

Review

Clay-Based Nanomaterials in Wound Healing: Therapeutic Roles, Mechanisms and Biomedical Applications

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Abstract

Clays, historically employed in traditional medical practices, have recently gained prominence within contemporary biomedical science, especially in the context of wound healing, due to advancements in nanotechnology and materials science. This review article investigates the physicochemical characteristics, biological processes, and therapeutic functions of clay materials—including bentonite, halloysite nanotubes, palygorskite, sepiolite, and synthetic clays like Laponite—in diverse wound-healing applications. These materials play a crucial role in the wound-healing process, including stopping bleeding, controlling inflammation, protecting against infection, and rebuilding tissue. They work through both passive and active methods. The layered or fibrous structure of these materials allows for efficient drug loading, controlled release, and mechanical support when used in hydrogels, films, and advanced drug delivery systems. Preclinical and initial clinical investigations have substantiated the biocompatibility, antimicrobial properties, and regenerative capabilities of these systems, although they have also revealed several challenges concerning toxicity, regulatory categorization, and standardization. Consequently, clay-based systems present a potentially valuable multifunctional platform for advancing next-generation wound-treatment therapies, necessitating additional translational and clinical research.

Keywords: clay minerals; bentonite; halloysite; wound healing; drug delivery; nanomaterials; regenerative medicine; antimicrobial; hydrogels; smart dressings



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1. Introduction

Wound healing, a complex biological process, involves a series of interconnected stages—hemostasis, inflammation, proliferation, and remodeling—that work together to restore tissue integrity after an injury [1]. Conventional wound dressings, such as gauze, hydrogels, and films, are widely employed; however, they often fall short in providing complete support, especially concerning infection control, the stimulation of angiogenesis, and the regulated release of therapeutic agents [1,2]. Consequently, research into novel wound-care materials has broadened to encompass nanotechnology and platforms derived from natural minerals.

Recent studies have significantly advanced our understanding of clay nanoparticles, suggesting they could be useful in biomaterial engineering and regenerative medicine [1–3].

Unlike many conventional nanomaterials, clay nanoparticles demonstrate exceptional biocompatibility, maintaining their suitability even at high concentrations; their degradation products are non-toxic, easily absorbed, and foster osteogenic cell activity [4–8]. A multitude of investigations have demonstrated that clay nanoparticles can directly and positively influence cellular behaviors, encompassing adhesion, proliferation, and differentiation, often in a concentration-dependent manner [4–6,9–12]. Clay nanoparticles, beyond their biological functions, have long been recognized for their ability to improve the mechanical strength and flow properties of polymeric hydrogels and scaffolds [9–14]. Their function as modifiers within drug delivery systems is similarly well documented, facilitating the controlled and prolonged release of active pharmaceutical ingredients [15,16]. These characteristics, taken together, underscore the considerable promise of clays in the creation of multifunctional bioactive scaffolds.

Clay minerals, also known as sheet silicates or phyllosilicates, constitute a class of inorganic, layered nanomaterials, conventionally characterized as “minerals which impart plasticity to clay, and which harden upon drying or firing” [17]. Historical and archaeological findings suggest that clays were fundamental to early medical practices, including geophagy and external treatments for wounds and bleeding [18,19]. Today, clays are still widely used in the pharmaceutical industry. They are key ingredients in both oral medications, like antacids and drugs that protect the gastrointestinal tract, and topical treatments, such as those for skin conditions and inflammation [20]. Excipients are also important in formulations, serving as disintegrants, binders, emulsifiers, and agents that control drug release [21–24].

Bentonite, a natural clay primarily made of montmorillonite, has become a key focus in wound-healing research. The exceptional swelling capacity, robust adsorption characteristics, and the ability to generate stable colloidal suspensions are the primary reasons for their widespread application (Figure 1) [3–5]. Moreover, bentonite’s versatility has been evidenced in nanocomposite systems that integrate silver nanoparticles, antibiotics such as levofloxacin, and naturally occurring substances such as propolis, thus enhancing its therapeutic potential without compromising biocompatibility [6–8].

The utilization of clay minerals in wound management transcends a simple revival of historical methods; it embodies a contemporary, multidisciplinary strategy that synthesizes materials science, nanotechnology, and biomedicine. Contemporary developments have facilitated the employment of clays for controlled drug release, as antimicrobial agents via metal-ion functionalization, and as scaffold materials within regenerative medicine [9,10].

Several recent reviews have discussed nanoclays in biomedical applications and wound management [25,26]. However, most have focused either on specific clay families or on general nanoclay-based biomaterials. In contrast, the present review provides an integrated overview of both natural and synthetic clay minerals used in wound healing, with particular emphasis on antibacterial mechanisms, advanced drug delivery systems, multifunctional wound dressings, and translational challenges associated with clinical implementation. Furthermore, recent developments reported during the last few years are critically summarized to provide an updated perspective on the field.

The move toward natural and sustainable biomaterials in health care further underscores the relevance of clay-based systems in current therapeutic landscapes. This review offers a critical assessment of contemporary research and technological progress concerning the application of clays, with a focus on bentonite, in the context of wound healing. This study will provide a detailed examination of the physical and chemical properties of these substances. It will also explore the biological processes that explain their therapeutic effects, their use in delivery systems, and an evaluation of their effectiveness in both laboratory

and clinical settings. In addition, the analysis will include a discussion of the relevant regulatory requirements and potential areas for future research.

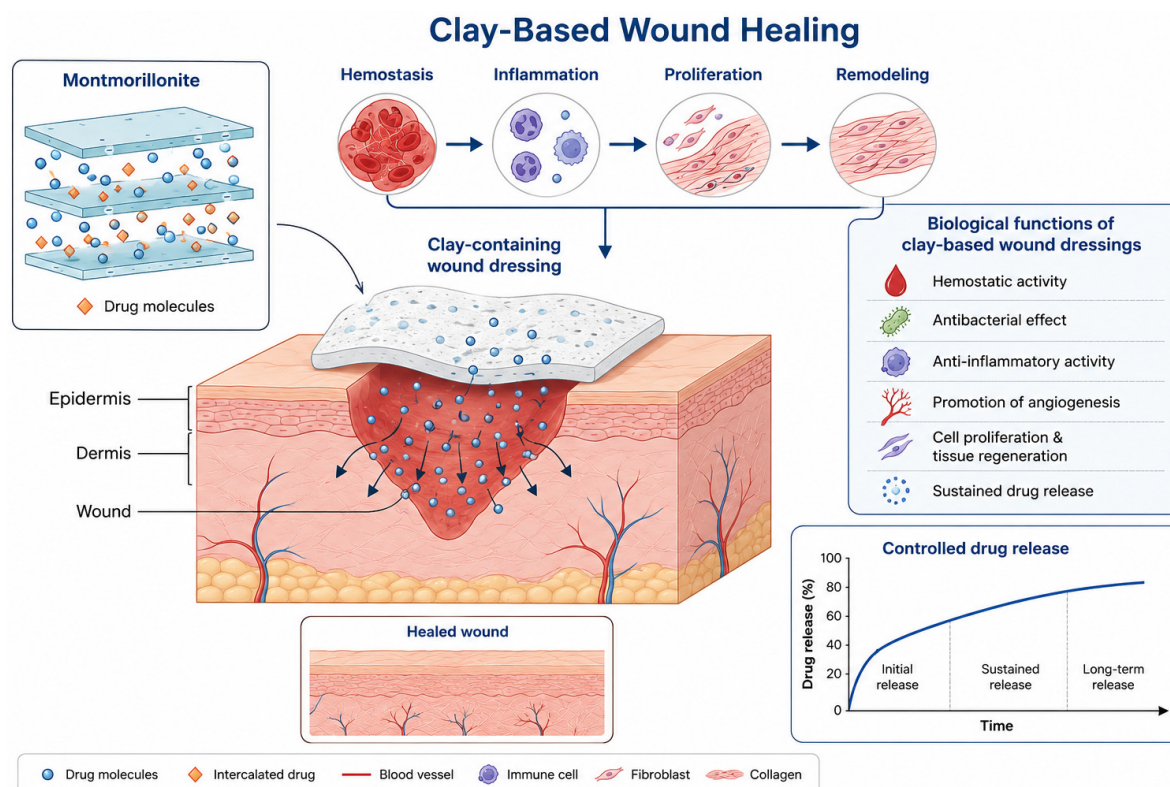


Figure 1. Schematic illustration of a clay-based wound-healing system using a bentonite-integrated hydrogel dressing (The horizontal arrows at the top indicate the sequential progression of wound healing through hemostasis, inflammation, proliferation, and remodeling. The curved arrow from montmorillonite to the wound dressing represents incorporation of drug-loaded clay into the dressing matrix. The downward arrow indicates the therapeutic contribution of the clay-containing dressing to the wound-healing process. Arrows extending from the dressing into the wound bed illustrate controlled drug release, diffusion, and distribution of therapeutic molecules within the injured tissue).

2. Overview of Clay Minerals

Clay minerals, a specific group of phyllosilicates, are hydrated aluminosilicates. They have layered tetrahedral and octahedral sheets, which give them unique physical and chemical properties. These properties make them very useful in medicine. Clay minerals usually form through weathering or hydrothermal alteration of rocks that contain silicates. They are known for their large surface area, ability to swell, and capacity to exchange ions [23].

Structurally, clay minerals have either 1:1 (T:O) or 2:1 (T:O:T) layers. In this structure, “T” refers to a tetrahedral sheet, usually made of Si^{4+} ions, and “O” refers to an octahedral sheet, typically made of Al^{3+} or Mg^{2+} ions. Clays with 1:1 layers, like kaolinite, have a structure made of one tetrahedral sheet and one octahedral sheet. This specific structure leads to a low ability to exchange cations and very little swelling.

In contrast, 2:1 clays, such as montmorillonite (Figure 2), which is the main component of bentonite, have a structure made up of two tetrahedral sheets surrounding an octahedral sheet. The structural arrangement allows for considerable space between layers, a higher charge density, and improved ion exchange properties [24–27]. Consequently, these characteristics favor the absorption of water and various cations by 2:1 clays, making them suitable for drug delivery and moisture control in wound care [28].

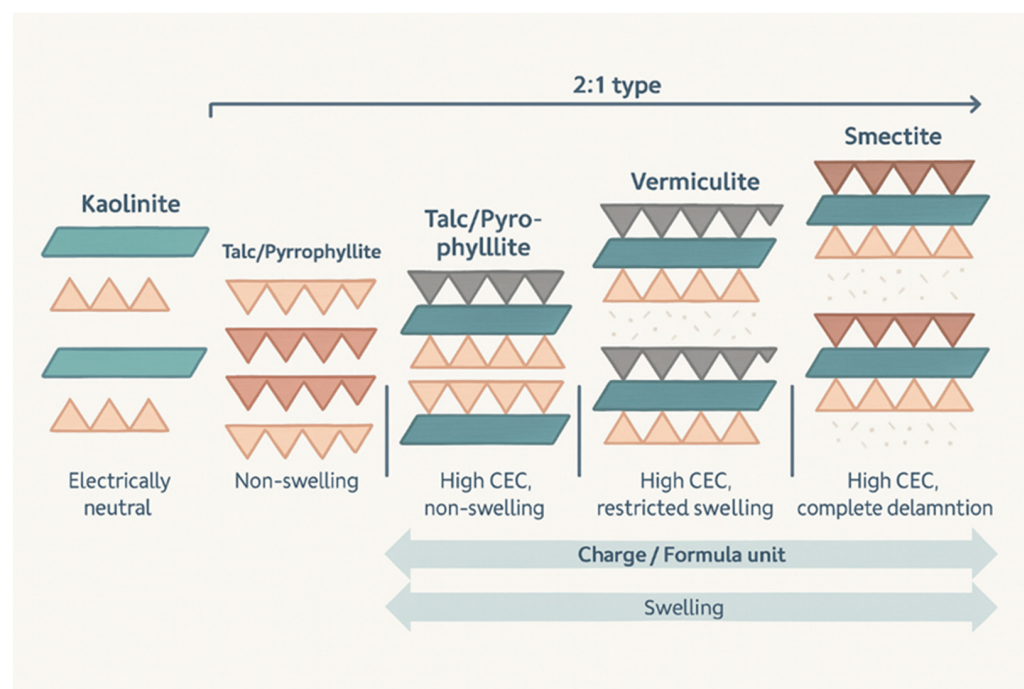


Figure 2. Layer structures and key properties of common clay minerals. (Triangular units represent tetrahedral silicate sheets, while horizontal plate-like units represent octahedral sheets. Orange and brown triangles distinguish tetrahedral sheets associated with different layer arrangements, whereas teal and gray plates represent octahedral sheets with differing dominant cation composition. The stacking sequence illustrates 1:1 and 2:1 clay mineral structures, and the variable separation between adjacent layers indicates differences in interlayer accessibility and swelling behavior. The arrows at the bottom show the general increase in layer charge per formula unit and swelling tendency across the mineral groups).

Example of 1:1 type: kaolinite (electrically neutral, non-swelling).

Example of 2:1 type: talc/pyrophyllite (high CEC, non-swelling) → illite → vermiculite (high CEC, restricted swelling) → smectite (high CEC, complete delamination).

The arrows beneath indicate the increasing trends in layer charge (charge per formula unit) and swelling capacity.

In addition to planar clays, fibrous clays such as sepiolite and palygorskite, and tubular clays like halloysite, possess non-planar morphologies and distinct interaction profiles with biological molecules and polymers. Halloysite nanotubes (HNTs), for instance, possess a positively charged internal lumen and a negatively charged exterior, thereby facilitating dual-mode drug loading and targeted delivery [28–30]. Recent studies have provided new insights into the potential uses of clay nanoparticles and composites in creating biomaterials and in regenerative medicine [6–8].

Unlike many other nanomaterials, clay nanoparticles show better biocompatibility, remaining safe even at high doses. Moreover, their breakdown products are not harmful, are easily absorbed, and may even help osteogenic cells work better [28–34]. Furthermore, a growing body of evidence suggests that these materials directly influence cell adhesion, proliferation, and differentiation in a concentration-dependent manner [33–36].

In addition to their bioactivity, clay minerals are well known for enhancing the mechanical and rheological properties of polymer matrices, such as hydrogels, films, and cryogels. Their ability to stabilize these formulations, modify drug release profiles, and interact favorably with both natural and synthetic polymers is of value in wound-dressing development [22,37,38]. Therefore, the use of clays in smart and bioresponsive systems is gaining more attention.

Historically, clays have been used in medicine since ancient times. Early uses, such as wound healing, detoxification (geophagy), and reducing inflammation, are well documented in Egyptian, Greek, and Roman medical practices [38–40].

Today, clays are still important in modern pharmaceutical science. They are used as active ingredients, providing therapeutic effects, and as excipients. As excipients, they act as disintegrants, thickeners, binders, or drug release modifiers in many different formulations [40–43].

In essence, the multifaceted roles of clay minerals in biomedical contexts stem from their structural heterogeneity and chemical adaptability. These inherent characteristics are crucial for their increasing use as therapeutic agents in wound healing and regenerative medicine.

3. Mechanisms of Action in Wound Healing

The process of wound healing unfolds through a precisely coordinated biological sequence, encompassing four interconnected phases: hemostasis, inflammation, proliferation, and remodeling. These stages necessitate a finely tuned equilibrium of biochemical signals, cellular actions, and extracellular matrix (ECM) dynamics to facilitate tissue restoration without the complications of scarring or infection [23]. Clay minerals, due to their unique physicochemical and biointeractive characteristics, can positively influence this cascade at various levels, thus expediting and improving tissue repair.

A key mechanism through which clay-based materials exert their influence is by promoting hemostasis. Specific clays, especially smectites like bentonite and fibrous clays such as sepiolite, exhibit a high surface area and absorbent capacity, which facilitates the rapid uptake of exudates and the concentration of clotting factors at the wound site. The swelling characteristics of clays, in turn, facilitate mechanical compression, thereby encouraging plate-like aggregation and the formation of fibrin [24,25]. Moreover, research indicates that negatively charged silicate surfaces can initiate coagulation pathways through the absorption of calcium ions and clotting proteins, thus functioning as pro-coagulant scaffolds [22].

A further significant attribute is the antibacterial efficacy of clay minerals, which stem from several interrelated factors. The ion exchange capacity of clays allows for the release of antimicrobial metal ions—such as silver, copper, and zinc—that are either present or introduced via modification [31,39]. These ions compromise bacterial cell walls, disrupt metabolic pathways, and instigate oxidative stress through the generation of reactive oxygen species (ROS) [41].

Furthermore, the physical arrangement of clay particles can compromise microbial membranes via direct interaction, a process especially evident in fibrous clays and exfoliated nanoclays [27]. It is important to note that the antimicrobial properties of clays are not consistent across all formulations, thereby highlighting the significance of mineralogical purity and ion composition [26].

Clays also influence the inflammatory response, a crucial stage in wound healing. Excessive or prolonged inflammation impedes tissue regeneration and elevates the likelihood of chronic wounds. Clay nanoparticles, specifically halloysite nanotubes and montmorillonite, have demonstrated the capacity to diminish inflammatory cytokine expression and macrophage activation, both *in vitro* and *in vivo* [28,32]. This immunomodulatory action could be attributed to the adsorption of inflammatory mediators and the creation of a more neutral wound microenvironment facilitated by buffering [22].

During the proliferation and remodeling phases, clays further aid in the process by acting as scaffolds that facilitate fibroblast adhesion, keratinocyte migration, and neovascularization. Their elevated surface area and surface hydroxyl groups facilitate interactions

with growth factors and ECM proteins, while their mechanical reinforcement of polymeric matrices ensures structural stability during tissue ingrowth [33,34]. Empirical findings indicate that clays encourage collagen deposition and re-epithelialization, potentially through both biochemical signaling and mechanical stimuli [35].

Ultimately, clay minerals have been widely utilized as drug delivery platforms, thereby augmenting the therapeutic efficacy of wound dressings. The interlayer and surface sites of these materials serve as reservoirs for antibiotics, anti-inflammatories, and bioactive molecules, thereby enabling a controlled release profile [36]. This controlled delivery is critical for sustaining therapeutic drug concentrations while simultaneously mitigating cytotoxic effects or the development of antibiotic resistance [37].

These mechanisms—hemostatic action, antibacterial activity, immunomodulation, scaffold support, and controlled drug release—collectively highlight the distinctive and multifaceted contributions of clay minerals to wound healing. Their incorporation into sophisticated wound-care systems exemplifies a fusion of conventional materials and contemporary biomedical engineering principles.

4. Types of Clays Used in Wound Healing

4.1. Bentonite (Montmorillonite)

Recent *in vivo* studies demonstrated that a novel bentonite (Figure 3) complex accelerates burn wound healing by promoting collagen synthesis, angiogenesis, and re-epithelialization, while concurrently downregulating inflammatory markers such as COX 2 and TNF α in a Yucatan minipig model [44]. A rabbit skin wound model corroborated these findings, showing accelerated wound closure and reduced edema compared to controls [45]. Moreover, bentonite has been formulated in carbopol gels enriched with peptides to deliver carnosine-loaded bentonite to burn wounds, resulting in improved epithelialization, angiogenesis, and fibroblast migration [46]. These studies reinforce bentonite's multifunctional role as an anti-inflammatory scaffold capable of delivering therapeutics effectively.

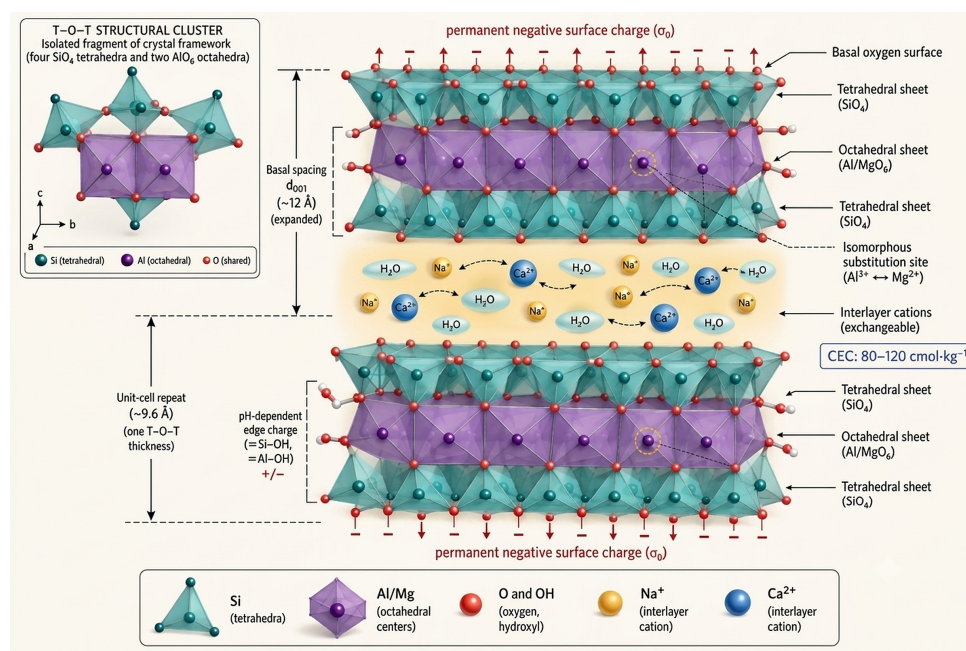


Figure 3. Three-dimensional structural model of bentonite (montmorillonite), a 2:1 phyllosilicate composed of two tetrahedral silica sheets sandwiching an octahedral sheet rich in $\text{Al}^{3+}/\text{Mg}^{2+}$. The diagram highlights the origin of permanent negative surface charge via isomorphous substitution in the octahedral layer and the presence of exchangeable interlayer cations (e.g., Na^+ , Ca^{2+}). pH-dependent edge charges are also illustrated, emphasizing the amphoteric nature of the sheet edges.

4.2. Halloysite Nanotubes (HNTs)

Halloysite nanotubes (HNTs), a naturally occurring clay mineral, are characterized by a unique tubular structure and dual-charged surfaces, properties that make them especially appealing for biomedical applications.

Integration in composite films: HNTs has been successfully incorporated into starch–gelatin films loaded with plant extracts or zinc oxide (ZnO), and several beneficial effects have been observed, including promotion of fibroblast proliferation, improved mechanical strength and sustained antimicrobial release.

Hydrogel applications: Chitosan/halloysite hydrogels were found to significantly improve the drug loading efficiency (up to 74%) and sustained drug release over a period of 20 days. In addition, good biocompatibility and hemostatic properties were also observed, indicating the potential of these systems for wound-care applications.

Broader applications: The potential of HNTs in tissue engineering and advanced wound-dressing platforms is also promising. A detailed discussion on these applications can be found in recent reviews on this topic [47,48].

4.3. Palygorskite and Sepiolite (Fibrous Clays)

Although less studied than bentonite and HNTs, fibrous clays like palygorskite and sepiolite (Figure 4) exhibit morphological advantages for wound healing. Sepiolite-based nanofibrous mats incorporating silver nanoparticles demonstrated rapid clot formation and strong antibacterial effects against common pathogens [49]. Additionally, palygorskite films developed via tape-casting showed impressive structural durability and favorable healing responses in ex vivo skin models. Sepiolite-containing hydrogels, combined with mineral-rich spring water, further enhanced fibroblast motility and supported chronic wound-repair scenarios.

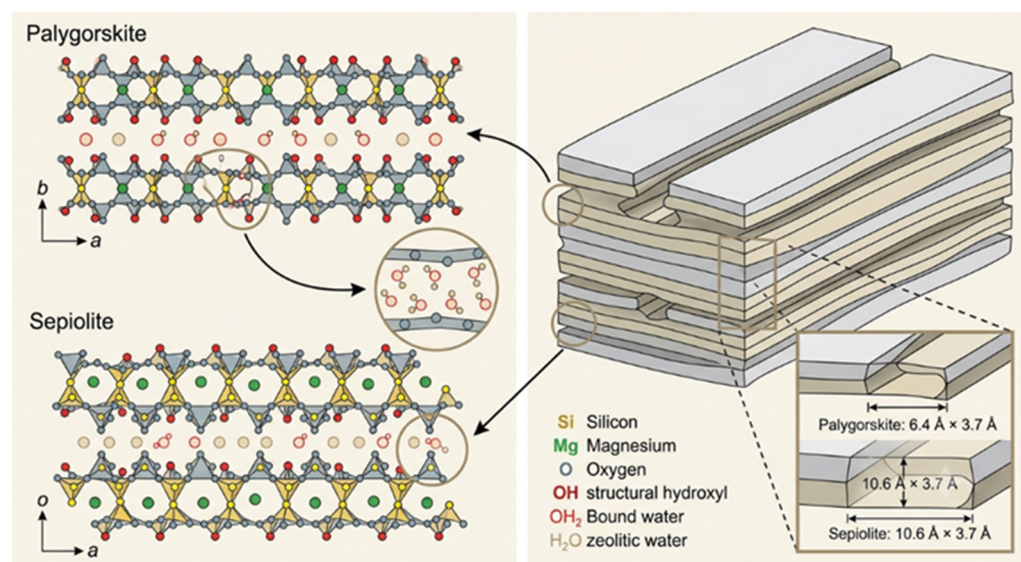


Figure 4. Molecular structure and channel arrangement of fibrous clay minerals—palygorskite and sepiolite. The figure displays atomic-level 2D structures, showing the arrangement of Si, Mg, O, and various water species (structural OH, bound H₂O, and zeolitic water), and a 3D schematic emphasizing the internal channel morphology. Differences in tunnel dimensions between palygorskite (6.4 Å × 3.7 Å) and sepiolite (10.6 Å × 3.7 Å) are highlighted, illustrating their potential for adsorptive and therapeutic applications in wound-healing materials.

4.4. Laponite and Other Synthetic Clays

Laponite, a synthetic smectite analogue, offers precise compositional control and excellent biocompatibility. Its incorporation into injectable hydrogels with gelatin or hyaluronic

acid enabled controlled release of ions such as Mg^{2+} , which stimulated fibroblast proliferation and improved scaffold integration [50]. Earlier work produced Laponite–mafenide composite films with sustained antibiotic release while reducing cytotoxicity, highlighting its potential in infection-resistant wound dressings [51,52]. Laponite’s modular nature and favorable safety profile aligns it well with injectable and topical wound therapies.

Collectively, both natural and synthetic clays offer diverse structural morphologies and unique physicochemical properties that are highly relevant to wound healing. From the high adsorption capacity of bentonite to the ion-releasing capabilities of Laponite, each clay type contributes distinct therapeutic benefits, such as antimicrobial activity, hemostasis, and controlled drug delivery. Table 1 provides a comparative overview of the major clay minerals discussed in this chapter, highlighting their key roles and recent biomedical applications. Table 2 provides a detailed overview of representative clay-based wound-healing systems, summarizing the clay morphology, formulation matrix and preparation strategy, as well as their key therapeutic functions and recent in vitro and in vivo applications.

Table 1. Summary of clay types and key applications.

Clay Type	Morphology	Key Properties and Roles	Recent Applications
Bentonite	Plate-like (2:1 clay)	High adsorption capacity; anti-inflammatory; regenerative	Burn care, carnosine gel
Halloysite NTs	Nanotubes	Heparinizable lumen; sustained release; hemostasis	Starch–gelatin films; hydrogels
Sepiolite/palygorskite	Fibrous	Exudate absorption; clotting; antibacterial	AgNP nanofibers, tapes, hydrogels
Laponite (synthetic)	Disk-like synthetic clay	Ion release; injectable scaffold; antimicrobial delivery	Hydrogels, antibiotic films
Vermiculite	Layered 2:1 clay (expandable)	High cation exchange capacity; water absorption; drug loading; polymer reinforcement	Polymer nanocomposites; drug delivery systems; bioactive scaffolds

Table 2. Clays and composites used in wound healing (* Representative recent study selected to illustrate the corresponding clay-based wound-healing system and its therapeutic application. ↑ indicates an increase or enhancement, whereas ↓ indicates a decrease or reduction in the specified parameter or biological effect).

Clay Type	Morphology	Dosage/Matrix	Typical Composition & Preparation Strategy	Key Therapeutic Functions (In Vitro/In Vivo)	Representative Recent Study *
Bentonite (montmorillonite)	Plate-like 2:1	Carbopol gel	Carnosine-enriched bentonite dispersed by high-shear mixing	Anti-inflammatory; ↑ collagen & angiogenesis in deep burns	Drobot M. et al. 2022 [53]
		Gelatin cryogel hydrogel	GelMA–bentonite nanocomposite formed by freeze–thaw cycling	Injectable; hemostatic; rapid contraction of full-thickness wounds	Singh M. et al. 2026 [54]
		Collagen sponge	Collagen/β-glucan scaffold impregnated with nano-bentonite	Moisture retention; accelerated re-epithelialization	Kulkarni D. et al. 2022 [55]
		Electrospun mat	PAN nanofibers loaded with exfoliated bentonite + $CaCl_2$	Rapid clotting (↓ clotting time ≈ 65%); broad antimicrobial	Sharma A. et al. 2026 [56]

Table 2. Cont.

Clay Type	Morphology	Dosage/Matrix	Typical Composition & Preparation Strategy	Key Therapeutic Functions (In Vitro/In Vivo)	Representative Recent Study *
Halloysite nanotubes (HNTs)	Hollow nanotubes	Flexible film	Chitosan/alginate/bentonite/ZnO film (solvent-casting)	99.9% bacterial reduction; flexible burn-dressing	Donato L. et al. 2026 [57]
		Collagen/alginate HA hydrogel	HNTs dispersed in CAH matrix via ionic crosslinking	3-D skin model; ↑ keratinocyte migration; photothermal kill	Bera R. et al. 2025 [58]
		Gelatin–starch shear-thinning ink	G–S–H ink 3-D-printed into personalized pads	Self-healing; conforms to irregular wounds; ≥4 log bacterial kill	Rando G. et al. 2022 [59]
		Adhesive HA–quercetin gel	Ago@HNTs embedded in HA; tissue-adhesive	Antioxidant, anti-biofilm, strong tissue seal	Mollaheydaralimoazem M. et al. 2025 [60]
		Starch–gelatin film	HNTs@Malva-CQD nanocomposite by green casting	UV-blocking; hemostatic; delayed oxidative stress	Abbaszadeh M. et al. 2025 [61]
Sepiolite	Fibrous nanorods	Chitin composite hydrogel	Au@HNT-chitin double network	NIR-triggered photothermal + hemostasis; 96% closure in 10 d	Zhao P. et al. 2023 [62]
		Chitosan film	Solution-cast CS/sepiolite (5–15%)	↑ WVTR & tensile strength; fibroblast proliferation	Dutta J., Devi N. 2021 [63]
		Self-healing hydrogel	PVA/sepiolite/Ca ²⁺ double-network	Fast gelation; stretchable; 99.9% <i>E. coli</i> kill; clot < 90 s	Jiang Y. et al. 2024 [64]
		Sepiolite@AgNP fibrous pad	Vacuum-impregnation of silver onto sepiolite	Rapid hemostasis; broad-spectrum antibacterial	Jiang Y. et al. 2023 [50]
		Cu-functional hydrogel	Cu ²⁺ /sepiolite incorporated PVA cryogel	Pro-angiogenic; skin-regenerative; ROS scavenging	Gul A. et al. 2024 [65]
Palygorskite (attapulgite)	Fibrous ribbons	CS/ZnO film	GA-ZnO/Pal in chitosan matrix (casting)	Enhanced barrier; >99% bacterial kill; faster closure	Zhang Q. et al. 2021 [66]
		Ceramic tape	Pal + PVA sheets via tape-casting & sintering	Breathable, high wicking; supports granulation tissue	Freitas A. et al. 2019 [67]
		DC/Pal nanofilm	Dencichine–Pal in CS/PVP (casting)	Superior hemostatic index; 2× faster clotting	Yang Y. et al. 2024 [68]
		Spring-water hydrogel	Pal + mineral spring water; manual homogenization	Anti-inflammatory; promotes re-epithelialization	Garcia-Villen F. et al. 2020 [69]
		PVA/CMC/Pal hydrogel	Pickering emulsion + freeze-dry	Highly porous; moisture control; angiogenic	Farid E. et al. 2022 [70]
Laponite® (synthetic smectite)	Disk-like platelets	Injectable self-healing gel	Zingerone–NP/Lap–gum hydrogel (ionic crosslinking)	Antioxidant; biofilm inhibition; complete closure in 9 d	Meena M. et al. 2025 [71]
		Antibiotic film	Lap/alginate/mafenide film via solvent casting	Sustained drug release; ↓ cytotoxicity vs. free drug	Ghadiri M. et al. 2014 [72]

Table 2. Cont.

Clay Type	Morphology	Dosage/Matrix	Typical Composition & Preparation Strategy	Key Therapeutic Functions (In Vitro/In Vivo)	Representative Recent Study *
		In situ forming film	Lap-based sprayable film-forming gel	Conforms to irregular wounds; Mg ²⁺ -mediated healing	Pineda A. et al. 2023 [73]
		Lap–Ag nanocomposite	Lap templating of AgNPs; film casting	Synergistic antimicrobial + pro-angiogenic effect	Long L. et al. 2025 [74]
		GGMA–Lap hydrogel	Gellan–gum–methacrylate + Lap (photocrosslink)	Shear-thinning; cell-laden printing; rapid vascularization	Ansari A. et al. 2024 [75]

4.5. Kaolinite

Kaolinite is a naturally occurring 1:1 layered aluminosilicate clay mineral characterized by low swelling capacity, good biocompatibility, chemical stability, and high adsorptive properties. Although it has received less attention in wound healing compared with bentonite or halloysite nanotubes, kaolinite has been investigated as a component of wound-dressing materials due to its ability to absorb wound exudate, support hemostasis, and improve the mechanical stability of polymeric matrices. Recent studies have demonstrated that kaolinite-containing composite hydrogels and wound dressings exhibit favorable water uptake, adhesive properties, antibacterial activity, and wound-healing potential, particularly when combined with antimicrobial agents or polymers such as poly(vinyl alcohol) (PVA). Furthermore, kaolinite has been recognized as a promising clay mineral for biomedical and pharmaceutical applications because of its safety profile and ability to enhance the functional performance of advanced wound-care systems. Nevertheless, compared with bentonite, halloysite, and Laponite, further in vivo and clinical studies are required to fully establish its therapeutic efficacy in wound healing [25,76–78].

4.6. Vermiculite

Vermiculite is a naturally occurring 2:1 phyllosilicate clay mineral of the hydrobiotite group. It is structurally related to the smectites, yet is characterized by its high layer charge and characteristically restricted interlayer swelling [79]. With its large specific surface area, elevated cation exchange capacity (CEC) and thermal stability, vermiculite is a widely exploited raw material for the preparation of nanofillers and polymer nanocomposites [80]. Both organic modification, by intercalation of quaternary ammonium salts or surfactants, and inorganic modification, by pillaring with metal oxide clusters or exchange with multivalent cations, have been used to tune the interlayer spacing and surface chemistry of vermiculite. This improves its compatibility with the polymer matrices and enhances drug adsorption capacity [43,81,82]. The incorporation of exfoliated vermiculite nanoplatelets in PVA or chitosan films have shown enhanced mechanical reinforcement and controlled release of antimicrobial agents, thus indicating potential for wound-dressing applications [83]. Furthermore, the biocompatibility of vermiculite-based materials at relevant concentrations has been demonstrated in several cytotoxicity studies, corroborating its candidacy as a safe nanofiller in biomedical composites [20,84–87]. Despite these properties, vermiculite has been underexplored in wound-healing research compared to montmorillonite or halloysite, and dedicated studies to evaluate its hemostatic, antimicrobial and tissue-regenerative performance are warranted [88–90].

5. Clay-Based Delivery Systems

The design of effective drug delivery systems (DDSs) for wound healing remains a cornerstone of modern regenerative therapy. Clay minerals, owing to their layered nanostructure, high surface reactivity, and controllable release behavior, have emerged as versatile platforms for both topical and implantable therapeutic systems. Their ability to carry, protect, and release biologically active agents under physiological conditions positions them at the intersection of materials science and biomedicine [44].

5.1. Intercalation and Adsorption-Based Drug Loading

The interlayer galleries and external surface sites of clay minerals allow for effective immobilization of diverse therapeutic agents through mechanisms such as cation exchange, hydrogen bonding, van der Waals interactions, and electrostatic forces. For example, montmorillonite has been extensively employed to intercalate antibiotics such as gentamicin, ciprofloxacin, and chlorhexidine, providing prolonged release profiles while maintaining their bactericidal efficacy over extended periods [83]. Halloysite nanotubes, with their positively charged lumen and negatively charged outer surface, offer a unique dual-loading mechanism for both hydrophilic and hydrophobic agents. This duality enables complex payloads to be delivered in a site-specific and sustained manner. Furthermore, intercalated drugs within clay structures benefit from enhanced chemical stability, reduced photodegradation, and improved solubility.

5.2. Hydrogel–Clay Composites

Hydrogels are widely used in wound healing due to their ability to mimic native extracellular matrix (ECM), retain moisture, and conform to wound topography. Incorporating clay nanoparticles into these hydrogels enhances their mechanical properties, rheological behavior, and biofunctionality. For instance, gelatin–Laponite hydrogels have demonstrated improved tensile strength, injectability, and bioresorbability, making them suitable for deep wounds and surgical sites [84]. Chitosan–montmorillonite and alginate–halloysite hydrogels have been engineered to co-load growth factors (e.g., VEGF, EGF) and antimicrobial agents (e.g., silver, triclosan), resulting in accelerated angiogenesis and infection control in chronic wound models. Notably, Laponite releases beneficial Mg^{2+} ions during degradation, further promoting fibroblast proliferation and ECM deposition [43]. The synergy between polymeric matrix and clay enhances both physical structure and controlled drug diffusion kinetics.

5.3. Film, Spray, and Membrane-Based Delivery

Beyond hydrogels, clay-based DDSs have been successfully implemented in solid film matrices, aerosolized sprays, and electrospun fiber membranes. These systems enable direct application, ease of storage, and reduced dosing frequency. For example, bentonite–PVA films doped with silver nanoparticles demonstrated sustained release of Ag^+ ions for up to 72 h while maintaining flexibility and breathability [12]. Such films also offer oxidative stability and barrier properties suitable for post-surgical dressings. Sprayable clay–polymer emulsions loaded with essential oils or antibiotics allow uniform coating over irregular surfaces, such as burns or traumatic lacerations. Electrospun nanofibrous membranes with sepiolite or halloysite enhance surface area for cell adhesion and can be functionalized with peptides or enzymes to promote targeted regeneration [87]. These designs ensure that drug release and wound protection occur simultaneously and adaptively.

5.4. Stimuli-Responsive and Smart Systems

Smart wound dressings represent a new generation of materials capable of sensing wound conditions and adjusting drug release accordingly. Stimuli such as pH shifts, temperature fluctuations, or oxidative stress—common in infected or chronic wounds—can be harnessed to trigger the release of therapeutic agents embedded in clay-based carriers. For example, halloysite–poly(N-isopropylacrylamide) (PNIPAm) hydrogels exhibit thermoresponsive behavior, releasing encapsulated antimicrobial peptides at elevated wound temperatures [88]. Similarly, montmorillonite-containing hydrogels loaded with anti-inflammatory drugs were shown to selectively release their cargo in acidic environments typical of infected wounds. This precision prevents overexposure of healthy tissue to cytotoxic agents and supports the natural healing timeline. Advanced smart systems are being integrated with wearable electronics for real-time monitoring and dosing adjustment.

5.5. Co-Delivery and Synergistic Therapeutics

Chronic wounds often involve a combination of infection, oxidative stress, poor vascularization, and impaired cell proliferation. Clay-based platforms provide an ideal scaffold for co-delivering multiple agents to address these complexities. Recent systems have demonstrated simultaneous delivery of antimicrobials (e.g., silver ions or gentamicin) and antioxidants (e.g., curcumin, quercetin) from layered montmorillonite carriers, yielding enhanced wound contraction and re-epithelialization in diabetic wound models [89]. Sequential release systems have also been engineered: halloysite nanotubes were loaded with EGF for immediate release and doxycycline for delayed antimicrobial effect, thereby coordinating growth promotion and infection control within the same scaffold. These co-delivery platforms offer tailored, multi-phase healing support that conventional dressings cannot replicate.

6. Antibacterial Nanoclays for Wound Healing

For this review, nanoclay will be used as a term to refer to clay minerals with at least one structural dimension on the nanometer scale, including layered nanoplatelets (montmorillonite and Laponite, for example), nanotubes (halloysite nanotubes) and fibrous nanostructures (sepiolite and palygorskite). The term “nanoclay” is based not only on average particle size, but also on the existence of nanoscale structural features such as interlayer galleries, nanotubular lumens and internal channels, which can serve as nanoreactors or reservoirs for the adsorption, intercalation and controlled release of bioactive molecules.

Depending on the chemical properties, some natural clays have antimicrobial and healing effects with light modifications. For this reason, clay-based nanomaterials have gained increasing interest for the design of multifunctional wound-care systems. It is already known that nanoclays can naturally be found as kaolinite, montmorillonite, halloysite nanotubes (HNTs), while palygorskite and sepiolite have demonstrated antimicrobial activity through different complementary mechanisms. The primary mechanisms include direct contact between nanoclay particles and bacterial cell surfaces. The surface of the nanoclays is charged, and it stimulates adhesion to microbe membranes, which can result in membrane destabilization, increased permeability and leakage of the intracellular context, causing direct damage to the cell [90–92].

Furthermore, except for physical disruption, nanoclays have shown antibacterial activity through ion-mediated mechanisms. According to the literature, many clay materials contain metal ions such as Fe^{2+} , Cu^{2+} , Zn^{2+} , and Cu^{2+} , which can be released to the surrounding environment. The ions penetrate bacterial cells and cause the generation of reactive oxygen species (ROS) like hydroxyl radicals. The oxidative stress in the cell disrupts cellular components, including DNA, proteins and lipids, which affect the

bacterial viability [87,90,91]. It was shown by Williams et al. that some clays have lethal characterization against bacterial pathogens [92]. They showed the movement of metal precipitations toward *E. coli* poles and formation of intracellular voids. The interactions with *E. coli* showed that nanoclay particles absorb on the bacterial surface and intracellular change is caused primarily through ion-mediated oxidative mechanisms. As shown in the study, Fe^{2+} ions break down membrane-associated regulatory systems, which leads to the formation of hydroxyl radicals that result in cellular destruction [50,93]. In addition, modified clays with Ag^+ , Zn^{2+} , or Cu^{2+} showed strong antimicrobial activity in the in vitro condition, and the fibroblast viability of the samples was 85% [94–100]. The results from these related studies highlight that nanoclays act by chemical toxicity and cell stress mechanisms rather than pure mechanical damage. A summary of nanoclays that have been studied for wound-healing experiments is provided in Table 3. Recent studies have demonstrated that nanoclay-based materials are effective against relevant wound pathogens such as *Staphylococcus aureus* (including MRSA), *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Enterococcus*, which are associated with acute and chronic wound infections. For example, Laponite-based hydrogels loaded with silver sulfadiazine exhibited high antibacterial and antibiofilm activity against *S. aureus*, *E. coli* and *P. aeruginosa*. They also showed sustained drug release, which can be effective in wound treatment [73,101–109]. The nanomaterial-integrated hydrogels incorporating metallic nanoparticles (AgNPs, ZnO) showed broad-spectrum antimicrobial activity and support for controlling infection in wound environments [110,111]. The antimicrobial activity of nanocomposites/nanoclays in wound healing depends on multimodal and synergistic mechanisms, which significantly support enhancement of nanocomposite systems. The antimicrobial activity mechanisms of nanoclays include electrostatic interaction and membrane disruption, metal-ion-mediated toxicity, ROS generation, and antibiofilm activity [27,97–114]. Regarding electrostatic interaction and membrane disruption, nanoclay surfaces are negatively charged because of isomorphic substitution within their lattice structure. This helps with strong interactions with the bacterial cell membranes, especially in Gram-positive bacteria. These types of interactions caused disruption of membrane integrity, with membrane permeability increasing as a result in intracellular components (proteins, DNA) and leaking to the environment [113–115]. For example, Nascimento et al. described that Laponite hydrogels enhanced antimicrobial activity against *S. aureus*, which is attributed to membrane destabilization [116]. The plate-like (montmorillonite), tubular (halloysite) or fibrous (sepiolite) nanoclay morphologies directly interact with bacterial cells, which causes structural deformation [117]. The disruption of protein function-induced oxidative stress is caused by nanoclays that are characterized by high cation exchange capacity. Therefore, nanoclays act as a reservoir for antimicrobial ions like Ca^{2+} , Mg^{2+} , Al^{3+} , Zn^{2+} , Fe^{2+} and Cu^{2+} , which produce antibacterial activity [114–119]. It has been reported that halloysite nanotubes attach to bacterial surfaces and cause morphological changes that lead to reduced viability [118]. This effect is important in wound dressings, where direct contact between the material and bacteria occurs [116–122].

Biofilm formation is a major problem in chronic wound infections, especially for *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. The antibiofilm activity of the nanoclays is developed through inhibition of initial bacterial adhesion and disruption of the extracellular polymeric substances, which induces penetration of antimicrobial agents [116,119,120]. As reported by do Nascimento et al., Laponite hydrogels loaded with antimicrobial agents exhibited major antibiofilm activity, with high inhibition compared to the conventional treatments [116,117]. Nanomaterial-integrated hydrogels have exhibited synergistic antimicrobial, anti-inflammatory and regenerative effects, making them highly suitable for advanced wound care [106,117–125].

Table 3. Antibacterial nanoclay composites for wound healing.

Major Component/System	Type of Nanoclay	Antimicrobial Mechanisms and Quantitative Parameters	Effect on Wound Healing	References
Chitosan–MMT/HNT hydrogels	MMT, halloysite	Electrostatic membrane disruption by chitosan combined with sustained release from clay Chitosan/PVA–OMMT film: inhibition zone up to 15 mm against <i>E. coli</i> and 19 mm against <i>S. aureus</i> ; HNT film: up to 12 mm against <i>E. coli</i> and 10 mm against <i>S. aureus</i> .	Wound-healing assay not directly tested; proposed as antibacterial wound-dressing film based on cytocompatibility and film properties.	Farrokhi et al., 2024; [123]
Rifampicin-loaded HNT/alginate hydrogel	Halloysite nanotubes	NIR-triggered rifampicin release from ALG-HPR hydrogel produced 1.8–7.4 µg/mL drug after 1–3 irradiation cycles, resulting in nearly 100% <i>S. aureus</i> killing after 3 cycles.	In infected rat wounds, ALG-HPR + NIR reduced bacterial load and inflammation while promoting angiogenesis, collagen deposition, and complete neo-epithelial coverage by day 21.	Ye et al., 2023; [124]
PVA/chitosan/clay hydrogels	MMT HNT kaolinite	Moist environment, antibacterial ion/drug release, and membrane damage PVA/chitosan/MMT hydrogel: MIC 0.625 mg/mL against <i>E. coli</i> and 0.625 mg/mL against <i>S. aureus</i> /MRSA; with clove oil, MIC 0.328 mg/mL against tested microorganisms.	No in vivo wound-healing assay; hydrophilic hydrogel surface and swelling behavior supported potential skin/wound application.	Bayraktar et al., 2023; [125]
HA–quercetin–Ag/HNT hydrogel	Halloysite	Sustained Ag ⁺ release, ROS generation, and antibiofilm action; strong antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> ; exact inhibition zone/log reduction.	Human dermal fibroblast assays showed high cell viability and proliferation.	Rao et al., 2025; [99]
Halloysite–chitosan nanohybrids	Halloysite	Sustained release, membrane disruption, and protein interaction Au@HNT–chitin hydrogel: review-level data indicate approx. 99% killing of <i>E. coli</i> and 98% killing of <i>S. aureus</i> .	In infected mouse wounds, untreated model retained about 40% wound area at day 7, whereas Au@HNT–chitin retained about 20% wound area; collagen deposition increased.	Zhao et al., 2023; [62]
Curcumin/ciprofloxacin–MMT hydrogel	Magnetic montmorillonite in chitosan/hyaluronic acid hydrogel, Chito/HA-mMMt	Controlled ciprofloxacin/curcumin release from pH-responsive magnetic MMt hydrogel; inhibition zones increased from Chito/HA to Chito/HA-mMMt2, reaching 43 ± 0.2 mm against <i>E. coli</i> and 36 ± 0.3 mm against <i>S. aureus</i> .	Scratch assay confirmed fibroblast migration after 48 h, while CIP/CUR-loaded Chito/HA-mMMt2 maintained ~98% L929 cell viability at 16 µg/mL after 72 h, indicating low cytotoxicity and good wound-healing potential.	Sayyar Z. et al., 2023 [102]
Halloysite-based biomedical systems	Halloysite	Drug delivery, ROS generation, and membrane disruption. Representative values depend on HNT modification. Examples include TA-HNT-AgNPs with MIC = 31.25 µg/mL and PMo/Ag-HNT systems with MIC = 0.25–0.50 g/L.	Promotes tissue repair and reduces infection risk.	Mobaraki et al., 2021 [104]
Biopolymer–nanoclay hydrogels	Nanoclay-reinforced biopolymer or photocrosslinkable hydrogel; e.g., Cloisite/nanoclay systems	Encapsulation of antimicrobial agent and sustained release from nanocomposite hydrogel matrix. Nafcillin-loaded nanocomposite hydrogels showed antimicrobial activity against Gram-positive bacteria; reported inhibition zones included 36 mm against <i>S. aureus</i> and 38 mm against <i>S. pyogenes</i> for one formulation.	Biomedical hydrogel designed as a drug carrier; not a full in vivo wound-healing study. Supports potential biomedical/wound-related antimicrobial application.	Toader et al., 2023 [126]

In conclusion, the effectiveness of nanoclay or nanocomposites against clinically relevant pathogens like *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*, combined with strong antibiofilm activity, has been demonstrated. According to the literature, nanoclays showed the most effective activity when it was integrated into hybrid systems. It improves dispersion, enhances mechanical properties, and stabilizes nanoparticles in hybrid systems.

6.1. Comparison with Conventional Wound Dressings

Results from recent studies show that clay-based wound systems cannot be discussed as a single treatment class. The antibacterial activity performance of these systems depends strongly on morphology, polymer matrix, functional addition, and dose [44,59,61–64,68,69,71–73,116]. Compared with conventional wound dressings, such as gauze, passive films and simple hydrogels, clay-based hybrid systems have additional properties, such as exudate adsorption, hemostatic activity, sustained antimicrobial release and tissue regeneration. On the other hand, unlike conventional dressings, clay-based systems require careful clinical investigation of the purity of the clay, particle size, ion release, metal nanoparticles and cytotoxicity. A comparative interpretation of recent research is summarized in Table 4. Bentonite/montmorillonite-based systems are applied to burns and wounds in which fluid adsorption, swelling, and anti-inflammatory activity are required. For example, modification of silk fibroin dressings with carnosine–bentonite nanosheets speeds up the repair of the second-degree burns. In bentonite-containing systems, improved burn wound healing was observed, and these systems are mainly useful for the regeneration of epithelial cells [44,116–122].

Table 4. Comparative quantitative performance metrics of selected clay-based wound-healing systems.

Clay Platform or Study System	Best-Fitting Wound Type or Clinical Need	Matrix/Tested Dose or Composition	Quantitative Wound-Healing and Hemostatic Metric	Toxicity and Safety Information	Reference
Bentonite/montmorillonite: regenerated silk fibroin dressing modified with carnosine–bentonite nanosheets	Second-degree burn wounds; inflammatory and exudative wounds requiring epithelial repair	Regenerated silk fibroin dressing containing carnosine–bentonite nanosheets	Accelerated healing of second-degree burn wounds; improved re-epithelialization and tissue regeneration compared with control dressing	Biocompatibility evaluated in the wound model; no major toxicity signal reported	Azimzadeh Asiabi et al., 2020; [122]
Halloysite nanotubes: Au@HNT–chitin composite hydrogel	Infected wounds requiring combined antibacterial, hemostatic, and regenerative activity	Gold nanoparticles loaded in HNTs and incorporated into chitin composite hydrogel	96% wound closure within 10 days; improved hemostasis and wound healing	Low cytotoxicity/good biocompatibility reported	Zhao et al., 2023; [62]
Halloysite nanotubes: gelatin/starch/HNT 3D-printable hydrogel	Irregular soft-tissue wounds requiring conformable or personalized dressing	Gelatin–starch–HNT shear-thinning, self-healing, 3D-printable hydrogel	Self-healing and shape-adaptable hydrogel suitable for irregular wounds and soft-tissue repair	Cytocompatibility reported in vitro and in vivo	Mollaheydar al-imoazzem et al.; [60]
Sepiolite: chitosan–sepiolite nanocomposite film	Exudative wounds needing absorbent, mechanically reinforced dressing	Chitosan film containing 5–15% sepiolite	Improved water-vapor transmission rate, tensile strength, and fibroblast-related wound-healing properties	Biocompatibility/cell compatibility evaluated; no major toxicity concern reported	Dutta and Devi, 2021; [63]

Table 4. Cont.

Clay Platform or Study System	Best-Fitting Wound Type or Clinical Need	Matrix/Tested Dose or Composition	Quantitative Wound-Healing and Hemostatic Metric	Toxicity and Safety Information	Reference
Sepiolite: antibacterial self-healing sepiolite-based hybrid hydrogel	Bleeding or infected wounds requiring rapid hemostasis and antibacterial protection	PVA/sepiolite/Ca ²⁺ double-network hydrogel	Clotting time < 90 s; self-healing and stretchable hydrogel behavior	Mammalian-cell compatibility should be considered, especially because of ion-containing formulation	Jiang et al., 2024; [64]
Sepiolite: sustainable sepiolite-based composite for fast clotting	Acute wounds requiring rapid clotting and wound repair	Sepiolite-based composite prepared for hemostatic wound dressing	Fast clotting and improved wound-healing performance	Safety evaluation reported; dose-dependent toxicity should be checked before translation	Jiang et al., 2023; [50]
Palygorskite/ attapulgite: glycyrrhizic acid–ZnO/palygorskite chitosan film	Infected wounds requiring antibacterial barrier film and faster closure	Chitosan film containing glycyrrhizic acid and ZnO/palygorskite	Faster wound closure compared with control film	ZnO-containing systems require dose-dependent cytotoxicity assessment	Zhang et al., 2021; [66]
Palygorskite/ attapulgite: dencichine/palygorskite nanocomposite film	Bleeding wounds requiring hemostatic film	Dencichine/palygorskite nanocomposite incorporated into chitosan/PVP film	Superior hemostatic index; approximately two-fold faster clotting	Biocompatibility should be considered for drug–clay composite film	Yang et al., 2024; [68]
Palygorskite/fibrous nanoclay: nanoclay/spring-water hydrogel	Chronic or difficult-to-heal wounds requiring re-epithelialization support	Fibrous nanoclay/spring-water hydrogel	Promoted wound-healing activity and re-epithelialization in experimental models	Biocompatibility and skin-cell response evaluated	García-Villén et al., 2020; [69]
Laponite: Laponite/mafenide antibiotic-eluting film	Infected wounds requiring sustained topical antibiotic release	Laponite–mafenide and Laponite–mafenide–alginate films; different Laponite/mafenide ratios	Designed for prolonged local antibiotic delivery in wound healing	Reduced cytotoxicity compared with free drug was reported	Ghadiri et al., 2014; [72]
Laponite: zingerone nanoparticle/Laponite natural gum injectable hydrogel	Chronic, diabetic, or irregular wounds needing injectable antioxidant and antibiofilm support	Zingerone nanoparticle and Laponite-embedded natural gum injectable hydrogel	Complete wound closure within 9 days	Safety/cytocompatibility evaluated; active-compound dose should be optimized	Meena et al., 2025; [71]
Laponite: sprayable in situ film-forming Laponite composite	Irregular wounds requiring sprayable, conformable dressing	Laponite-based in situ film-forming system	Conforms to irregular wound surfaces; Mg ²⁺ -associated healing support discussed	Synthetic clay composition supports reproducibility; formulation safety depends on loaded agents	Pineda-Álvarez et al., 2023; [73]

Halloysite nanotube-based systems demonstrated strong wound-related outcomes, including biocompatible hydrogel behavior, and they showed good antibacterial and hemostatic performance and wound closure within 10 days in the case of Au@HNT–chitin hydrogel [59,61]. The palygorskite-based films exhibited a hemostatic barrier and

regeneration of epithelial cell function. The films and hydrogels were designed based on sepiolite systems from the literature, which were associated with improved wound-dressing properties [62–64,68,69]. Laponite-containing systems should be promising agents for chronic, infected or irregular wounds, which require sustained drug release. Laponite-based systems are suitable for designing sprays, injections or antibiotic-eluting smart dressings [71–73]. The toxicity risk is actually low for purified pharmaceutical-grade clays, but it is important to determine whether metallic nanoparticles, high ion release, poorly purified minerals or cationic polymers are incorporated into the systems [42,72,95,102].

6.2. Clinical, Regulatory, and Safety Perspectives

Clinical translation is required to evaluate the preclinical efficacy of the clay-based wound-healing systems that showed promising antimicrobial, hemostatic, and anti-inflammatory effects [122–125]. According to the clinical perspectives, these materials should be tested based on the wound type, wound depth, infection status and presence/absence of treatment agents [126–129]. In general, clay-containing dressings are designed to maintain moisture and create a barrier to provide fast regeneration of wounds. Clay-based systems incorporate antibiotics, silver, copper or bioactive agents [26,105,130–132]. In this case, the designed wound materials should be evaluated not only for wound closure and antimicrobial activity, but also for patient tolerance, pain reduction, and compatibility with current wound-care practice. In the United States, wound-dressing materials that cover wounds, absorb exudate and maintain moisture in the skin environment are generally considered medical devices [127–129]. Similarly, regarding the European Medical Device Regulation, wound condition, duration of contact and the product's incorporation of a medicinal substance are examined in terms of the pharmacological efficacy [131]. Furthermore, a safety evaluation has to be carried out for risk-based approaches. The following key biological tests are mandatory for clay-based systems in contact with wounds: cytotoxicity, skin irritation, hemocompatibility, systemic toxicity, genotoxicity and local tissue response. In safety and risk evaluation processes, clay-specific parameters are also important, such as purity of clay, particle size distribution, swelling behavior, cation exchange capacity, endotoxins, and residual impurities and batch-to-batch reproducibility. Assessing these parameters is mandatory because natural clays may contain trace metals or several mineral compositions. Pharmaceutical-grade purification and physicochemical standardization are important before clinical testing [132]. Furthermore, antibiotic-incorporated systems also need to be studied in order avoid any therapeutic exposure, which can cause antimicrobial resistance. For this reason, MIC values, inhibition-zone diameter in relation to the release kinetics, cytotoxic concentration and therapeutic index should be included in the reports. Manufacturing and sterilization involve other translational challenges, including gamma irradiation, ethylene oxide, autoclaving and aseptic processing, which may change clay dispersion, hydrogel structure, drug release, swelling capacity and strength. For this reason, the final sterilized product should again be investigated for antimicrobial activity, release behavior, mechanical integrity and biocompatibility. In conclusion, clay-based wound dressings required standardized pre-clinical testing, comparison with commercial dressings, long-term safety investigation and well-designed clinical studies before clinical implementation [26,128–132].

6.3. Limitations and Future Directions

From a translational perspective, the clinical maturity of clay-based wound-healing systems is still heterogeneous. While some clay-containing formulations, particularly bentonite-based formulations and pharmaceutical-grade clay materials, have been used clinically or commercially, most of the advanced nanocomposite systems based on hal-

loysite nanotubes, sepiolite, palygorskite and Laponite are still at the preclinical stage, with the majority of the data coming from in vitro and animal studies. Future efforts should be directed towards clinical validation, long-term safety assessment, and regulatory standardization to promote their successful translation into routine wound-care practice.

Despite the promising therapeutic potential of clay-based wound-healing systems, several limitations still exist. Most of the existing studies are limited to in vitro experiments and small animal models, and well-designed clinical trials are still lacking. Differences in mineral composition, purification protocols and physicochemical properties may pose a concern for reproducibility and therapeutic efficacy. Furthermore, the long-term safety of functionalized clay systems, in particular those containing metallic nanoparticles or bioactive additives, remain to be further investigated [25,26,43,108]. Future studies should be directed towards the establishment of standardized characterization protocols, scalable manufacturing strategies, optimization of drug–clay interactions and extensive clinical validation. The incorporation of clay minerals in smart, stimuli-responsive and personalized wound-dressing matrices is a very promising avenue for future development.

7. Conclusions

Clay-based nanomaterials, particularly those derived from bentonite, halloysite, palygorskite, sepiolite, and synthetic analogues like Laponite, have emerged as promising multifunctional platforms in modern wound care. Their unique physicochemical properties, including high surface area, ion exchange capacity, swelling ability, and structural tunability, have enabled applications ranging from passive moisture control to active therapeutic delivery. As wound healing requires a multifaceted approach involving hemostasis, inflammation resolution, microbial control, and tissue regeneration, the integration of clay minerals into biomedical systems aligns closely with these clinical demands.

Over the past decade, advances in nanotechnology and material engineering have expanded the utility of clays beyond traditional use, enabling their incorporation into injectable hydrogels, nanocomposite films, electrospun membranes, and stimuli-responsive delivery systems. These innovations have demonstrated strong preclinical efficacy, including enhanced re-epithelialization, neovascularization, antimicrobial action, and cytokine modulation in both acute and chronic wound models. Additionally, early-phase clinical applications have confirmed favorable outcomes in terms of safety, patient tolerance, and dressing functionality.

Nevertheless, the clinical translation of clay-based systems still faces significant challenges. Issues of long-term biocompatibility, potential metal-ion toxicity, lack of standardization in characterization and testing, and regulatory ambiguity must be systematically addressed. Current studies support the general safety of purified clay minerals at therapeutic concentrations, but the addition of functional agents—such as silver or copper—requires cautious dose optimization. Furthermore, achieving pharmaceutical-grade consistency in large-scale production will be essential for regulatory approval and commercial viability.

Looking forward, clay-based materials are positioned at the convergence of bioinspired design, nanomedicine, and regenerative therapy. Their affordability, adaptability, and proven therapeutic potential make them compelling candidates for next-generation wound management solutions. Future work should focus on multidisciplinary collaborations to standardize manufacturing protocols, optimize drug–clay interactions, and validate efficacy through large-scale clinical trials. As these goals are achieved, clay nanomaterials are poised to become integral components of smart, bioactive wound dressing technologies.

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