



Clinical Study

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Stimuli-Responsive Polymeric Nanoparticles for Controlled Release in Chronic Wound Care

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Abstract

Chronic wounds -- diabetic foot ulcers, venous leg ulcers, and pressure injuries -- affect an estimated 6.5 million patients in the United States alone, at an annual treatment cost exceeding US\$25 billion, yet the conventional dressings used to manage them remain largely passive barriers that cannot sense or respond to the wound's own biochemistry. This article synthesizes the literature on stimuli-responsive polymeric nanoparticles engineered specifically to close that gap in chronic wound care. We trace the pathophysiological basis for triggered release -- the elevated and variable pH, sustained protease activity, oxidative burden, and infection-associated heating that distinguish a non-healing wound bed from intact skin -- and review how pH-, enzyme-, redox-, thermal-, and light-responsive polymer chemistries, developed largely in oncology, have been adapted into nanoparticle, nanocomposite-hydrogel, and nanofiber architectures for topical antimicrobial and growth-factor delivery. Particular attention is given to protease-gated release systems that exploit the same matrix metalloproteinase dysregulation responsible for degrading therapeutic payloads in chronic wounds. Read together, the evidence supports stimuli-responsive nanoparticle-based dressings as a coherent and increasingly well-evidenced engineering pattern for active wound care, while leaving biofilm penetration, rodent-to-human translational validity, manufacturing reproducibility, and multi-trigger system design as an open research agenda.

Keywords: stimuli-responsive nanoparticles; controlled drug release; chronic wound healing; polymeric nanocarriers; diabetic wound care

1. Introduction

A chronic wound is, in the plainest clinical sense, a wound that has stopped following the script. Acute wounds move through hemostasis, inflammation, proliferation, and remodeling in a matter of weeks; chronic wounds — venous leg ulcers, diabetic foot ulcers, pressure injuries — stall, typically in a prolonged, self-perpetuating inflammatory phase, and can remain open for months or years. The scale of the problem is not a niche clinical curiosity. In the United States alone, chronic wounds affect an estimated 6.5 million patients, with an estimated excess of US\$25 billion spent annually on their treatment [1], and the broader literature on chronic wound management describes a comparably sobering picture of recurrence, amputation risk, and disproportionate impact on elderly and diabetic populations [2]. Conventional wound dressings — gauze, foams, hydrocolloids — are fundamentally passive: they manage moisture and provide a barrier, but they do not sense what is actually happening in the wound bed and they do not adjust what they deliver in response. A growing body of work in polymer chemistry and nanomedicine has spent the last two decades trying to close that gap, building nanoparticle carriers that release their cargo — antibiotics, growth factors, anti-inflammatory agents, antioxidants — only when the local wound environment signals that release is warranted.

This article synthesizes that literature specifically as it applies to chronic wound care. Stimuli-responsive polymeric nanoparticles are not a new idea in drug delivery generally; the underlying chemistry — pH-sensitive ionizable groups, enzyme-cleavable linkers, thermoresponsive phase transitions, redox-sensitive bonds, light-absorbing chromophores — was developed largely in oncology, where tumor pH, tumor-associated proteases, and externally applied light or heat provided convenient, if imperfect, triggers [3]. Chronic wounds turn out to offer an unusually rich and unusually convenient set of analogous triggers of their own. The wound bed of a non-healing ulcer is not a passive surface; it is a biochemically distinct microenvironment, persistently more alkaline than intact skin, persistently rich in proteolytic enzymes, frequently colonized by bacteria whose metabolism further shifts local pH and redox state, and often locally warmer than surrounding tissue during active infection. Each of these departures from normal physiology is,

from a materials-design standpoint, a trigger waiting to be exploited, and each has been exploited, with varying degrees of maturity, in the nanoparticle and nanocomposite-hydrogel literature reviewed here.

Our synthesis is organized around five themes. We begin with the pathophysiology of the chronic wound bed itself, because the entire premise of stimuli-responsive delivery rests on the wound environment actually being different enough from healthy tissue to serve as a reliable trigger. We then review the core design chemistries — pH-responsive, enzyme/protease-responsive, redox and reactive-oxygen-species (ROS)-responsive, thermoresponsive, and light/photothermal-responsive polymeric systems — as they have been adapted specifically for topical, wound-facing delivery rather than systemic or tumor-targeted delivery. We survey the architectures that have moved beyond single-trigger nanoparticles toward nanocomposite hydrogels and nanofiber scaffolds that combine a stimuli-responsive nanoparticle payload with a macroscopic dressing format, since that combination, rather than the free nanoparticle alone, is what actually reaches a wound bed in most reported designs. We then discuss what the literature reports about growth-factor and antimicrobial cargo specifically, since these are the two payload classes that dominate the chronic-wound-focused work. We close with an honest accounting of open challenges — biofilm penetration, batch-to-batch reproducibility, the gap between rodent models and human chronic wounds, and regulatory pathway questions — that the field has not yet resolved.

It is worth being explicit about scope and confidence. This is a literature synthesis, not a report of new experimental work, and we have been careful throughout to attribute specific numeric claims to the studies that reported them rather than presenting them as general facts of the field. Readers should also note that "chronic wound care" spans several distinct clinical entities — diabetic foot ulcers, venous leg ulcers, pressure injuries — that share overlapping but not identical pathophysiology, and that much of the nanoparticle literature discussed here has been validated primarily in diabetic wound models, which are the most standardized and most frequently used preclinical system in this space.

Framing the problem this way also clarifies why

"controlled release" is doing more work in this literature than the phrase might suggest at first pass. In an oncology context, controlled release usually means extending a drug's circulation time or concentrating it at a tumor site relative to systemic exposure. In a topical wound-care context, the comparison is not against systemic exposure at all — the drug is already applied locally — but against the much more mundane failure mode of a topical formulation simply washing out in wound exudate, diffusing away from the site that needs it, or being degraded by the wound's own enzymes before it has had time to act. Stimuli-responsive nanoparticle encapsulation is, in this sense, less a targeting technology than a protection-and-timing technology: it keeps an otherwise fragile or short-lived active ingredient intact and sequestered until the wound's own biochemical signal indicates the moment has come to release it, and it is that timing and protection function, more than any spatial targeting effect, that recurs across essentially every system reviewed in the sections that follow.

2. Chronic Wound Pathophysiology and the Case for Localized Control

Healthy, healing skin follows a temporal and biochemical trajectory that is reasonably well conserved across acute injuries: an initial acidic surface pH that gradually normalizes, a self-limiting burst of neutrophil and macrophage activity that resolves within days, and a proteolytic environment that is active just long enough to clear damaged extracellular matrix before giving way to matrix deposition and re-epithelialization. Chronic wounds depart from this trajectory in ways that are now reasonably well characterized. Surface pH in chronic, non-healing wounds is persistently elevated relative to intact skin and to healing acute wounds, sitting in a neutral-to-alkaline range rather than the mildly acidic range characteristic of the epidermal acid mantle; this single departure affects bacterial growth, protease activity, and the ionization state of many drug and polymer functional groups simultaneously, which is precisely what makes it such an attractive design trigger [4]. Alongside the pH shift, chronic wounds sustain an inflammatory phase that in an acute wound would have resolved within one to two weeks, with continued neutrophil infiltration driving elevated levels of matrix metalloproteinases (MMPs) and other proteases well beyond the point where they are constructively remodeling tissue, so that MMP activity begins instead

to degrade newly deposited matrix and sequester or destroy growth factors before they can act [5]. This protease-rich, growth-factor-depleted environment is a major reason growth factor therapies applied as simple topical solutions have had disappointing clinical results: the factor is degraded or washed away faster than it can act, motivating exactly the kind of protected, triggered-release delivery vehicle this article surveys [6].

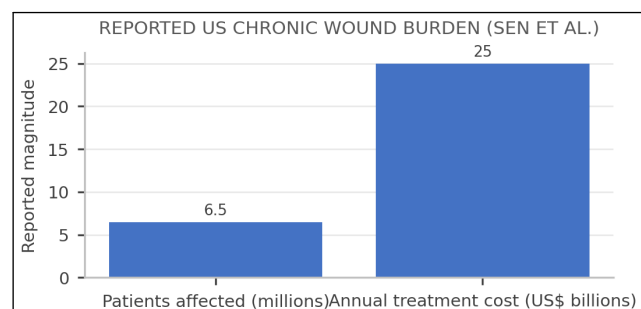


Figure 1: The reported scale of the chronic wound burden in the United States -- 6.5 million patients affected and an estimated excess of US\$25 billion spent annually on treatment -- the clinical and economic backdrop motivating the controlled-release engineering effort surveyed in this article [1].

Infection and biofilm formation compound the picture further, and are themselves a moving biochemical target rather than a static one. Bacterial colonization in a chronic wound bed further acidifies or alkalinizes local microenvironments depending on species and metabolic state, generates localized reactive oxygen species as part of both the bacterial and host inflammatory response, and, when established as a biofilm, creates a structurally distinct, drug-resistant niche that most systemically or topically applied antimicrobial agents penetrate poorly [2]. Taken together, this cluster of physiological features — elevated and variable pH, sustained elevated protease activity, an oxidative, ROS-rich local environment, intermittent bacterially-driven local heating, and biofilm-associated barrier effects — is what nanomedicine researchers mean when they describe the chronic wound bed as offering multiple orthogonal, exploitable triggers. Figure 1 summarizes, from a widely cited assessment of the clinical and economic scale of this problem, just how large the population affected by this pathophysiology actually is, which is the underlying reason the controlled-release engineering effort surveyed in this article has attracted sustained investment [1].

The clinical stakes of getting the timing of drug release right are not abstract. A dressing that releases an antibiotic on a fixed schedule regardless of bacterial

burden risks both under-dosing during a flare and unnecessary, resistance-promoting exposure during quiescent periods; a dressing that releases growth factor on a fixed schedule regardless of local protease activity risks releasing it directly into an environment that will degrade it before it reaches a receptor. Stimuli-responsive nanoparticle systems are, in this light, best understood not as a way to deliver more drug, but as a way to deliver the right amount of the right drug at the moment the wound's own biochemistry indicates it is needed — closing the loop between wound state and dressing behavior that a passive gauze or hydrocolloid simply cannot close [7].

3. pH- and Enzyme-Responsive Nanoparticle Chemistries

The most extensively developed trigger in this literature is pH, both because chronic wound pH departs reliably from healthy skin pH and because pH-responsive polymer chemistry is mature, having been worked out over decades of oncology and gastrointestinal drug-delivery research before being repurposed for wound care [4,3]. The underlying mechanisms are a small, well-understood set: ionizable pendant groups (carboxylic acids, tertiary amines) that change the polymer's hydration and swelling state as pH crosses their pKa, acid-labile linkages such as hydrazone or acetal bonds that hydrolyze faster as pH rises or falls past a threshold, and pH-triggered disassembly of self-assembled micelle or polymersome structures once a critical fraction of ionizable groups are charged. For a wound dressing specifically, the practically useful direction is a system that stays relatively intact and low-release at the mildly acidic pH of healthy or healing skin and releases its payload as the wound's local pH shifts toward neutral-to-alkaline, since that is precisely the pH excursion associated with non-healing or infected tissue.

Enzyme-responsive systems exploit the second major chronic-wound departure from normal physiology: sustained, elevated protease activity, particularly matrix metalloproteinases. The design logic here is arguably even more elegant than pH-responsiveness, because it converts the pathological process most directly responsible for degrading therapeutic payloads — excess MMP activity — into the trigger that releases more payload to counteract it, a self-limiting feedback arrangement in principle. A recent and directly on-topic

example is a spatiotemporally programmed hyaluronic acid/polyglutamate hydrogel carrying an MMP-9-responsive cleavable linkage, explicitly engineered so that the local burden of MMP-9 in a diabetic wound — itself a marker of unresolved inflammation and poor healing — determines the rate of payload release, with the authors reporting accelerated closure in a chronic diabetic wound model as a direct result of this protease-gated release scheme [8]. This design pattern, where the material is built from or crosslinked with a substrate the offending protease itself will cleave, appears repeatedly across the enzyme-responsive wound literature and represents one of the more mechanistically satisfying trigger choices available, precisely because MMP dysregulation is not incidental to chronic wounds but one of their defining pathological features [5,6].

Chitosan-based nanoparticle systems deserve separate mention because chitosan itself is both pH-responsive (its primary amines protonate and the polymer becomes more soluble and swollen as pH drops, and correspondingly more compact as pH rises toward physiological and pathological wound values) and intrinsically antimicrobial, giving chitosan nanoparticle platforms a kind of dual utility that purely synthetic polymers lack. A representative recent example incorporates a fluoroquinolone antibiotic into a chitosan-coated zeolitic imidazolate framework nanoparticle explicitly designed as a stimuli-responsive nursing-care wound dressing component, combining the pH-modulated release behavior of the chitosan coating with the antibacterial payload the wound-care literature consistently identifies as the most urgently needed cargo class for infected chronic wounds [9]. The broader PLGA nanoparticle literature, reviewed comprehensively by Chereddy and colleagues specifically for its wound-healing relevance, shows a similar pattern: PLGA's hydrolytic, and to a lesser extent pH-sensitive, degradation kinetics have been engineered across a range of formulations to slow or accelerate payload release depending on the target indication, with wound healing applications specifically favoring formulations tuned toward the several-day to several-week release windows that match a healing trajectory rather than the more rapid release profiles favored in acute-indication drug delivery [10].

4. Thermoresponsive, Redox/ROS-Responsive,

and Light-Triggered Architectures

Thermoresponsive polymers, most commonly built around poly(N-isopropylacrylamide) (PNIPAM) or PNIPAM-copolymer backbones, undergo a sharp coil-to-globule transition at their lower critical solution temperature, and this transition has been engineered into wound-care carriers in two distinct ways. First, some systems are tuned so that a nanoparticle or hydrogel matrix collapses and expels payload as local wound temperature rises above the transition point, exploiting the localized warmth associated with active bacterial infection and inflammation as an infection-gated release trigger. Second, and just as commonly in the applied literature, thermoresponsive behavior is used constructively at the point of application rather than as an in-wound sensing trigger: a formulation that is a free-flowing liquid at room or below-body temperature and gels *in situ* once applied to the (warmer) wound bed, giving clinicians an easy-to-apply liquid that becomes a conformal, retained gel exactly where it is needed. The fundamental physical chemistry underlying both use cases — how the LCST transition depends on comonomer composition, molecular weight, and the balance of hydrophobic and hydrophilic pendant groups — was established well before wound-care applications existed and remains the standard reference framework the applied wound literature builds on [4].

Redox- and ROS-responsive systems target the oxidative component of the chronic wound microenvironment directly. Persistent, unresolved inflammation in chronic wounds is associated with sustained local production of reactive oxygen species by infiltrating neutrophils and macrophages, a state that is pathological in excess but that also provides another chemically exploitable trigger: polymers built around ROS-cleavable linkages (thioether bonds, phenylboronic ester groups, selenium- or tellurium-containing backbones) degrade preferentially in the ROS-elevated wound bed relative to normal tissue, releasing payload in rough proportion to local oxidative burden. Because excess ROS is itself part of what perpetuates the non-healing state in chronic wounds, several of these designs pair triggered release with an antioxidant or ROS-scavenging function built into the carrier material itself, so that the vehicle is not merely inert scaffolding for a separate drug but is doing therapeutic work as it degrades — a design logic that mirrors the self-limiting feedback structure seen in

MMP-responsive systems.

Light-responsive and specifically near-infrared (NIR)-responsive architectures take a different approach: rather than relying on an endogenous wound signal, they introduce an externally applied, clinician- or patient-controlled trigger, most often by incorporating a photothermal agent (gold nanostructures, polydopamine, or other NIR-absorbing nanomaterials) into an otherwise conventional hydrogel or nanocomposite dressing. A representative and directly relevant example is a conductive, self-healing nanocomposite hydrogel dressing built specifically for photothermal therapy of infected full-thickness skin wounds, in which NIR irradiation is used both to generate localized heat for direct antibacterial photothermal killing and, in related designs, to accelerate payload release from the same matrix on demand [11]. This external-trigger approach sacrifices the fully autonomous, wound-state-responsive quality of pH- or enzyme-triggered systems, but gains something clinically valuable in return: the release event can be scheduled and controlled by a caregiver rather than left entirely to the wound's own unpredictable biochemistry, which may be preferable for acute-flare antimicrobial dosing where a clinician wants direct control over timing.

5. Nanocomposite Hydrogels, Nanofiber Scaffolds, and Multi-Trigger Systems

A broader survey of the nanomaterials-for-wound-healing literature makes a useful observation that helps explain why the field has converged so strongly on composite formats rather than free nanoparticle suspensions: nanoparticles alone, regardless of how well their release chemistry is engineered, still have to be held in contact with the wound bed for long enough, and in high enough local concentration, to matter, and a free suspension applied topically simply does not stay put the way a mechanically coherent dressing does [12]. This is a practical, almost mundane observation rather than a subtle one, but it is consequential for design: it means the choice of macroscopic carrier format is not a secondary packaging decision made after the "real" nanoparticle chemistry is finalized, but is instead as central to whether a stimuli-responsive system will actually perform *in vivo* as the release-trigger chemistry itself.

Few of the systems reviewed here are deployed clinically, or even preclinically, as free nanoparticles suspended in solution; nearly all are embedded within a macroscopic dressing format — most commonly a hydrogel, less commonly an electrospun nanofiber mat — that provides the mechanical integrity, moisture management, and conformability a wound dressing actually needs, with the stimuli-responsive nanoparticles doing the fine-grained release control within that larger structure. This nanocomposite-hydrogel architecture has become close to the default design pattern in the recent literature, and for good functional reasons: hydrogels alone already provide much of what a modern wound dressing needs (moist wound healing environment, exudate absorption, a matrix broadly similar in mechanical compliance to native tissue) as established in the foundational pharmaceutical hydrogel literature [13], and layering a stimuli-responsive nanoparticle payload on top adds triggered pharmacological control without sacrificing those baseline mechanical and moisture-management properties. An illustrative example combines injectability, rapid self-healing after mechanical disruption, and intrinsic antibacterial adhesive character in a single hydrogel dressing explicitly designed for joint and skin wound sites where dressing integrity under repeated mechanical stress is itself a clinical problem, showing that the mechanical-design and stimuli-responsive-design problems are increasingly being solved together rather than as separate engineering tracks [14].

A second architecture worth distinguishing is the multifunctional sensing-and-releasing hydrogel, where the stimuli-responsive chemistry is used as much for diagnostic monitoring as for therapeutic release. A representative zwitterionic hydrogel platform incorporates optical reporters for both local pH and glucose concentration directly into a pro-healing hydrogel matrix, allowing simultaneous non-invasive monitoring of two of the most clinically relevant chronic-wound and diabetic-wound biomarkers alongside the dressing's therapeutic function [15]. This theranostic convergence — using the same responsive chemistry that gates drug release to also report on wound state, whether through a colorimetric, fluorescent, or electronic readout — is a design direction the field appears to be moving toward more broadly, since a dressing that both senses and responds

addresses the practical clinical problem that a chronic wound is not routinely biopsied or laboratory-tested between clinic visits.

Electrospun nanofiber scaffolds represent a third and historically important architecture, particularly for growth-factor delivery. Early and still-influential work in this space immobilized epidermal growth factor (EGF) directly onto electrospun nanofiber mats and demonstrated accelerated healing in a diabetic ulcer model relative to unmodified scaffolds or free EGF solution, establishing that the nanofiber format itself — high surface area, tunable porosity, straightforward functionalization chemistry — could meaningfully improve growth factor retention and bioactivity at the wound site [16]. Follow-on work extended this single-factor immobilization approach to coaxial nanofiber architectures capable of binary, differentially timed release of multiple growth factors from a single scaffold, using the core-shell geometry of coaxial electrospinning to give each factor its own distinct release kinetics within one physical dressing, which is a more clinically realistic model of healing than single-factor delivery given that natural wound healing depends on a temporally overlapping cascade of multiple growth factors rather than any single one acting alone [17]. Growth-factor delivery more broadly is a payload class with a documented history of disappointing clinical translation when delivered as simple topical formulations, precisely because of the rapid proteolytic degradation described earlier in this article, and the engineered-delivery literature is explicit that solving the delivery and protection problem, not discovering new growth factors, is now the binding constraint on clinical impact [5,6].

6. Antimicrobial and Growth-Factor Cargo: What the Literature Actually Delivers

Two payload classes dominate the chronic-wound-focused stimuli-responsive nanoparticle literature, and it is worth being explicit about why, and about the state of evidence for each. Antimicrobial payloads — conventional antibiotics such as fluoroquinolones, silver and other metal-based antimicrobials, and increasingly antimicrobial peptides — are the more frequently reported cargo, reflecting the clinical reality that infection and biofilm formation are the single most common reason a chronic wound fails to progress and the most common trigger for escalation of

care. Stimuli-responsive delivery is attractive here specifically because it offers a route to concentrate antibiotic exposure at the moment and location of active bacterial burden (signaled by local pH shift, elevated protease activity, or localized heat) rather than exposing the wound and surrounding tissue to a constant low-level antibiotic dose that does little against an established biofilm and may promote resistance; the chitosan-coated levofloxacin-loaded nanoparticle system discussed earlier is a direct, recent example of this logic applied specifically to the wound-care nursing context [9], and photothermal designs that pair NIR-triggered local heating with direct bactericidal effect represent a complementary, non-antibiotic route to the same infection-control goal [11].

Table 1: Representative stimuli-responsive trigger mechanisms exploited in polymeric nanoparticle and nanocomposite systems for chronic wound care, the wound-relevant physiological cue each trigger targets, and a representative reported platform. [8,9,11,14,15,17].

Trigger	Wound cue exploited	Representative platform	Reported outcome
Enzyme (MMP-9)	Elevated protease activity in non-healing tissue	MMP-9 cleavable hyaluronic acid and polyglutamate hydrogel [8]	Protease-gated release reported to speed closure in a diabetic wound model
pH (chitosan)	Alkaline shift in chronic, infected wound surface pH	Chitosan coated levofloxacin loaded zeolitic nanoparticles [9]	pH-modulated antibiotic release from a wound dressing component
NIR light (photothermal)	External trigger applied for infection control	Conductive photothermal nanocomposite hydrogel [11]	NIR-triggered heating gives direct antibacterial effect on infected wounds
Mechanical, antibacterial	Repeated disruption at mobile wound sites, joints and skin	Injectable self healing antibacterial adhesive hydrogel [14]	Rapid self healing and sustained antibacterial adhesion after damage
pH plus glucose sensing	Combined pH shift and hyperglycemia in diabetic wounds	Pro-healing zwitterionic sensing hydrogel [15]	Optical monitoring of wound pH and glucose alongside healing function
Nanofiber, staged release	Need for staged, multi-factor growth factor delivery	Coaxial electrospun nanofibers [17]	Binary, differently timed release of two growth factors from one scaffold

Growth-factor and pro-regenerative cargo represents the second major payload class, and the literature here is

candid that the central problem has never been the biological activity of the factors themselves — platelet-derived growth factor, vascular endothelial growth factor, and EGF all have well-established roles in normal wound healing — but their vulnerability to the same elevated-protease wound environment this article has described repeatedly [5]. Encapsulation within a nanoparticle, whether that nanoparticle is delivered as a free suspension, embedded in a hydrogel, or immobilized on a nanofiber scaffold, addresses this vulnerability directly by physically sequestering the factor from ambient protease activity until a controlled release event exposes it, and the enzyme-responsive and pH-responsive PLGA-based systems reviewed by Chereddy and colleagues, alongside the coaxial nanofiber work discussed above, both frame this protective, triggered-release function as the primary mechanistic reason nanoparticle-based growth factor delivery outperforms free growth factor application in the reported preclinical literature [10,17]. A smaller but growing set of designs pursue a related strategy with heparin and other glycosaminoglycan-class cargo, which act less as direct pro-proliferative signals themselves and more as stabilizing co-factors that protect co-delivered growth factors and modulate the local coagulation and inflammatory cascade; a representative example entraps heparin-loaded PLGA nanoparticles within a sericin/gelatin nanofiber scaffold specifically for topical wound-healing delivery, illustrating how these cargo classes are increasingly combined within a single nanocomposite dressing rather than delivered as isolated single-agent systems [18].

A dedicated review of wound dressings specifically as growth-factor delivery platforms is useful here because it frames the design problem in terms clinicians, rather than materials scientists, would recognize: a workable platform has to balance sustained-enough release to matter biologically against a release rate slow enough that the factor is not simply dumped and degraded within hours, all while the dressing continues to perform its more basic jobs of exudate management and mechanical protection [19]. That review's synthesis of the growth-factor delivery literature converges on much the same conclusion reached independently by the protease-responsive and nanofiber-encapsulation work discussed above: the dominant failure mode of early, non-encapsulated growth-factor dressings was never insufficient biological potency of the factor itself, but

premature loss of that potency to the wound's own proteolytic and exudate-clearance processes before the factor could engage its receptor, which is exactly the problem a well-designed stimuli-responsive nanoparticle carrier is positioned to solve [19,5].

Table 1 summarizes representative stimuli-responsive trigger mechanisms across this literature, mapping each trigger to the wound-relevant physiological cue it exploits and to a representative reported platform, and is intended as a compact reference for how the design logic surveyed across this section maps onto specific published systems.

7. Open Challenges

Several limitations recur across this literature and deserve to be stated plainly. First, and most fundamentally, the great majority of reported stimuli-responsive nanoparticle systems for wound care have been validated in rodent wound models — most commonly diabetic mouse models — rather than in human chronic wounds, and the translational gap between a controlled, single-etiology rodent excisional wound and a human venous or diabetic ulcer, which typically presents with mixed comorbidities, variable biofilm burden, and a far less standardized healing trajectory, is substantial [2,12]. Reported acceleration of wound closure, reduction in bacterial burden, or improvement in granulation tissue quality in a mouse model is not automatically predictive of comparable human clinical benefit, and the field's own review literature is candid about this gap rather than treating rodent efficacy as a proxy for clinical readiness.

Second, biofilm penetration remains a substantially unsolved problem for essentially all of the antimicrobial delivery architectures surveyed here. A stimuli-responsive nanoparticle that releases antibiotic efficiently in free solution or against planktonic bacteria does not automatically penetrate the extracellular polymeric substance matrix that defines an established biofilm, and chronic wounds are disproportionately associated with mature, drug-tolerant biofilms rather than planktonic infection; triggered release addresses the timing and concentration of antibiotic exposure but does not, on its own, solve the separate physical and pharmacokinetic problem of getting that antibiotic through a biofilm matrix to reach embedded bacteria [20]. Third, the manufacturing and regulatory path for combination nanoparticle-hydrogel wound dressings is

considerably less mature than for either component technology alone; nanoparticle drug products face batch-to-batch reproducibility and characterization requirements that are already demanding in isolation, and combining them with a hydrogel or nanofiber carrier format, itself subject to its own medical-device-adjacent regulatory pathway, compounds rather than simplifies the translation problem, a point the smart-dressings literature raises explicitly when discussing why so few of these systems have reached clinical trial relative to the volume of preclinical publications [7].

Fourth, most of the individual trigger chemistries reviewed here were validated for a single stimulus in isolation, while a real chronic wound presents multiple dysregulated signals — elevated pH, elevated protease activity, elevated ROS, intermittent local heat from infection — simultaneously and with substantial patient-to-patient and even wound-to-wound variability. Systems that combine two or more trigger mechanisms, or that pair a stimuli-responsive release function with a built-in sensing/reporting function as in the pH/glucose-monitoring hydrogel discussed above, are a comparatively recent development, and head-to-head evidence that multi-trigger designs outperform well-optimized single-trigger systems in a clinically relevant model is still thin [15]. Fifth, and more mundane but no less consequential: reporting standards across this literature vary considerably in what outcome measures are used (wound closure rate, re-epithelialization percentage, bacterial colony-forming-unit reduction, histological granulation scoring) and over what time frame, which makes direct, quantitative cross-study comparison difficult and is a gap the field would benefit from addressing through more standardized preclinical reporting.

8. Conclusion

The literature synthesized here supports a fairly specific and, in our reading, well-evidenced claim: stimuli-responsive polymeric nanoparticles, whether deployed as free carriers, embedded in nanocomposite hydrogels, or immobilized on nanofiber scaffolds, offer a coherent and increasingly mature engineering answer to a genuine limitation of conventional wound dressings — the inability to adjust drug release to match the wound's own, biochemically distinct and dynamically changing local environment. The chronic wound bed's departures

from healthy skin physiology — elevated and variable pH, sustained protease activity, an oxidative, ROS-rich milieu, infection-associated local heating, and biofilm-associated drug resistance — are not incidental complications to be worked around but are, in this literature's own framing, the design substrate that makes triggered, localized release possible in the first place [1,4,5].

Making this pattern clinically consequential rather than merely preclinically elegant depends on treating the challenges surveyed in the previous section as a research and translation roadmap rather than as reasons for pessimism: closing the rodent-to-human translational gap with more clinically representative preclinical models, solving biofilm penetration as a problem distinct from triggered release timing, building manufacturing and regulatory pathways suited to combination nanoparticle-hydrogel products, and moving deliberately from single-trigger toward validated multi-trigger and sensing-integrated designs [20,7,15]. The consistent convergence of independent groups on structurally similar design logic — protease-gated release keyed to the same MMP dysregulation that damages healing tissue, pH-gated release keyed to the same alkaline shift that marks a non-healing wound, photothermal designs that turn an externally applied trigger into both a direct antibacterial effect and a release mechanism — is, in our view, the strongest available evidence that this is a genuine architectural pattern for the next generation of active wound care, rather than a collection of isolated, non-generalizable material-science demonstrations, and one that merits continued, clinically grounded empirical scrutiny [3,8,11,10].

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The authors declare that they have no competing interests relevant to the content of this article.

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Ethical Approval

Not applicable. This review did not involve human participants, animal subjects, or the collection of primary clinical or experimental data.

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