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Review Article

HALLOYSITE NANOTUBE-BASED COMPOSITE IN WOUND MANAGEMENT: A REVIEW

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ABSTRACT

Nanotechnology is a rapidly growing field with numerous applications in science and technology, industry, environment, and energy, to name a few. Halloysite is an abundant, commercially viable clay nanomaterial available in many forms and dimensions, including short tubules, spheroids, and platy clays (kaolin and mountain morillonite). Halloysite nanotubes (HNTs) are suitable for wound healing due to their high mechanical strength, biocompatible properties, and hemostasis. They have been extensively studied for their use as biocompatible nanocontainers with controlled and gradual release of antiseptics. Therefore, they can be used for the treatment of antibacterial and antiseptic injuries. In addition, they can also be used as a medium for drug delivery and are a viable alternative for wound healing applications. The incorporation of HNTs into porous sponges improves their flexibility, compressive strength, and tightness of the elastic module. In this review, the use of HNT-based composites in wound management is summarized, focusing on their controlled release properties.

INTRODUCTION

Nanotechnology is a rapidly growing field with numerous applications in science and technology, industry, environment, energy, and other fields. As this field has promising future prospects, intensive research is being conducted to expand its scope of applications. Nanotechnology has played an important role in environmental studies, for example, in the sensing and cleanup of pesticides, and in the removal of pollutants such as nitrates [1]. Other prominent applications include the development of nanomaterials for thin-film transistors, wearable electronics, artificial skin and muscles, and nanoelectronic solar panels [2]. Many different forms of nanomaterials occur naturally or can be artificially produced through top-down and bottom-up processes for use in a variety of applications [3].

Halloysite is an abundant, commercially viable clay nanomaterial. It is anaturally occurring aluminosilicate nanoclay with a characteristic hollow, tubular helical structure. Halloysite has been shown to be biocompatible and can aid in blood clotting [4]. Halloysite nanotubes are less hazardous than saline, and macrophages can rapidly clear them from the body. Halloysite nanotubes (HNTs) have been shown in several trials to be safe for use as oral drug delivery systems, lotions, implants, and wound treatment materials [5]. The most commonly used HNTs are elongated tubes of halloysite particles in various forms and dimensions, including short tubules, spheroids, and platy clays (kaolin and mountain morillonite) [6].

HNTs are attractive nowadays due to their properties such as mechanical strength, excellent biocompatibility, and hemostasis. HNTs are tubular halloysite structures that chemically simulate kaolin. They have a molecular formula, $(Al_2Si_2O_5(OH)_{4n}H_2O)$ and exhibit a layered structure. The outer diameter is about 40-70 nm, while the inner diameter is about 10-20 nm [7]. Halloysite-based nanotubes have various biomedical uses, including tissue engineering, wound healing, and drug delivery.

Chronic injuries are a persistent health problem with catastrophic effects on individuals, and impose significant costs on healthcare systems and communities. These injuries can lead to impaired body function. They are typically characterized by persistent or excessive inflammation, persistent infection, and the inability of cells to respond to repair stimuli [8]. In the United States, total Medicare expenditure for each type of injury has been estimated to range from $28.1 billion to $96.8 billion. The enormous cost burden attributable to amputations ranges from $6.1 billion to $18.7 billion for diabetic foot ulcers (one of the most important chronic wounds). Therefore, there is a need to develop and apply innovative wound healing procedures and medical devices [3].

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The problem of chronic injuries is exacerbated in people with certain conditions, such as uncontrolled diabetes, which can cause circulatory problems. When circulation decreases, blood flows more slowly, making it more difficult for the body to deliver nutrients to wounds. As a result, wounds may take a long time to heal, or they may not heal at all. However, with the use of HNTs in such wound treatment, the process is likely to be more effective [9]. Therefore, this paper focuses on the controlled release properties of HNT based on previous research on wound treatment.

Halloysite Nanotubes in Wound Treatment

Wound dressings can be classified into traditional, interactive, and bioactive types based on the biomaterials used. Recent studies have shown that biomaterials such as polysaccharides are optimal materials for wound dressings, because they are nontoxic, naturally accessible, nonimmunogenic, biocompatible, and biodegradable. Hydrogels, for example, are widely used for wound dressings because of their biocompatibility, ability to load and release bioactive substances, high water content, and flexibility. In addition, HNTs have been added to polysaccharides such as alginate and chitosan to improve the weak mechanical strength of hydrogels[10]. The composites used for this purpose include a nanofiber membrane, composite dressing, film composite, sponge composite, scaffold, and hydrogel, which are listed in Table 1.

Table 1 Classification of halloysite-based nanotubes in wound management

Material	Biomaterial form	Experimental approach	Result	Reference
PCL-PDSBMA-HNT	Nanofibrous membrane	*In vivo* treatment	The HNT nanocarrier with the dual drugloading pathway conferred both robust initial antibacterial activity and sustained bacteriostaticability against *S. aureus* and *E. coli*to the composite membranes for at least 16 days and was able to promote skin regenerationbetter	[11]
vancomycin	Composite dressing	*In vitro* treatment	Vancomycin immobilized on HNTs APTS and encapsulated in alginate gel can be considered as a potential material for wound dressing	[12]
Plasticized starch (PS)	Film composite	*In vitro* treatment	The HNTs are uniformly distributed in the starch matrix due to the effect of PEG, and the tensile strength of the film was successfully improved and was better for wound healing	[13]
Pure chitosan	Sponge composite	*In vivo* treatment	The highly porous structural and mechanical properties of chitosan-HNT composite sponges allow gas and fluid exchange, stop bleeding and absorb excess exudate, improve and spread cell adhesion, and promote wound healing, making them one of the most suitable wound dressings	[14]
Fibroblasts	Scaffold	*In vivo* treatment	Scaffolds containing 2% and 5% of both clay minerals promoted cell growth, with the strongest proliferative response observed with HNT 2%	[15]
Oxidized dextran (ODEX) adhesive hydrogels	Hydrogel	*In vivo* treatment	The natural antibacterial properties of CS and ODEX gave the hydrogels a strong bactericidal effect	[16]

DISCUSSION

Composite Dressing

The potential of a double-barrier HNT for wound dressings was explored by Kurczewska *et al*. and showed improvement over the previous wound dressings, as it served as an effective antibacterial agent with the antibiotic vancomycin [12]. The release rate of the drug decreased after replacing the previously studied silica with halloysite nanotubes. The presence of amine groups on the inorganic surface is important to prevent the burst release of the immobilized drug. The halloysite structure allows outer and inner surfaces containing organic ligands to be functionally useful. This results in the immobilized drug being released at different rates, depending on where it is placed. This process takes longer than releasing the drug only at the outer surface. Changing the gel structure by adding gelatin had a positive effect on slowing the drug release from the proposed dressing. However, this change had a negative effect on the antibacterial properties of the system. Although all the systems studied, i.e., alginate and gelatin/alginate gels, had antibacterial properties, only the former had adequate antibacterial activity. The reduction in the vancomycin release rate of HNTs (3-Aminopropyl)-trimethoxysilane (APTS) in gelatin/alginate gel was so substantial that the results of antibacterial activity after 24 hours were significantly worse than those of the reference sample. Therefore, only vancomycin immobilized on HNTs APTS and encapsulated in alginate gel can be considered as a potential wound dressing material [12]. The proposed novel dressing exhibits a high degree of stability and neutrality towards the living organisms used in bioassays [17].

On the other hand, better skin re-epithelialization and reorganization have been reported by combining halloysite and chitosan to create a nanocomposite that is independent of the use of either material [9]. The use of montmorillonite as a carrier that reduces drug cytotoxicity improved the *in vivo* therapy of infected wounds with nanoscale silver particles [18]. Montmorillonite has also shown a healing effect in combination with chitosan and polyvinylpyrrolidone polymers [19]. Compared to formulations without clay, bentonite-containing nanocomposite films improved the *in vivo* wound healing processes in mice. For example, wound closure after 16 d was 92–93% for the samples without clay and 95–97% for the montmorillonite samples, which was higher than that in the adverse control group (84%) [19].

HNTs were also used in an alginate wound dressing as vancomycin carriers. Compared to living organisms used in bioassays, the new dressing has shown excellent stability and neutrality. The studies showed that a future wound dressing with suitable properties could be a viable way to control long-term wounds. A gelatin elastomer was combined with CIP- and polymyxin B-carrying HNTs (HNT-B) to form elastic and antibacterial nanocomposites for dual drug delivery. The antibacterial CIP was distributed throughout the nanocomposite matrix, whereas HNT-B was first injected into the HNT and then dispersed throughout the matrix. CIP and HNT-B showed positive effects on physical properties, cytotoxicity and fibroblast proliferation, which was attributed

to the enhanced *in vitro* drug release and antibacterial activity. This bionanomaterial offers advantageous properties such as high-water absorption, low cytotoxicity, tunable biodegradability and exceptional flexibility. Pavliáková *et al*. usedHNTs to improve the elastic material made of nanofibrous PCL and gelatin, which in turn can be used as a dressing for long-term drug delivery for wound dressings[20].

Wound healing dressings were also prepared with nanocomposites based on HNTs. The incorporation of HNTs increased the compressive strength and durability of the three-dimensional, porous, and flexible chitosan composite sponges. The ability of chitosan to coagulate blood was also enhanced by HNTs [14]. The composite sponges were found to be cytocompatible with improved wound healing properties in *in vivo* experiments. Chitosan oligosaccharides-modified HNTs were shown to result in better and finer reepithelialization and restructuring than HNTs or chitosan alone. The prolonged release of HNTs and chitosan oligosaccharides (N-acetylglucosamine and D-glucosamine homo- and hetero-oligomers) accelerated wound healing, making this nanocomposite a viable wound healing agent [9].

Film Composite

Kim *et al*. reported the use of translucent films prepared from cellulose/HNTs solutions [21]. Due to the repulsive force of their surface charge, HNTs could be uniformly distributed in the cellulose, and the hydrogen bonding between HNTs and cellulose broke the cellulose chain-to-chain connections[21]. The introduction of HNTs increased the turbidity of the film, but the permeability diffusion was maintained. To solve the problem of agglomeration of HNTs, Xie *et al*. prepared dispersed starch/HNTs composite films by ball milling the HNTs with amylose [13]. However, the extraction of amyloseis costly and time-consuming. Therefore, polyethylene glycol (PEG) has been explored as a dispersing agent to mill, modify, and disperse HNTs in various solvents. In one study, glycerin and a modified HNT suspension were added to the slurry. After stirring and casting onto a stainless-steel plate, the composite films were prepared. SEM images of the treated HNTs and HNTs/starch films showed that they contained 3% and 7% HNTs, respectively. The HNTs are uniformly distributed throughout the starch matrix due to the effect of PEG, and the tensile strength of the film was successfully improved.

Sponges Composite

HNTs in the composite improve the nano-ruggedness of sponge porosity, by promoting the capture of over-repair factors (such as proteases or reactive oxygen species) and stimulatingthe progressive release of active fragments that have been shown to recruit and activate leukocytes or mesenchymal cells [14]. In addition, HNTs influence the phenotype and process of cell differentiation by improving the mechanical properties of chitosan sponges. In short, the highly porous structural and mechanical properties of chitosan-HNT composite sponges enable gas and fluid exchange, stop bleeding and absorb excess exudate, improve and spread cell attachment, and promote wound healing, making them one of the most suitable wound dressings [14].

Scaffold

The presence of HNTs and montmorillonite in the scaffolds increased the porosity of the system, as higher clay mineral concentration led to an increase in pore size, although this difference was not statistically significant. Porosity and fiber diameter appear to be essential to facilitate skin cell adhesion because skin porosity can convert the scaffold from a surface to a network of fibers that can serve as a cell carrier [15]. Dry HNTs improved the breaking strength and elasticity of the system, while MMTs up to a concentration of 2% strengthened the structure of the groove, and increased the rupture resistance and elasticity of the system [15]. The infusion of HNTs as scaffolds were significantly deformed, which was greater than empty scaffolds. Hydration resulted in a significant reduction in breakage resistance, deformation, and loss of elasticity. Although clay minerals appear to strengthen the structure of the scaffold, particles in the polymer matrix can disrupt the interweaving of the polymer chains when their concentrations exceed a certain threshold and eventually lead to deterioration of the scaffolds.

Sandri *et al*. made a comparison between fibroblasts grown on standard growth medium with and without the addition of HNT scaffolds. After three days of cell growth, the cells grew similarly, although other growth medium compositions resulted in a significant decrease in cell viability. After six days, cells on the empty and HNT-loaded scaffolds (2% and 5%) grew to levels comparable to the control samples, except for the 1% HNT-loaded scaffolds, which showed no proliferation at all. After ten days, cells grown on standard growth medium failed to proliferate further due to significant cytotoxicity issues. However, scaffolds loaded with 2% and 5% of the two clay minerals showed sustained cell growth, with the strongest proliferation response observed with 2% HNT.

Hydrogel

Polysaccharide/HNT swelling ratios were studied in NaCl. Compared to hydrogels composed of pure sodium alginate (SA), moderate swelling ratio under the same relaxation conditions rapidly reduced the loading of HNTs. The HNTs had lower adsorption than SA, which may be due to the fact that the content of hydrophilic polymer decreases when HNTs are incorporated into the composite hydrogels. In addition, hydrogen bonding can significantly strengthen the alginate-tapering connections between the HNTs used as physical crosslinking sites and restrict the mobility of the chains, resulting in a significant decrease in water absorption [22]. The high-water content of hydrogels ensures that granulation tissue and epithelium are localized in a moist environment (70%-90%). During would healing, the soft-elastic properties of hydrogels make it easy to apply and remove without causing damage. By lowering the temperature of the skin wound, hydrogels have a soothing and cooling effect. Hydrogels are useful for chronic dry wounds, necrotic injuries, pressure sores, and burns. The addition of HNTs increased the thermal stability and regenerative capacity of cellulose. However, it decreased the moisture absorption capacity of the nanocomposite at constant relative humidity [23]. These dressings are composed of clear, sticky polyurethane that transfers water vapor, oxygen, carbon dioxide, and autolytic eschar debridement as well as bacterial resistance from the wound. Originally, nylon derivatives with adhesive polyethylene frames were used as carriers for the occlusive films. Due to limited absorbency, which resulted in maceration of the lesion and surrounding healthy tissue, film dressings made of nylon were initially avoided for highly draining

wounds [2, 24]. On the other hand, these dressings are incredibly elastic and flexible, allowing them to conform to any shape without additional tapping. Transparent films can also be used to assess wound closure without the need to remove the wound dressing.

Hydrogel dressings are suitable for all four stages (haemostasis, inflammation, proliferation, remodeling) of wound treatment except for infected and heavily draining wounds. Li *et al*.found that non-irritating hydrogel pads do not react with living tissue and allow metabolites to pass through. Solution casting was used to prepare regenerated nanocomposites of cellulose/HNTs in an ionic liquid of 1-butyl-3-methylimidazolium chloride. Due to the strong contact with the cellulose, the HNTs were dispersed in the cellulose. The modulus and tensile strength of the nanometric films increased by 100% and 55.3%, respectively, when the HNTs were loaded at 6 wt%, which was attributed to the tubular geometry and higher stiffness of the HNTs [16].

Recent research studies have identified polysaccharides that are nontoxic, naturally accessible, nonimmunogenic, biocompatible, and biodegradable as efficient wound healing materials [25]. Hydrogels are the most commonly used wound dressings due to their biocompatibility, loading, and delivery of bioactive compounds, high water content, and flexibility [26]. In addition, HNTs have been incorporated into polysaccharides such as alginate and chitosan to compensate for the low mechanical strength of hydrogels [27]. A dual barrier containing antibacterial vancomycin was developed for the alginate-HNTs wound dressing. Vancomycin is suitable as a wound dressing only when immobilized in HNTs-(3-aminopropyl)-trimethoxysilane (APTS) and encapsulated in alginate hydrogels [12].

Hydrogels have been studied for the controlled delivery of biomolecules ranging from small molecular weight pharmaceuticals to biomacromolecules such as nucleic acids, polysaccharides, and proteins, to name a few. In addition, various natural components have been used to prepare biocompatible and biodegradable hydrogels. Due to their low toxicity, high biocompatibility, and degradability by human enzymes, chitosan-HNTs composite hydrogels have received much attention [28]. When comparing pure HNTs to chitosan-coated HNTs, the latter was found to release fewer drug payloads. For example, at Day 9, the chitosan-coated HNTs released only 78% of the total drug payload, whereas the uncoated HNTs released 88% [28]. The drug release rate was extremely low, and after 20 days, the residual content was less than 10% of the loaded compound. The additional barrier provided by chitosan, through which the drug must diffuse, is the reason why the chitosan-coated HNTs have a lower drug release rate. Chitosan-based hydrogels are widely used for cancer therapies, subcutaneous release, and oral delivery. The significant relationship between plasticizer nature and drug release behavior has been exploited in recent years, leading to the preparation of starch/HNTs composite films for drug release by the melt blending method [28]. In addition to drugs, other agents such as antibacterial agents, DNA, and proteins can also be loaded for controlled release.

CONCLUSION

Tubular HNTs are suitable for wound healing due to their high mechanical strength, biocompatible properties, and hemostasis. HNTs have been investigated for their use as biocompatible nanocontainers for the regulated and gradual release of antiseptics. Nanotubes can be used in numerous studies for the treatment of antibacterial and antiseptic injuries. Due to their mechanical strength, better biocompatibility and hemostasis, tubular HNTs are a viable alternative for wound healing applications. In the studies reviewed, wound-healing dressings were prepared with HNT nanocomposites. The integration of HNTs into porous and flexible sponges improves the flexibility, compressive strength, and tightness of the elastic module. In addition, understanding the cellular transport channels of HNTs could help in the rational design of new drug delivery systems and be of great benefit to biotechnology. HNTs could be an important technology for drug delivery and future biological applications due to their high biocompatibility. Due to their mainly perinuclear location as a result of cellular internalization, HNTs seem to be promising candidates for intracellular drug delivery.

Conflict of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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