International Journal of Research and Review
Vol. 9; Issue: 6; June 2022
Website: www.ijrrjournal.com
E-ISSN: 2349-9788; P-ISSN: 2454-2237

Review Paper

A Potential of Halloysite Nanotube as a Delivery Vehicle in Wound Treatment

Syahirah Mohd Noor[a], Rohardiyana Roslan[a], Soon Chin Fhong[b], Nadirul Hasraf Mat Nayan[a,b]

[a]Faculty of Engineering Technology, Universiti Tun Hussein Onn Malaysia, Pagoh Higher Education Hub, KM 1 Jalan Panchor, 84600 Pagoh, Johor.
[b]Microelectronic and Nanotechnology-Shamsuddin Research Centre (MiNT-SRC), Integrated Engineering Institute, Universiti Tun Hussein Onn Malaysia, 86400 Parit Raja, Johor.

Corresponding Author: Nadirul Hasraf Mat Nayan

DOI: https://doi.org/10.52403/ijrr.20220631

ABSTRACT

Nanotechnology is a field that is growing quickly and has many uses in science, industry, the environment, energy, and other areas. Halloysite is a common, economically viable nanomaterial composed of clay. Widely employed in the biomedical area are elongated tubes of halloysite particles in a variety of shapes and dimensions, including shorter tubules, spheroidal and platy clays (caolin and mountain morillonite). This research investigates the utilisation of halloysite nanotube (HNT) composites in wound healing and drug-carrying vehicles. The review indicates that tubular HNTs are suitable for wound healing due to their high mechanical strength, biocompatibility, and hemostasis. It was looked into whether HNTs could be used as biocompatible nanocontainers for the controlled and gradual release of antiseptals. Nanotubes have also been found in many studies looking for ways to treat antibacterial and antiseptic wounds. When HNT is added to porous and flexible sponges, it makes the elastic module more flexible, stronger, and tighter.

Keywords: Halloysite nanotube, drug delivery, mechanical strength, biocompatible, wound healing

1. INTRODUCTION

Nanotechnology is a fast-expanding field that has several applications in science and technology, industry, the environment, energy, and other fields. Because this area has promising future prospects, significant research is being conducted to widen the scope of its applications. Nanotechnology has played an important role in environmental studies, such as pesticide sensing and cleanup, as well as pollutant removal such as nitrates [1]. Among other applications, nanomaterials are being developed for thin-film semiconductors, wearable technologies, tissue engineering, and nanoelectronic solar cells [2]. Numerous types of nanomaterials occur naturally or can be synthesised artificially by top-down and bottom-up methods for employment in a variety of applications [3].

Halloysite is an abundant, commercially practical clay nanomaterial. Halloysite is an aluminosilicate nanoclay with a distinctive hollow tubular scroll structure seen in nature [4]. It has been shown to be biocompatible and to aid in blood clotting [5]. The most commonly used are elongated tubes of halloysite particles in a number of forms and dimensions, including shorter tubules, spheroid and platy clays (caolin and mountain morillonite) [6]. HNTs is attractive nowadays because of their properties in terms of mechanical strengths, superior biocompatibility, and haemostasis. HNTs are tubular halloysite structures that simulate kaolin chemically. They are high aspect ($Al_2Si_2O_5(OH)_{4n}H_2O$) and have layered structure. The outside diameter is roughly 40-70 nm. The internal diameter is about 10-20 nm [7]. Halloysite nanotubes have various uses in biomedical uses, including tissue engineering, wound cure, and medication carriers.

Chronic injuries constitute an ongoing health issue with a catastrophic effect on individuals, leading to significant expenses for health systems and communities. The result of this damage is often prolonged or excessive inflammation, persistent infections, and failure of cells to repair impulses [8]. The total US expenditure on Medicare ranging from $28.1 to $96.8 billion for every kind of injury was projected. The biggest cost burden attributable to amputations was diabetic foot ulcers (one of the major chronic sores) of $6.1 to $18.7 billion. Circulation complications may occur in individuals with uncontrolled diabetes. When circulation is impaired, blood moves more slowly, impeding the body's ability to heal wounds. As a consequence, injuries may take an extended period of time to heal or never heal completely. However, the use of HNT in such wound management, this process is likely to be more effective due to its valuable properties [9].

In tissue engineering, there are many composites as a medium vehicle that were study with various method applied to enhance the properties and optimized the functional in research area. This study highlights previous research on halloysite nanotube as material that used in wound healing application as well as drug-carrying vehicles in different types of biomaterial form.

2. Characterization of Halloysite Nanotube

Halloysite nanotubes (HNTs), a naturally occurring clay mineral with nanotubular properties, are recently gaining researchers attention. Berthier, in 1826 described HNTs, a highly crystallised form of kaolin as a dioctahedral 1:1 clay mineral of the kaolin group [6]. They are often found in soils across the globe. Several countries, including China, France, Belgium, and New Zealand, have deposits of HNT. As previously reported, HNTs have inner and outer hydroxyl groups that are situated between layers and on the surface of the nanotubes. Due to the multilayer nature of HNTs, the bulk of the hydroxyl groups are on the inside, with just a few on the surface. The siloxane surface of HNTs can be validated by Fourier transform infrared spectra, which demonstrate significant absorption of O–Si–O (1030 cm^1), indicating that the surface is mostly made up of O–Si–O groups. As a result, HNTs have a much lower density of surface hydroxyl groups than other silicates such as kaolinite and montmorillonites.

Table 1: Representative analysis data of HNT [10]

Analysis data of HNT	
Length	400 – 1000 nm
Inner diameter	10 – 70 nm
Aspect ratio (L/D)	9 - 50
Average tube diameter	20 – 200 nm
Mean particle size in aqueous solution	143 nm
Particle size range in aqueous solution	50 – 400 nm
Typical specific surface area	22.1 – 81.6 $m^2. g^{-1}$
Lumen space	10.7 – 39%
Pore space	14 – 47%
Density	2.14 – 2.59 g. cm^{3-1}

3. Types and application of composite form

3.1 Composite dressing

Kurczewska et al. investigated if current wound dressings might be improved by including a double barrier [11] and offered an improvement to the prior one as an antibacterial agent with the antibiotic vancomycin. The release rate of the medication reduced following the replacement of previously investigated silica by halloysite nanotubes. However, the presence of amine groups on the inorganic surface was critical in preventing the burst process of drug release. Outer and inner surfaces containing organic ligands may be functionally helpful due to the halloysite structure. This results in a varied pace of release of the immobilized medicine depending on where it is placed. This procedure takes longer than the release of the medication on the external surface solely. The addition of gelatin to the gel structure improved the rate of medication release from the suggested dressing. However, this modification had a detrimental effect on the system of antibacterial characteristics. Although the antibacterial characteristics of all of the systems studied, namely alginate and gelatin/alginate gel, only the former demonstrated adequate results. The decrease in the rate of vancomycin release from HNTs APTS in Gelatin/Alginate gel was considerable enough that the antibacterial activity values after 24 hours were considerably poorer than the sample material.

On the other hand, when halloysite and chitosan are mixed to generate a nanocomposite that may be employed independently of both materials, better skin reepithelization and reorganisation have been observed [9]. Using silver nanoscales as a carrier reduced drug cytotoxicity and improved in vivo wound therapy [12]. Montmorillonite has also shown a healing effect in combination with chitosan and polyvinylpyrrolidone polymers [13]. In comparison to formulations without clay, bentonite-containing nanocomposite films improved the healing processes of the in vivo wounds in mouse. For example, wound closure after 16 days was 92–93 % for samples without clay and 95–97 % for montmorillonite samples, which was greater than the unfavourable control (84%) [13].

Another technique involved creating wound-healing dressings utilizing nanocomposites based on HNT. Compression strength and strength have been increased in the three-dimensional, porous, and flexible Chitosan Composite Sponges by the addition of HNT. The ability of chitosan to coagulate blood was also shown to boost HNT. The composite sponges were found to be cyto-compatible with improved wound healing characteristics in in vivo experiments. Chitosan oligosaccharides modified HNT performed better in terms of reepithelization and restructuring and finer reepithelization and restructuring than HNT or chitosan alone. The extended release of HNT and chitosan oligosaccharides (N-ACetylglucosamine and D-glucosamine Homo- and Hetero-oligomers) accelerates wound healing and makes this nanocomposite a viable wound healing medicine [9].

3.2 Film composite

Kim et al. described the fabrication of transparent cellulose films from cellulose/HNTs solutions [14]. Due to the repulsive force of their surface charge, HNTs distributed uniformly in cellulose, and hydrogen bonding between HNTs and cellulose destroyed the cellulose chain-to-chain linkages [14]. The insertion of HNTs enhanced the film haze, but the diffuse transmittance could be maintained. Chang et al. developed dispersed starch/HNTs composite films by ball-milling amylose to encapsulate the HNTs [15]. The extraction of amylose, on the other hand, is costly and time-consuming. In one study, polyethylene glycol (PEG) was used to grind, modify, and disperse HNTs in a range of solvents, and the slurry was then supplemented with glycerin and modified HNTs suspension. After stirring and casting on a stainless-steel plate, the composite films were created. SEM images of treated HNTs and HNTs/starch films, containing 3% and 7% HNTs, respectively. The HNTs are dispersed equally throughout the starch matrix. Due to the action of PEG, the treated HNTs were effectively dispersed throughout the starch matrix, and the film tensile strength was successfully enhanced.

3.3 Sponges composite

HNTs in the composite enhance the nano-ruggedness of the sponges porosity (i) can encourage trapping by over-repair factors (such as protectases or reactive oxygen species), (ii) stimulate progressive liberation of active fragments which have been demonstrated as leukocytes or mesenchymal cells to recruit and to activate and (iii) increasing the amount of leucocytes and mesenchymal cells [16]. In addition, HNTs affect the phenotypic and process of differentiating of cells through improving the mechanical features of chitosan sponges. Briefly speaking, Chitosan-HNT composite sponges highly porous structural and mechanical properties allow for gas and fluid exchanges, end bleeding and take excess exudates, enhance and spread cell attachment and favor wound healing, making them one of the most appropriate wound dressing agents, in other words [16].

3.4 Scaffold

The work published by Sandri et al. shown that despite the presence of HNT in the scaffolds did not exhibit significant alterations, the system porosity increased, and the pore size increased with increased clay mineral concentration. Porosity and fiber diameters seem to be essential to facilitate cell attachment of the skin and the porosity of the skin can convert it from a surface to a network of fibres, which can server the cells home [17]. Dry HNT improved breakage force and system elasticity, while MMT reinforced the structure of the groove, increased rupture resistance and system elasticity until 2% of concentration [17]. The scaffolds were significantly deformed, which was greater than blank scaffolds. Hydration has resulted in a significant reduction in breakage resistance, deformation and elasticity loss. Although clay minerals appear to strengthen the structure of the scaffold, particles in the polymer matrix may interrupt polymer chain entanglements by their concentration exceeding a specific threshold and lead to scaffolds becoming worse.

3.5 Hydrogel

According to Li et al., hydrogel dressings are acceptable for all four stages of wound therapy excluding infected and severe drainage wounds [18]. They discovered that non-irritating hydrogel pads are non-reactive to live tissue and allow for the passage of metabolites. The solution casting technique was utilised to regenerate cellulose/HNT nanocomposites in an ionic liquid of 1-butyl-3-methylimidazolium chloride. Due to the strong contact with cellulose, the HNTs were disseminated in cellulose. Due to the tubular design and enhanced stiffness of HNTs, the modulus and tensile strength of nanometric films for Youth increased by 100% and 55.3%, respectively.

The high-water content of the hydrogels in a moist environment (70%-90%) supports granulation tissues and epithelium. During the healing of a wound without causing any damage, it is easy to apply and eliminate due to the soft elastic properties of hydrogels. By lowering the skin wounds temperature, hydrogels are a calming and cooling impact. Hydrogels are useful in chronic dry wounds, necrotic injuries, pressures and burn injuries. The inclusion of HNT increased the thermal stability and charging of cellulose regeneration, however lowered nanocomposites moisture absorption capacity to constant relative humidity [19]. These dressings are composed of clear, sticky polyurethane, which transmits water vapor, oxygen, carbon dioxide and autolytic eschar debridement and bacterium resistance from the wound.

Hydrogels have been researched for their potential to transport biomolecules ranging in size from small molecule medications to biomacromolecules such as nucleic acids, polysaccharides, and proteins. Furthermore, diverse natural components were used to make biocompatible and biodegradable hydrogels. Chitosan-HNTs composite hydrogels have garnered considerable interest due to their low toxicity, great biocompatibility, and degradability by human enzymes [20]. When comparing pure HNTs to chitosan-coated HNTs, it was discovered that the chitosan-coated HNTs released less. On day 9, for example, the chitosan-coated HNTs had released just 78% of the whole drug payload, while the uncoated HNTs had released 88% [20]. The rate of drug release was very slow, and after 20 days, the leftover material contained less than 10% of the loaded stuff [20]. The extra barrier produced by chitosan, across which the medicine must diffuse, is responsible for the lower drug release rate of chitosan-coated HNTs. In practical applications, chitosan-based hydrogels have been used for cancer therapy, subcutaneous release, and oral delivery.

4. CONCLUSION

The paper has reviewed the previous studies on the controlled release of drug that encapsulated in HNT-based from previous study in wound treatment. Tubular HNTs are suited for wound healing because of their great mechanical strength, biocompatible characteristics and haemostasis. The feasibility of using HNTs as biocompatible nanocontainers for the controlled and progressive release of antiseptals was investigated. Nanotubes can be used in numerous investigations for the treatment of antibacterial and antiseptic injuries. Due to their mechanic strength, better biocompatibility and haemostasis, tubular HNTs are a viable alternative for wound healing applications. From the studies reviewed, wound-healing dressings were made with HNT nanocomposites. Integration of HNT in pore and flexible sponges enhances the flexibility, compression strength and tightness of the elastic module. Additionally, knowing the cellular transport channels of HNTs may assist in the rational design of novel drug delivery systems and may be immensely beneficial in biotechnology. Due to its high biocompatibility, HNT may be an important technology for drug delivery and future biological uses. Halloysite nanotubes appear to be interesting candidates for intracellular medication delivery due to their mainly perinuclear position as a result of cellular internalization.

Acknowledgement:

The authors wish to express their heartfelt gratitude to the Universiti Tun Hussein Onn Malaysia (UTHM) through Geran Penyelidikan Pascasiswazah (GPPS-Vote number H730) as well as Ministry of Education Malaysia (MOE) through the Fundamental Research Grant Scheme (FRGS-Vote number K220).

Conflict of Interest: None

Source of Funding: None

REFERENCES

1. D. Rawtani, N. Khatri, S. Tyagi, and G. Pandey, “Nanotechnology-based recent approaches for sensing and remediation of pesticides,” *J. Environ. Manage.*, vol. 206, pp. 749–762, 2018.
2. D. Daksh, D. Rawtani, and Y. K. Agrawal, “Recent developments in bio-nanoelectronics devices: A review,” *J. Bionanoscience*, vol. 10, no. 2, pp. 81–93, 2016.
3. M. Tharmavaram, D. Rawtani, and G. Pandey, “Fabrication routes for one-dimensional nanostructures via block copolymers,” *Nano Converg.*, vol. 4, no. 1, p. 12, 2017, doi: 10.1186/s40580-017-0106-1.
4. S. R. Levis and P. B. Deasy, “Characterisation of halloysite for use as a microtubular drug delivery system,” *Int. J. Pharm.*, vol. 243, no. 1–2, pp. 125–134, 2002.
5. H.-Y. Liu, L. Du, Y.-T. Zhao, and W.-Q. Tian, “In vitro hemocompatibility and cytotoxicity evaluation of halloysite nanotubes for biomedical application,” *J. Nanomater.*, vol. 2015, 2015.
6. Y. Lvov and E. Abdullayev, “Functional polymer–clay nanotube composites with sustained release of chemical agents,” *Prog. Polym. Sci.*, vol. 38, no. 10–11, pp. 1690–1719, 2013.
7. S. Satish, M. Tharmavaram, and D. M.E Phd, “Halloysite nanotubes as a nature’s boon for biomedical applications,” *Nanobiomedicine*, vol. 6, p. 184954351986362, Jul. 2019, doi: 10.1177/1849543519863625.
8. S. R. Nussbaum *et al.*, “An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds,” *Value Heal.*, vol. 21, no. 1, pp. 27–32, 2018.
9. G. Sandri *et al.*, “Halloysite and chitosan oligosaccharide nanocomposite for wound healing,” *Acta Biomater.*, vol. 57, pp. 216–224, Jul. 2017, doi: 10.1016/j.actbio.2017.05.032.
10. M. Fizir, P. Dramou, N. S. Dahiru, W. Ruya, T. Huang, and H. He, “Halloysite nanotubes in analytical sciences and in drug delivery: A review,” *Microchim. Acta*, vol. 185, no. 8, 2018, doi: 10.1007/s00604-018-2908-1.
11. J. Kurczewska, P. Pecyna, M. Ratajczak, M. Gajęcka, and G. Schroeder, “Halloysite nanotubes as carriers of vancomycin in alginate-based wound dressing,” *Saudi Pharm. J.*, vol. 25, no. 6, pp. 911–920, 2017.
12. C.-Y. Chu *et al.*, “Nanohybrids of silver particles immobilized on silicate platelet for infected wound healing,” *PLoS One*, vol. 7, no. 6, p. e38360, 2012.
13. K. Shanmugapriya, H. Kim, P. S. Saravana, B.-S. Chun, and H. W. Kang, “Fabrication of multifunctional chitosan-based nanocomposite film with rapid healing and antibacterial effect for wound management,” *Int. J. Biol. Macromol.*, vol. 118, pp. 1713–1725, 2018.
14. Y. Kim, Y. Song, and H. Kim, “Preparation of transparent cellulose film with controlled haze using halloysite nanotubes,” *Cellulose*, vol. 25, no. 2, pp. 1239–1248, 2018.
15. Y. Xie, P. R. Chang, S. Wang, J. Yu, and X. Ma, “Preparation and properties of halloysite nanotubes/plasticized Dioscorea opposita Thunb. starch composites,” *Carbohydr. Polym.*, vol. 83, no. 1, pp. 186–191, 2011.
16. M. Liu, Y. Shen, P. Ao, L. Dai, Z. Liu, and C. Zhou, “The improvement of hemostatic and wound healing property of chitosan by halloysite nanotubes,” *RSC Adv.*, vol. 4, no. 45, pp. 23540–23553, 2014, doi: 10.1039/c4ra02189d.
17. G. Sandri *et al.*, “Halloysite-and montmorillonite-loaded scaffolds as enhancers of chronic wound healing,” *Pharmaceutics*, vol. 12, no. 2, p. 179, 2020.

18. Z. Li *et al.*, "Ultrafast in-situ forming halloysite nanotube-doped chitosan/oxidized dextran hydrogels for hemostasis and wound repair," *Carbohydr. Polym.*, vol. 267, p. 118155, 2021.
19. M. Soheilmoghaddam, M. U. Wahit, S. Mahmoudian, and N. A. Hanid, "Regenerated cellulose/halloysite nanotube nanocomposite films prepared with an ionic liquid," *Mater. Chem. Phys.*, vol. 141, no. 2–3, pp. 936–943, 2013.
20. Y. Wu, Y. Zhang, J. Ju, H. Yan, X. Huang, and Y. Tan, "Advances in Halloysite nanotubes-polysaccharide nanocomposite preparation and applications," *Polymers (Basel).*, vol. 11, no. 6, 2019, doi: 10.3390/polym11060987.

How to cite this article: Syahirah Mohd Noor, Rohardiyana Roslan, Soon Chin Fhong, Nadirul Hasraf Mat nayana. A potential of halloysite nanotube as a delivery vehicle in wound treatment. *International Journal of Research and Review*. 2022; 9(6): 290-295. DOI: *https://doi.org/10.52403/ijrr.20220631*

******