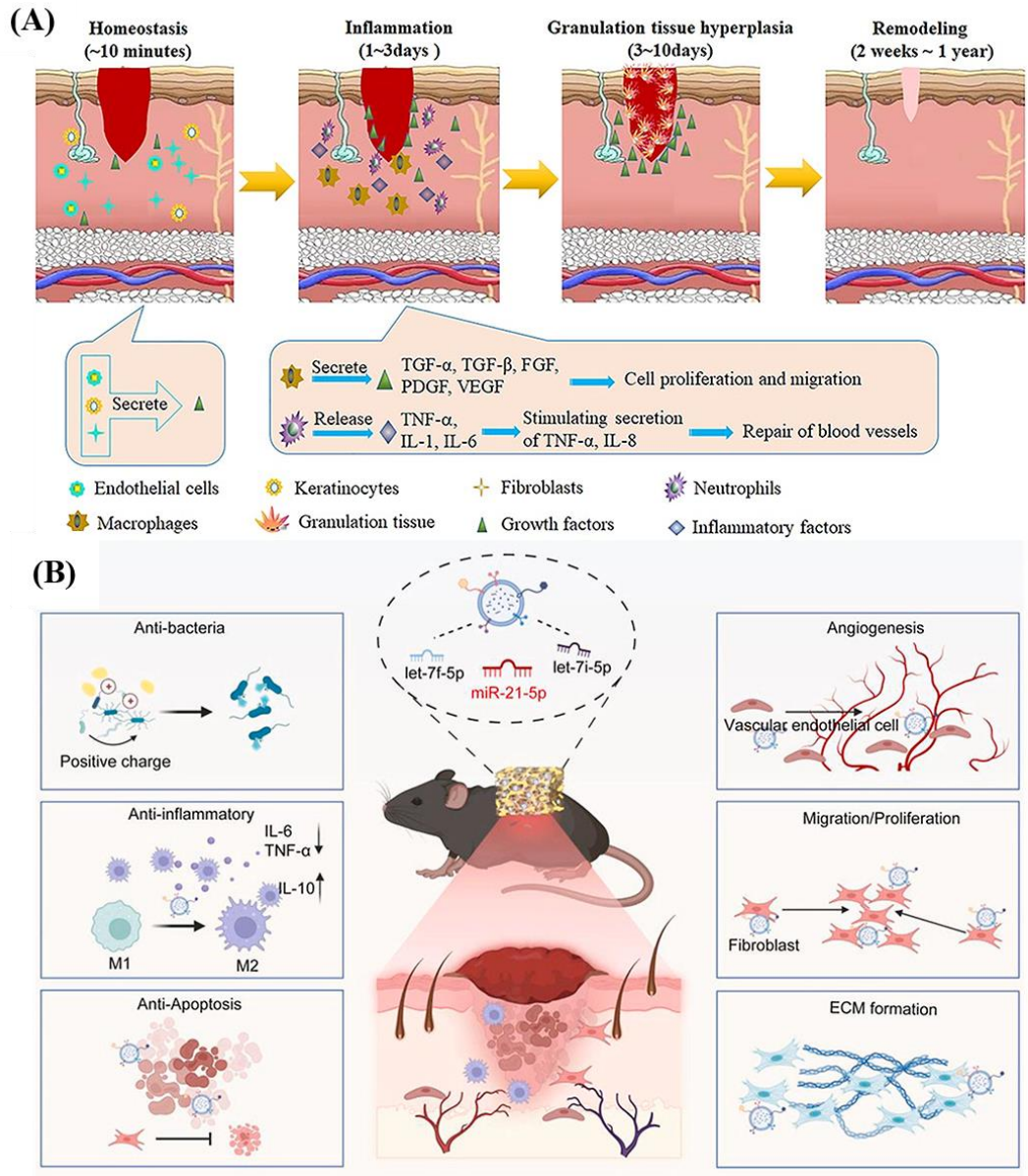


Figure 6. Mechanistic overview of burn wound healing and the therapeutic effects of HD-DP7/Exo. (A) Key growth factors and cytokines involved in burn wound repair, together with the preparation of HD-DP7 hydrogel and HucMSC-Exo-loaded HD-DP7/Exo [96]. (B) Proposed mechanisms underlying scar-free healing of infected deep second-degree burns by HD-DP7/Exo, including antibacterial activity, suppression of apoptosis and inflammation, promotion of angiogenesis and re-epithelialization, and regulation of extracellular matrix remodeling [97].

5.5. Topical nanogels, sprays, and dressing-integrated lipid systems

Direct delivery to the wound site, minimal systemic exposure these advantages explain why topical therapy remains the standard for chronic wounds. Creams, gels, ointments make up the usual formulations, all working to improve local availability of bioactive molecules and support the cellular activities repair depends on [92]. Recombinant PDGF, marketed as Becaplermin, stands among the growth factor-based topical products that have actually reached clinical application, showing real benefit in diabetic foot ulcers by speeding closure when paired with standard wound care [92].

One step further along, nanogel-based systems represent a more sophisticated class of topical carrier, built for stronger retention at the wound and tighter interaction with damaged tissue. Two things set them apart high loading capacity, and the ability to stay anchored to the wound surface while ferrying therapeutic cargo efficiently to where it's needed [98]. One example makes the case well: a polyvinyl alcohol/alginate nanohydrogel, built specifically to deliver mesenchymal stem cell-derived exosomes locally. In vitro, endothelial cells showed more proliferation, more migration, stronger angiogenic activity. Diabetic wound models given this hydrogel healed faster than the ones treated with free exosomes [100]. Histology confirmed it: re-epithelialization came out stronger, collagen built up more, and tissue regeneration looked distinctly more organized than in the controls. Angiogenesis markers such as CD31 and α-SMA showed upregulation too, and VEGF activation through the ERK1/2 pathway pointed toward sustained exosome retention within the nanogel as the likely explanation behind the stronger vascularization and repair observed [98].

Keeping fragile therapeutic molecules stable while boosting local availability is where lipid-based delivery systems earn their place as well. Surface modification widens what's possible here, and PEGylation is the go-to method PEG chains attached to the nanoparticle surface build a hydrophilic coating that limits protein binding and cuts down recognition by the reticuloendothelial system, extending circulation time and, along with it, how long the therapeutic effect lasts [14,23]. Liposomes contribute their own protective role too, guarding bioactive agents against enzymatic degradation, immune inactivation, and chemical instability protection that extends functional lifetime once the formulation reaches the skin [99]. Human epidermal growth factor makes the point well: once encapsulated in liposomes, it remained at the wound site longer and outperformed the free growth factor on therapeutic grounds [99]. Residence time was extended further by working hEGF-loaded liposomes into a chitosan-based film-forming spray, which spread a uniform protective layer across the wound surface [99]. Sustained growth factor release followed from this combination, along with better drug distribution over the wound and considerably easier application for patients. High encapsulation efficiency, physicochemical stability through storage, and accelerated healing in vivo rounded out the picture complete closure achieved by day 6, ahead of both free hEGF and non-sprayed liposomal hEGF. Liposomal protection paired with controlled release from the film matrix together account for this stronger outcome [99].

Hybrid lipid-based nanogels emerge from merging structural biopolymers with lipid nanocarriers, another category of topical delivery built to sharpen treatment outcomes. A clear division of labor defines the design: the lipid phase protects the drug and engages with cell membranes, while the polymer network takes charge of controlled release and holds the whole system stable [100]. Nanocellulose/lipid hybrid nanogels in particular have demonstrated prolonged drug release paired with sustained local exposure. Loaded with ofloxacin, one such formulation extended antibacterial activity well past what the free drug managed, suppressing bacterial growth for longer stretches. Compatibility with human skin fibroblasts held up reasonably well too, and scratch assays pointed to enhanced wound closure evidence that antimicrobial action and tissue regeneration can proceed side by side rather than working against each other. On balance, lipid-containing nanogels look like a genuinely promising direction for topical treatment, capable of controlling infection and supporting skin repair at the same time [100].

What nanoscale carriers ultimately contribute to topical formulations comes down to stability, retention, and controlled release of therapeutic agents right at the wound site. Nanogels, spray-based systems, lipid-integrated carriers each sustains local bioactivity and shields fragile molecules in ways conventional formulations simply can't replicate. Chronic wounds depend on this most of all, since healing there hinges on prolonged, localized delivery of regenerative and antimicrobial agents [92,99,100].

5.6. Multifunctional nano-bioactive wound platforms

Multifunctional nano-bioactive wound platforms took shape less as a linear improvement on earlier designs and more as a response to a genuine complication: chronic wounds almost never involve one isolated defect. Infection, inflammation, poor regeneration these rarely show up alone. Each one feeds the others. That probably explains why single-therapy approaches so often fall flat once they reach clinical testing [101,102].

That overlap reshaped design thinking entirely. Increasing a single drug dose, or repeating the same mechanism, stopped being the answer. Newer systems attempt something different combining several functional roles within one

structure, sometimes packing everything into a single nanomaterial, with the goal that antibacterial action, redox regulation, and tissue regeneration operate simultaneously rather than in sequence [101].

Take systems built around polydopamine, loaded with silver nanoparticles and antibiotics such as vancomycin. Their antibacterial effect doesn't come from one pathway alone bacteria face attack from multiple directions at once, chemical toxicity from silver working alongside antibiotic action. This combination drives down bacterial survival and allows lower antibiotic doses to remain effective, a real advantage for limiting resistance risk [101].

PDA is far from a passive carrier here. Exposed to light, it generates local heat, shifting the environment around bacteria quickly enough to weaken their stress response. The system doesn't merely release drugs, then it actively reshapes conditions to sharpen killing efficiency [101]. PDA carries antioxidant properties too, and supports cell adhesion, effects that become more evident during later healing stages. Animal models show faster closure alongside better-organized tissue structure, suggesting the benefit isn't confined to antibacterial action alone it extends into how tissue actually rebuilds once infection comes under control [101]. Penetration remains a real obstacle, though. Most nanosystems act largely at the surface, leaving deeper tissue harder to reach. Some designs address this by pairing metal organic frameworks with microneedle systems, improving delivery into deeper wound regions [102].

Every component in these platforms has its own job to do. Silver, zinc, and copper kill bacteria mostly through direct toxicity. Magnesium works differently it supports cell migration and helps new blood vessels form. Gallic acid does something else again, cutting down reactive oxygen species and pulling redox balance back into line. None of these elements act alike, and yet they end up converging within a single platform, hitting infection and regeneration at the same time [102]. None of these platform’s rests on a single therapeutic axis anymore. What they amount to instead are multifunctional systems antibacterial, antioxidant, and regenerative roles folded into one architecture, where the outcome depends less on any one strong agent and more on how the components work together. In chronic wounds especially, this matters, since a single mechanism rarely gets the job done on its own [101,102].

6. Preclinical and clinical evaluation

6.1. *In vitro* cellular models for wound healing assessment

Testing lipid-based nanocarriers in wound healing research relies heavily on in vitro cellular models simple by design, but genuinely useful for controlled observation, with much of the biological variability introduced by whole-organism systems removed, which makes comparing samples considerably easier. Keratinocytes (HaCaT), fibroblasts (NIH/3T3 and human dermal fibroblasts), endothelial cells (HUVECs), macrophages (RAW264.7) these are the standard cell types, each representing a different facet of skin repair. Not every study uses all of them together, but between them, most of the basic wound environment gets covered.

Cell viability comes first, typically, checked through MTT, CCK-8, or SRB assays that measure metabolic activity following exposure to nanocarriers. Viability tends to stay fairly high even at moderate to high concentrations somewhere around 100–200 μg/mL in several systems with no sharp drop in survival across epithelial, fibroblast, or endothelial cells [48,99,100]. Longer exposure sometimes brings a slight reduction, though not in any consistent pattern, and dose- and time-dependency get checked mainly to see whether toxicity climbs gradually or not at all.

Cell movement matters just as much. Scratch assays remain the standard method, transwell migration a secondary option. Fibroblasts and keratinocytes usually take center stage, with endothelial cells added when angiogenesis enters the picture. The results tend to be fairly clear-cut treated groups close the scratch gap faster than controls [82,99,100], and in some cases this difference shows up early rather than only at the endpoint. Proliferation follows a comparable trend, with higher cell growth often reported for lipid-based systems, though this varies by formulation and dose.

Oxidative stress gets measured in many of these studies too. ROS levels are typically checked with fluorescent probes like DCFH-DA, mitochondrial condition through JC-1 staining or ATP assays. Results aren't identical across every system, but in several cases, ROS levels drop following treatment, and mitochondria stay stable under most conditions no clear disruption in energy production reported in those instances [48]. NRF2 and HO-1 protein levels sometimes get assessed via Western blot as well, changes in these markers used to describe stress-related responses, though results here vary with the formulation.

Angiogenesis testing relies mainly on endothelial cells, HUVECs serving as the standard model. Tube formation assay is the key method cells form capillary-like structures on Matrigel, and lipid-based systems sometimes produce

more branching or longer tube networks as a result [82]. Migration and proliferation of these endothelial cells get measured too, often increasing in treated groups, and this part of the model functions as an indirect indicator of vascular activity during wound healing.

Some experiments move toward more complex setups co-culture systems, or conditioned media from mesenchymal stem cells, count among the common examples. These mix multiple cell responses together: fibroblasts, keratinocytes, endothelial cells, sometimes immune cells too, all responding simultaneously. MSC-conditioned media generally boosts migration and proliferation across several cell types at once [93], an effect that isn't confined to just one pathway. What these systems offer is a closer simulation of real tissue interaction, though they remain simplified compared with actual in vivo conditions.

Macrophage models find their way into some studies as well, RAW264.7 cells being the line most frequently chosen. Their main purpose is checking inflammatory response and compatibility, viability assays sometimes paired with cytokine measurements [87], with attention typically focused on whether nanocarriers disturb immune cell balance

6.2. Animal models and translational relevance

Evaluating lipid nanoparticle-based therapies typically relies on rodent models spanning both normal and impaired wound healing. C57BL/6 mice and genetically diabetic db/db mice (BKS.Cg-Dock7m +/+ Leprdb/J) show up most often in these in vivo studies. The diabetic model tends to carry more clinical weight, given how closely it mirrors human type II diabetes chronic inflammation, hyperglycemia, delayed re-epithelialization, all present [89].

Wounds are created on anesthetized animals, full-thickness excisional injuries cut into the dorsal skin, typically 7–8 mm wide, meant to model clinically relevant skin damage. A design feature that recurs across studies is the double-wound model each animal carries two wounds, one serving as internal control, which cuts down on variability between animals in healing outcomes [89,103]. Standardizing the injury this way gives researchers a consistent platform for comparing therapeutic performance across different lipid nanoparticle systems.

Administration usually happens topically; formulations applied directly onto the wound bed. Defined volumes of drug- or siRNA-loaded solutions carry out delivery in most cases, and hydrogel-based systems often step in to maintain localized, sustained exposure at the injury site [89]. Diabetic conditions sometimes call for repeated dosing, a reflection of how prolonged the inflammatory and proliferative phases become under impaired healing chronic disease pathology at work [89]. For mRNA-based systems specifically, hydrogel-assisted delivery improves both retention and in vivo expression at the wound site; bioluminescence imaging has shown higher expression compared with conventional lipid nanoparticles like MC3 or free mRNA [103].

Wound healing progression gets tracked consistently through longitudinal digital imaging paired with planimetric analysis. Formulations and delivery strategies vary across studies, yet nanoparticle-treated groups generally show accelerated closure relative to controls an effect particularly visible in diabetic models, where baseline healing already runs impaired [89,103]. In the db/db model specifically, IL4 mRNA-loaded lipid nanoparticles improved closure kinetics considerably, reaching roughly 80% closure within 12 days and complete closure by day 18 outperforming both free mRNA and MC3-based formulations [103].

Structural evidence from histological and molecular analysis backs up these surface-level observations rather well. Better epidermal organization, greater epidermal and dermal thickness, stronger tissue remodeling than untreated diabetic controls treated wounds across studies show this pattern consistently [89,103]. Staining with H&E, Masson's trichrome, and Sirius red reveals improved epidermal regeneration and higher collagen deposition in treated groups, skin structure often ending up close to normal [103]. Some reports push further still, noting that collagen maturation supports better ECM remodeling, marked by a higher share of organized collagen fibers linked to improved healing [104,105].

Structural regeneration isn't the only outcome worth attention here inflammatory regulation keeps showing up too, across study after study. Diabetic wound models keep showing the same pattern: inflammatory cells drop in number, and the shift from inflammation into the proliferative phase happens sooner [104,105]. Not every study lines up exactly, but the direction rarely changes.

A clearer picture of macrophage behavior emerges in some systems, mRNA-loaded LNPs particularly. M1 macrophages drop off, M2 macrophages become more abundant, and flow cytometry along with immunofluorescence staining has confirmed this polarization shift across several studies [103]. These cellular changes don't always line up precisely with visible wound closure, interestingly enough, though they remain detectable at the molecular and cellular level regardless. What this immunological shift tends to track with, fairly consistently, is improved tissue regeneration paired with faster closure overall. At the molecular level, diabetic wounds treated with advanced LNP systems show something else worth noting: oxidative stress drops. ROS levels fall significantly after treatment, which points to effective scavenging within the wound microenvironment in vivo [103]. Angiogenic activity picks up alongside this drop in oxidative burden CD31-positive vascular structures increase, α-SMA expression goes up, and together these point to better neovascularization and more mature tissue as healing progresses [103].

Where optimized systems like TS2 LNP actually stand in translational terms becomes clearer through comparative work against clinically approved lipid nanoparticle formulations SM102, ALC-0315 among them. Higher mRNA delivery efficiency, faster wound healing in diabetic models relative to existing FDA-approved platforms these comparisons show this consistently[103], a pattern that underscores just how much lipid structure optimization matters for delivery performance and therapeutic efficacy alike in pathological wound environments.

Excision wound models in mice and rats have held their place as the standard mainly because they track human wound healing reasonably closely inflammation, proliferation, and remodeling phases overlap enough with the human process to justify their translational relevance [105]. That said, real limitations remain, and several studies point to them directly: skin thickness differs, rodent healing leans heavily on contraction in ways human healing doesn't, and the whole timeline runs considerably shorter than what people experience details worth keeping in mind whenever preclinical results get extrapolated toward clinical settings.

6.3. Safety, toxicity, and immunogenicity

How safe lipid-based nanocarriers like SLNs and LNPs turn out to be depends largely on their physicochemical makeup. Size matters. Surface characteristics matter too, and both can shift biological response quite a bit. Some lipid excipients already hold GRAS status, which gives a baseline assumption of biocompatibility but that status alone says nothing about how the same material behaves once it's shrunk down to the nanoscale. Interactions with proteins and cell membranes in biological systems can shift outcomes in ways that aren't always predictable in advance, which is precisely why systematic toxicological evaluation remains necessary before any clinical translation gets attempted [106]. Nanotoxicology, in this sense, offers essential insight into nano–bio interactions playing out at multiple biological levels.

Preclinical safety assessment usually starts with in vitro cytotoxicity testing before moving toward in vivo toxicological work, a fairly standard progression across the field. In vitro assays generally examine nanoparticle–cell interactions, and primary cells tend to offer more physiologically relevant toxicity information than immortalized cell lines manage [106,107]. Cell viability, membrane integrity, apoptosis, metabolic activity: these get checked routinely, though interpretation isn't always straightforward, since nanoparticle interference can distort results and complementary methods often become necessary for reliable conclusions [107]. What in vitro work can't capture, in vivo experiments pick up biodistribution, organ accumulation, whole-body biological response, none of which cell culture can replicate on its own [106]. These studies evaluate toxicity across acute, subacute, subchronic, and chronic stages, identifying target organs and dose-dependent adverse effects under controlled conditions[106]. Standard safety endpoints follow a fairly consistent set: survival rate, changes in body weight, hematological and biochemical parameters, histopathological examination of major organs post-exposure [107]. Regulatory bodies such as the OECD push this further, recommending oral, dermal, and ocular toxicity testing alongside LD50 determination to build a genuinely comprehensive safety profile [107].

Distinct from general toxicity, immunotoxicity deserves recognition as its own critical safety dimension. Hemotoxicity, complement activation, thrombosis, acute hypersensitivity reactions like hemolysis and anaphylaxis these all fall within the range of immune-related responses worth watching for [107]. PEGylated liposomes and related lipid- or polymer-based nanocarriers show up particularly often in connection with complement activation-related pseudo-allergy, or CARPA, a dose-limiting concern that remains well recognized in the field. Given this, blood-

contacting applications demand evaluation of erythrocyte compatibility, complement activation, and acute immune response, regardless of what the broader application context happens to be. At the molecular level, opsonization triggers recognition by the mononuclear phagocyte system, shaping clearance rate, circulation time, and biodistribution downstream [107]. PEGylation remains the standard approach for lowering MPS uptake and extending circulation time, though repeated exposure carries its own risk accelerated blood clearance, driven by anti-PEG IgM formation [107].

Physicochemical properties largely determine how immunogenic and toxic lipid-based systems turn out to be particle size, surface charge, lipid composition, aggregation state, all factor in [106,107]. Smaller particles tend toward greater reactivity, a consequence of their proportionally larger surface area [106]. Within SLN formulations specifically, common surfactant s like polysorbate 80 and poloxamer 188 generally show acceptable safety profiles, though overall cytotoxicity still depends heavily on the specific formulation context [106].

Immune response owes a lot to surface charge specifically Cationic liposomes do improve cellular uptake but immune activation goes up right along with it, more than what neutral or anionic versions produce [107]. Part of these traces back to electrostatic interaction with negatively charged cell membranes, and part to heightened ROS generation; both look like plausible drivers of inflammation and cytotoxicity [107]. In vivo work backs this up. Cationic formulations tend to show dose-dependent toxicity along with lung inflammation, while neutral and anionic systems generally come out looking more biocompatible. Highly charged nanoparticles carry a further risk too, showing up more frequently alongside membrane disruption and genotoxic effects [107].

Charge isn't the only structural factor at play in immunogenicity, though. Particle size influences cellular uptake and immune activation on its own, while lipid phase transition temperature and vesicle lamellarity shape immunostimulatory potential in a different way multilamellar systems with high transition temperatures tend to provoke stronger immune responses than simpler vesicle structures manage [107]. Depending on physicochemical desig, liposomal formulations may trigger CARPA as well, a reminder of just how much formulation optimization matters for hemocompatibility and overall immune safety [107].

Properly designed lipid-based nanocarriers are generally considered biodegradable and biocompatible, yes, but safety still demands experimental validation in every case no universal toxicity rule governs nano–bio interactions reliably enough to skip this step [106,107]. What determines nanocarrier safety, on the whole, is a combination of size, surface properties, dose, and chemical composition working together, rather than any single defining parameter [106].

7. Challenges and future directions

7.1. Limitations and computational optimization of lipid nanocarrier technologies

Although lipid nanocarriers offer considerable potential for wound healing, their clinical translation remains limited by several overlapping technical challenges. Liposomes illustrate one of these limitations: drug leakage during storage can compromise their long-term stability and shorten their shelf life [15,16]. SLNs were developed in part to address this limitation. A solid lipid core does improve physical stability, true enough, but a new problem takes its place the crystal structure ends up too ordered, and drug loading suffers as a result [12,32]. Storage can even push the drug back out entirely, which defeats much of the purpose. One property improves, another worsens; stability and loading capacity seem to pull in opposite directions rather than moving together. Solid lipid nanoparticles (SLNs) were developed partly to address some of these limitations. Although their solid lipid matrix can improve physical stability, its highly ordered crystalline structure may restrict drug incorporation and contribute to drug expulsion during storage [12,32]. Consequently, improvements in stability do not necessarily translate into higher drug-loading capacity or better drug retention.

Nanostructured lipid carriers (NLCs) attempt to overcome some of these limitations by incorporating liquid lipids into the solid matrix, thereby reducing lipid crystallinity and potentially increasing drug-loading capacity. Nevertheless, their production can involve processing challenges, including high-pressure homogenization and the need to optimize surfactant concentrations [33]. Excessive surfactant levels may also raise concerns about cytotoxicity in wound tissue [20], highlighting the need to balance formulation stability, drug loading, and biocompatibility.

Other lipid-based systems face distinct challenges. Although cubosomes and hexosomes offer useful structural characteristics for drug delivery, their suitability for systemic administration depends on formulation-specific factors, including biocompatibility and interactions with blood components [45]. Scale-up also remains challenging for biomimetic vesicles, including extracellular vesicle-mimetic systems (EMVs), because of potentially low yields, batch-to-batch variability, and the lack of standardized production protocols [51]. Overall, these limitations highlight the difficulty of optimizing stability, drug-loading capacity, safety, and scalability simultaneously. More systematic approaches are therefore needed to identify suitable formulation compositions and processing conditions while minimizing unnecessary experimental work.

Lipid nanocarrier design involves multiple interacting variables, including lipid composition, lipid-to-drug ratio, surfactant concentration, and processing conditions [40]. Exploring these variables through conventional trial-and-error experiments can be time-consuming and resource-intensive. Machine-learning (ML) approaches offer a potential means of identifying relationships between formulation parameters and critical quality attributes. Models such as random forests and artificial neural networks can be used to investigate or predict properties including particle size, polydispersity index, zeta potential, and encapsulation efficiency from formulation and process data [108]. Such predictions may help prioritize promising formulations and reduce unnecessary experiments. However, predictive performance depends on the quality, size, and diversity of the training data, and model predictions require experimental validation.

Molecular dynamics (MD) simulations provide complementary molecular-level information by examining drug–lipid interactions, lipid organization, and the localization and mobility of drug molecules within lipid assemblies. For example, MD simulations have been combined with experimental formulation and skin-permeation studies to screen active–lipid combinations and investigate how formulation composition influences drug incorporation and transport [109]. These approaches can help explain molecular interactions that are difficult to characterize using experimental measurements alone, although their predictions should be interpreted in light of the assumptions and limitations of the simulation models.

High-throughput formulation and characterization platforms can further facilitate the systematic preparation and evaluation of multiple lipid nanocarrier formulations under different experimental conditions. The resulting datasets can be used to identify promising formulations and guide iterative ML-based optimization of composition and processing parameters [110]. Integrating high-throughput screening with computational modeling may improve the efficiency of formulation development and support more systematic comparisons of candidate nanocarriers. Data-driven methods could also be explored for optimizing multicomponent formulations containing antimicrobial or antioxidant agents; however, claims regarding improved biofilm disruption or reduced toxicity require direct evidence for the specific formulation [101,102].

Taken together, ML models, MD simulations, and high-throughput screening may support a more systematic, prediction-guided approach to lipid nanocarrier development. Nevertheless, computational predictions alone cannot establish therapeutic effectiveness. For wound-healing applications, optimized formulations must still be evaluated for biocompatibility, drug-release behavior, and healing outcomes in appropriate experimental models.

7.2. Regulatory and ethical considerations

Regulatory hurdles loom large for lipid nanocarriers, particularly given how chronic wounds involve exposure that runs long and repeats often. At the bulk level, most lipids sit comfortably within GRAS status [18], but behavior shifts once these same materials shrink to the nanoscale surface area expands considerably, cellular interaction intensifies, and distribution patterns stop resembling what bulk-level assumptions would predict. Deeper cellular uptake sometimes follows from this, occasionally with real intracellular accumulation, and if the wound barrier happens to be compromised, systemic entry becomes possible too [8] meaning the effect isn't confined to the local wound site alone.

Manufacturing introduces yet another layer of difficulty. During scale-up, even small process variations end up shifting particle size, surface charge, and release profile [20], and these aren't trivial fluctuations they alter performance in ways that matter directly for therapeutic outcome. Regulatory complexity only compounds further with more advanced systems. Gene-loaded or siRNA-carrying liposomes raise genuine ethical and safety questions of their own,

off-target effects still not fully understood [50]. In practical terms, approval ultimately comes down to two things biological safety, and production consistency and neither proves easy to guarantee once manufacturing moves to scale.

7.3. Integration with smart dressings and biosensing platforms

Chronic wounds resist any notion of stability; conditions shift constantly, whether it's pH, temperature, or fluctuating enzyme activity such as MMPs [23]. Given this instability, constant, unresponsive drug release stops making much sense as a strategy. Responsive systems have taken shape as one answer to this. Embedding lipid nanocarriers within smart dressings or electronic skins pursues a fairly simple goal release the drug only when it's genuinely needed, on trigger rather than continuously. From there, the logical extension is biosensing integration: sensors picking up signals such as bacterial activity, oxygen levels, or cytokine presence [26], which opens up real-time monitoring as a real possibility.

When abnormal signals do appear, the system responds accordingly. Light or a mild electrical input can activate release, delivering antimicrobial agents or growth factors right to the affected micro-area [26]. Treatment, in this framing, stops being something scheduled by the clock and becomes something the wound itself sets in motion.

7.4. Personalized nanomedicine approaches

Chronic wounds are not identical between patients. Even similar ulcers behave differently. Some are infected. Some are ischemic. Biofilm density and immune response also vary[70]. Because of this variability, standard treatment often gives inconsistent results. Personalized nanomedicine adjusts the carrier design. Lipid nanocarriers are modified based on wound condition. Not fixed formulation. For example, bacterial biofilms often carry negative charge. Cationic systems like DOTAP-modified carriers can improve binding and penetration [17]. Simple electrostatic effect. In ischemic wounds, the problem is low blood supply. So, carriers may carry VEGF or bFGF to stimulate angiogenesis. Stem cell secretomes are also used sometimes [92,93]. Diagnosis comes first. The wound environment is analyzed, then formulation is chosen. Not reversed.

8. Conclusion

Lipid-based nanocarriers have attracted considerable attention as potential tools for improving wound management, particularly in chronic wounds where persistent inflammation, oxidative stress, microbial infection, and impaired tissue regeneration frequently occur simultaneously. The studies reviewed in this article demonstrate that the therapeutic value of these systems extends beyond their ability to encapsulate and deliver bioactive compounds. Their composition, internal architecture, surface properties, and release behavior can all influence how therapeutic agents interact with the wound environment and contribute to different stages of tissue repair. Liposomes, solid lipid nanoparticles, nanostructured lipid carriers, lipid–polymer hybrids, and other advanced lipid assemblies each offer specific advantages, although their suitability depends largely on the therapeutic objective and the biological characteristics of the wound. An important direction in this field is therefore the development of multifunctional formulations capable of addressing several interconnected pathological processes rather than targeting individual mechanisms in isolation. Combining antimicrobial activity with inflammation control, antioxidant protection, angiogenesis, and tissue regeneration may offer a more effective strategy for managing wounds that are otherwise difficult to heal.

Nevertheless, promising experimental findings do not necessarily translate into clinical success. Differences in lipid composition, formulation stability, drug-release behavior, and manufacturing procedures can substantially affect therapeutic performance and make comparisons between studies difficult. In addition, the biological complexity of chronic wounds is not always adequately represented by conventional in vitro assays or animal models. Addressing these limitations will require more standardized characterization methods, reliable preclinical models, and systematic assessment of long-term safety and therapeutic efficacy. Further integration of lipid nanocarriers with advanced wound dressings, responsive delivery systems, biosensing technologies, and personalized treatment approaches may also provide new opportunities for improving wound care. Computational modeling and artificial intelligence could further support formulation development by helping identify optimal combinations of lipid components, therapeutic cargo, and release characteristics. Ultimately, the clinical relevance of these platforms will depend on whether their

technological advantages can be translated into reproducible, safe, and meaningful improvements in wound healing. Achieving this goal will require closer collaboration between materials scientists, pharmaceutical researchers, clinicians, and biomedical engineers.

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