Hindawi
Journal of Nanomaterials
Volume 2022, Article ID 1068536, 7 pages
https://doi.org/10.1155/2022/1068536

Review Article

Potential Applications of Halloysite Nanotubes as Drug Carriers: A Review

Dhanraj Ganapathy,[1] Rajeshkumar Shanmugam,[2] Sivaperumal Pitchiah,[1] Preethika Murugan,[1] Arunachalam Chinnathambi,[3] Sulaiman Ali Alharbi,[3] Kaliannan Durairaj,[4] and Ashok K. Sundramoorthy[1]

[1]*Department of Prosthodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Poonamallee High Road, Velappanchavadi, Chennai, 600077 Tamil Nadu, India*
[2]*Nanobiomedicine Lab, Department of Pharmacology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai, 600077 Tamil Nadu, India*
[3]*Department of Botany and Microbiology, College of Science, King Saud University, PO Box-2455, Riyadh 11451, Saudi Arabia*
[4]*Zoonosis Research Center, School of Medicine, Wonkwang University, Republic of Korea*

Correspondence should be addressed to Ashok K. Sundramoorthy; ashok.sundramoorthy@gmail.com

Received 13 January 2022; Accepted 4 April 2022; Published 20 April 2022

Academic Editor: Adolfo Speghini

Halloysite nanotubes (HNTs) are naturally occurring tubular clay nanomaterials that are made from multiple-rolled aluminosilicate kaolin panels. The aluminol and siloxane groups on the surface of HNT facilitate the formation of hydrogen bonds with biomaterials on its surface. It is a cost-effective nanomaterial that found applications in a variety of fields of science and technology. The biocompatible properties of HNT resulted in various applications such as in nanomedicine, biomedicine, tissue engineering, drug delivery, sequence delivery, cancer, stem cells isolation, bioimaging, and sensors. Due to its tubular form, it has played a vital role as drug delivery carriers, superior nanocarrier for numerous medicines, and biological agents with larger loading capacity and longer releasing kinetics. HNT has also been investigated and used extensively in targeted drug transfer applications with a variety of medicines. These studies provided positive outcomes which have led to versatile medicinal applications. Herein, we have highlighted the latest developments on HNT-based drug carriers.

1. Introduction

Nanotechnology is indeed a rapidly growing field with a myriad of applications in innovation and technology, industry, environmental, energy, and other specialities. This domain has promising future prospects; thus, much research is being done to broaden the scope of its capabilities [1]. Halloysite nanotubes (HNTs) constitute one of the most versatile nanomaterials utilized in several biomedical applications [2–4]. Halloysite is a commercially available effective clay nanomaterial obtained from deposits that are abundant in nature. Halloysite particles come in a variety of shapes and sizes, including short tubular and spheroidal with elongated tubes being the most frequent. HNTs are tubular patterns of halloysite that resemble kaolin chemically [5]. They are layered aluminosilicates with a hollow tubular geometry ($Al_2Si_2O_5$ $(OH)_4nH_2O$). The external diameter is estimated in the range of 40–70 nm, the internal diameter is about 10–20 nm, and the length is around 500–1500 nm, respectively [6]. Due to their lumens, high aspect length–diameter ratio, and low hydroxyl density on their surface, they have become a promising material for numerous applications. In addition, because of the increased surface area, positively entrusted internal surfaces with Al–OH groups, and negatively entrusted external surfaces with Si-OH and Si–O–Si groups, HNTs can connect with a wide range of synthetic and biological components. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier

transform infrared spectroscopy, and X-ray diffraction (XRD) were commonly used to characterize HNT. The multifunctional groups present on the surface of HNT's were also helped to load negatively charged macromolecules into the nanotube's positive inner lumen, such as DNA encapsulation. HNT gold and silver nanoparticle composites have been utilized to analyze DNA damage through interactions of DNA and the HNT [7]. Di Paola et al. [8] studied the evaluation of HNT's biocompatibility before and after coating with poly(ethylene glycol) on its surface, and it has been reported to elevate its biocompatibility, extend circulation time, and avoid protein adsorption and accumulation in biological surroundings.

In normal pH settings, the exterior strip of HNT stays negatively charged, while the internal lumen remains positively charged, allowing for a wide range of changes. This composition, coupled with expanded biocompatibility as well as lower cytotoxicity, makes them ideal for recent applications in biomedical sciences, such as the development of novel medication and gene delivery vehicles, tissue engineering, wound bandages, malignant cells isolation, and improved human cell adhesion [9]. The main disadvantages of various drugs such as antibiotics, anticancer drugs, antifungal drugs, and anti-inflammatory drugs are minimal bioavailability and not being highly water soluble [10]. Many researchers tried to solve these problems by developing new carriers to achieve the sustained and controlled release properties of these drugs. HNT's are promising drug carriers because of their biocompatibility, low toxicity, and drug-carrying capacity (Scheme 1). The HNT consists of a nanopore which is the active center for the drug entrapment. The HNT drug has also been coated with various polymers to better control its persistence. The release of active pharmaceutical ingredients from HNT has moved into the important focus of this review article.

2. Structure and Behavior of HNT

HNTs spread well in water as singular particles and also in polar polymers with no need for exfoliation. The behavior and colloidal characteristics of HNT in an aqueous biological fluid are very similar to those of silicate nanoparticles. Although pristine HNT has a smaller zeta potential than those of pristine silica particles, the method of embarking on negatively charged medicines enhances the amplitude of HNT's zeta potential, culminating in colloid formation that is sustainable for longer periods.

Various approaches can be used to functionalize the silica exterior surfaces, permitting for increased binding of drugs. HNT has a single-dimensional tube with a porous pattern on the mesoporous (2–50 nm) and perhaps even the macroporous, viz., greater than 50 nm scale, which makes it far broader than the many manufactured porous materials such as the carbon nanotubes. This characteristic has a wide range of uses, including nanoscale support for loading functional elements. Because HNT has a greater inner diameter, it can hold not just tiny drug molecules, but also proteins and nucleic acids [11].

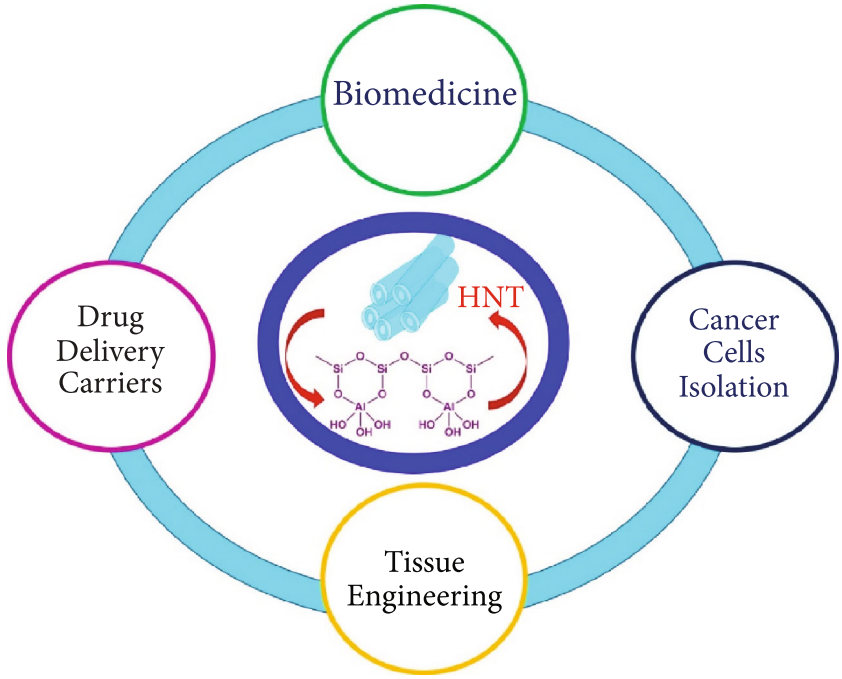
HNT contains dual kinds of hydroxyl units on the inside and exterior that can be employed as active domains for drug loading but also functionalization. HNT's inner lumen has been loaded with a variety of medication types. HNTs were also proven to be a unique and promising medium for the gene as well as anticancer medication delivery in treatment, like curcumin and adriamycin, as described by Liu et al. towards improved anti malignant effectiveness [12]. HNTs were additionally coupled with 3-amino-propyl-triethoxysilane (APTES) and given as an antisense oligonucleotide to the HeLa cells in another work [13].

3. Halloysite Nanotubes

HNTs are also nonhomogeneous and lengthy nanotubes (100 nm–2 m) that are commercially accessible. Long nanotubes have been suggested as potential inductors of cell damage and inflammation. As a result, investigations have suggested that nanoparticles with a diameter of lesser than 200 nm render more suitable as drug delivery carriers due to their high endocytosis compared to nanoparticles with greater diameters. This property of HNT, however, also does not limit its application because smaller diameter nanotubes may be made by ultrasonically processing long HNTs.

HNTs have emerged as a one-of-a-kind support system for immobilizing biomolecules because it allows for increased enzyme loading without affecting their activities, as demonstrated by their usage as nanosupport for immobilizing amylase. In addition, the HNT support's curved surface can inhibit interactions between neighboring enzymes while facilitating multidimensional bond formation. This reduces the likelihood of the enzyme aggregation upon that support surface, which serves to regulate the structural propriety and also the biocatalytic participation of the enzyme to a large extent. The addition of metallic nanoparticles onto HNT improved the catalytic performance of HNT-predicated nanocomposite biological and ecological applications. This has a lot of possibilities in terms of catalysis and biosensing. Due to their outstanding features, HNT-based nanocomposites are addressed in a variety of other fields, including optical, electrical, and magnetic applications [14] as shown in Figures 1(a) and 1(b).

3.1. Drug Delivery. HNTs are being used as nanoreservoirs and nanocarriers for the delivery of drugs as well as the targeted drug delivery mediums in several research reports. Adsorption, intercalation, and tubular entrapment are the most common methods for loading medicines into the lumen as well as on the surface of HNT [15]. Camptothecin (CP), doxorubicin, paclitaxel, quercetin, curcumin, and 5-fluorouracil are the most antitumor drugs used to make different HNT-based powerful carriers. For example, CP is a cytotoxic or antineoplastic, anticancer, and therapy drug primarily used for colon cancer. But, the CP is an irritation compound that leads to inflammation of the vein and tissue damage [16]. Furthermore, poor solubility in aqueous media is the main drawback that limits the oral administration of CP. Therefore, to overcome such shortcomings, clay-based



Scheme 1: Representation of various HNT applications in biomedical engineering.

nanocarriers like HNT are capable nanomaterials with perception in drug delivery. Rizzo et al. [17] synthesized a supramolecular gel hybrid with the aid of using self-assembly of fluoromethoxycarbonyl-l-phenylalanine in the existence of functionalized HNT and acts as a carrier for the CP molecule drug administration.

HNT is commonly used as a delivery agent by undergoing some form of alteration, either to the outside surface or to the lumen because natural HNT has a weak affinity with medicines in many circumstances, making prolonged-release impractical. Natural HNTs have been reported to be employed as core substances for layer-by-layer (LbL) microencapsulation in the past. This ensued in greater loading and continuous drug dissemination for around 100 hours, and the creation of tube-end plugs aided in the prolongation of drug release [18]. Natural HNTs were exploited to develop biocompatible rabeprazole sodium (RAB) medication delivery agents to combat the acidic degradation of the medication in the stomach. The results were good, with the medication releasing slowly and having a higher bioavailability [19].

Several techniques have been used to alter the surface of HNT antecedent to drug loading. Remodeling the surfaces of HNT using APTES is one of the approaches. The silanol groups introduced by APTES form hydrogen bonds with the hydroxyl entities over the HNT surfaces. HNTs engineered with APTES were utilized as aspirin carriers, with findings showing an enhancement in aspirin loading from 3.84 wt. percent to 11.8 wt. percent (without modification). Aspirin's material state changed from nanocrystalline to amorphous due to the confined area of HNT, although this boosted the dissolution rates induced by an initial hour of release rate [20].

Ibuprofen modified (APTES-HNT) and unmodified HNT release profiles were investigated. According to the Korsmeyer–Peppas model, the APTES-HNT showed improved drug loading but also release profile [21]. APTES-HNT was employed as a nanovehicle for ciprofloxacin to provide sustained release and also to prevent the antibiotic from forming a combination with iron, which decreased the bioavailability of the drug. The functionalized HNT had a 70 percent of 1.7% ciprofloxacin loading and a 92% of 3% sustained discharge in phosphate buffered saline for up to 9 hours. Within two hours, the functionalized nanotube reduced iron absorption by 90% of 1.3 percent.

HNT modified with chitosan is also gaining popularity as a porous microsphere for drug delivery. For drug release tests, chitosan-configured HNT was doped with aspirin into the porous microspheres at a rate of 42.4 wt%, which is almost 20 times greater than the pure halloysite (2.1 wt. percent). CP, an anticancer medication, was explored as a delivery mechanism using folic acid- (FA-) conjugated chitosan-oligosaccharide-magnetic HNTs. HNT had a high CP storage capability, and in vitro studies showed that CP release from the nanocarriers at pH 5 was significantly higher than at pH levels 6.8 and 7.4. Because the milieu in tumor tissues, endosome, and lysosomal regions is acidic, this pH-dependent release research is critical. To test toxicity, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays revealed that the CP-loaded HNT inhibited colon cancer cell proliferation more effectively [22].

Doping HNT together into a matrix as a support system and also as for regulated medication release is a widely used technique. A ceramic support system was created in one study utilizing an HNT-adsorbed polymeric matrix into which utile compounds were inserted. The nanotube was

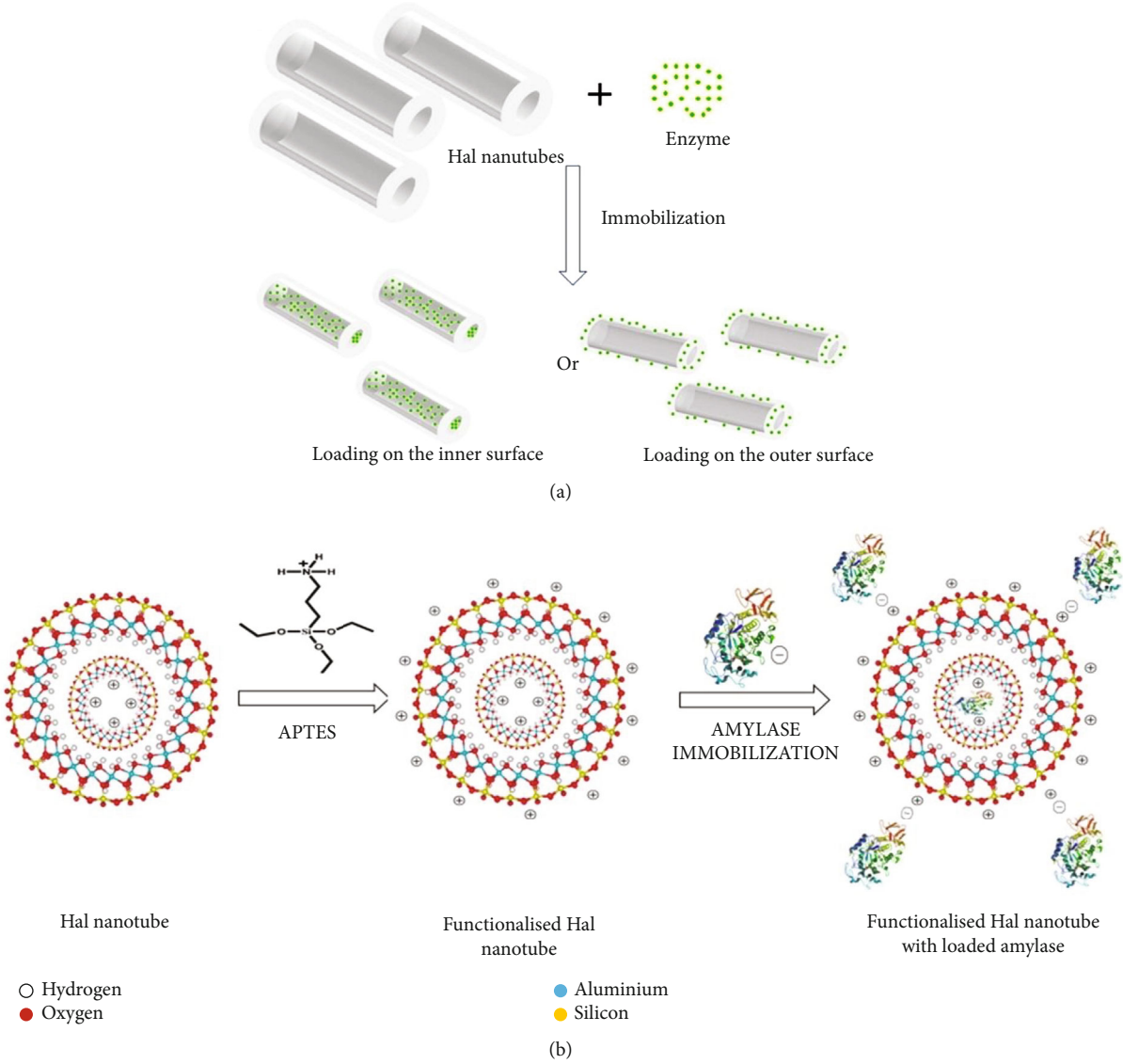


Figure 1: (a) Immobilization of enzymes on the inner and outer surface of HNT and (b) graphical representation of loading of amylase (immobilization) on HNT [14].

further modified by adding artificial nanocaps to the tube ends and enlarging the lumen by selective etching. The loading capacity was increased by around 30%, and the release time was increased from 10 to 200 hours. Even though HNT had no surface changes, it was nevertheless miscible with medium and high polarity. Another work used sodium alginate-hydroxyapatite-HNT nanocomposite hydrogel beads to create controlled drug acquittance matrices in situ. The nanotubes were loaded with diclofenac sodium (DS), and the release incidence and entrapment effectiveness were measured, which reached up to 75.11 percent with a consistent discharge [23].

HNT was examined for impacts of alkylation and then infused with ofloxacin in a unique manner (OFL). The OFL that was adsorbed onto the surface of HNT was released for a long time using this approach. This provided an effective strategy for increasing cationic drug adsorption plus release [24]. For sodium salicylate release tests, researchers used HNT that had been acid-treated and polymer-halloysite composite methods. Augmented loading and moderated in vitro release of the medication were observed in both situations. The polymer/HNT compound had a prolonged period of sustained release than acid-treated and untreated HNT [25] as shown in Figure 2.

To improve structural uniformity, HNT was included in electrospun polycaprolactone (PCL) scaffolds. Antibacterial drugs such as amoxicillin, gentamicin sulfate, doxycycline, iodine, and potassium clavulanates were carried out via the HNT in the scaffold. These nanocomposites were found to have a one-month inhibitory effect on bacterial growth. The results suggest that such nanocomposites can be used for surgical bandages and sutures with no jeopardy of the material properties [26].

For thermoresponsive curcumin release investigations, bioactive poly(N-isopropylacrylamide) was pruned onto HNT. The HNT deployment system was pixelated with

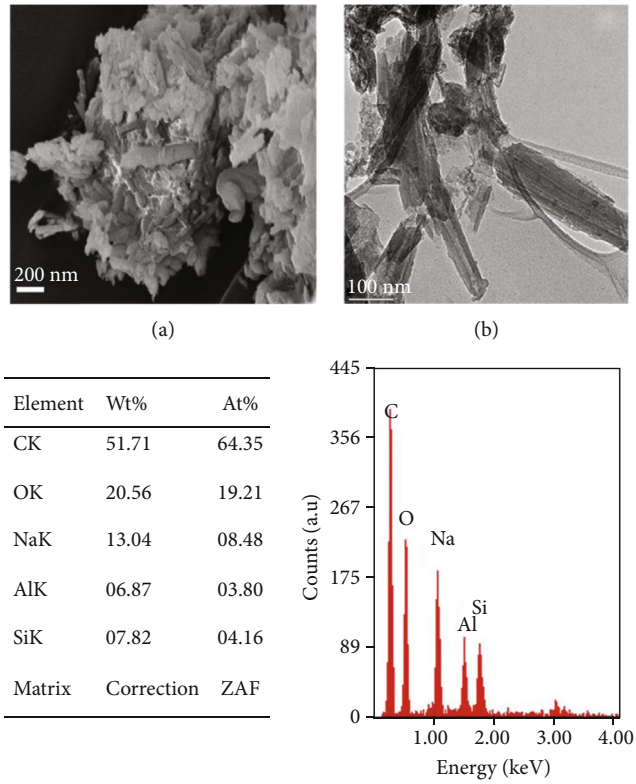


Figure 2: (a) SEM image of HNT, (b) TEM image, and (c) EDS analysis of drug loaded and acid-treated HNT [25].

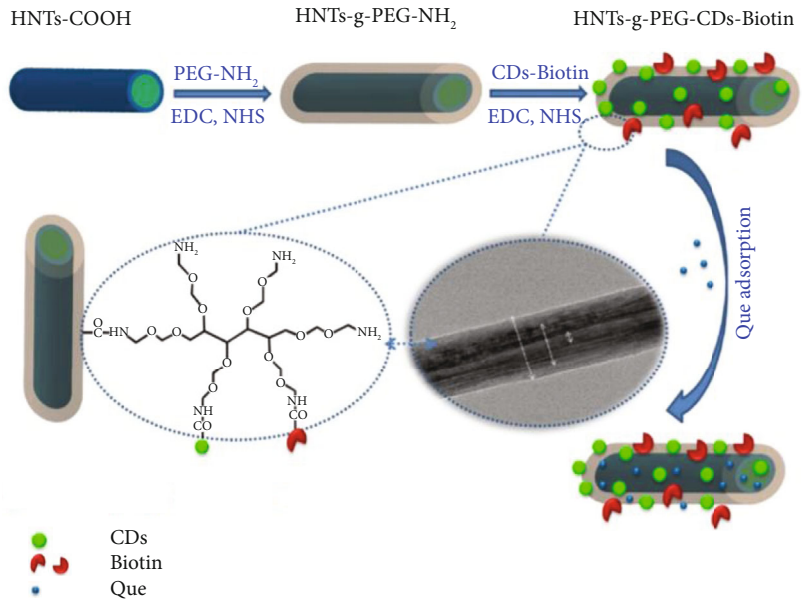


Figure 3: The schematic diagram for HNTs-g-PEG-CDs-Biotin, followed by Que adsorption [29].

curcumin, an organic anticancer drug, and in vitro studies were performed to imitate the alimentary transit of the HNT delivery device. The findings revealed that the active drug was released into the intestine in a controlled manner [27]. Paclitaxel, an anticancer medication, was encased in HNT for investigations on drug transport in the intestines. For maximal medication release in the digestive system, the pH-responsive polymer poly(methacrylic acid-co-methyl methacrylate) was sprayed over HNT. Triggered drug release was detected at higher pH levels, such as those

found in the digestive tract. Tablets containing HNT and paclitaxel with controlled drug release features were created. The drug's anticancer properties were tested in vitro on human tumor cells with promising findings. Doxorubicin (DOX), another anticancer medication, was conjugated into the multifunctional HNT and tested for targeted administration and long-term drug release. In vitro experiments on targeted and nontargeted HNT revealed that targeted HNT accelerated cancer cell death [28]. To increase the loading and long-term release of quercetin, a water-insoluble drug, PEG-grafted HNTs adorned with carbon dots for extra fluorescence characteristics were utilized. Because quercetin has antioxidant qualities, it was chosen to target malignant tissues. Biotin was coupled to the PEG's unbound amine groups for easier targeting and improved cellular absorption [29] as shown in Figure 3.

Dendrimer functionalization is a more modern technique that has shown promise in drug delivery trials. For drug transport experiments with chlorogenic acid, ibuprofen, and salicylic acid, HNTs were functionalized with polyamidoamine dendrimer. This dendrimer-functionalized HNT had a greater adsorption capacity for three medicines. The dendrimer-functionalized HNT revealed no harm to living organisms in vivo [30]. As a result, HNTs are organic nanocontainers for loaded drugs as well as a sustained release for both limited water-soluble drugs and water-soluble drugs with promising results, demonstrating the versatility of the HNTs as nanocarriers for drug loading and release. It can be utilized in tablet form for oral formulations, doped into the polymer matrices for various uses, or amended in a variety of methods for controlled drug release. In addition, in vivo, HNTs are safe and nearly harmless to bacterial and human cytoblasts [31].

The lack of human research for pharmaceutical formulations is a major impediment to the usage of HNT. While HNT can be used as an excipient in the oral delivery of pharmaceuticals and is not harmful up to 1000 mg/mL, it is nonbiodegradable in the blood and hence is not recommended for candid injections into live systems since it can cause thrombosis. This expands yet another field of investigation for HNT, allowing it to be used in a wider application for the topical formulations with extended clinical efficacy.

4. Conclusion

HNTs are biocompatible, cylindrical, hollow nanocarriers that can be functionalized by polymeric coating or layer-by-layer polyelectrolyte. HNTs in addition to being naturally occurring and cost-effective material have very promising applications in medicine and therapeutics as an effective carrier for target drug transfer in several disease conditions. The most important feature of halloysite is its inner lumen whose diameter is capable of entrapping chemical molecules. The electrostatic interactions can be utilized to aim the adsorption site of targeted molecules. The selective drug release was attained by covalent linkage on HNT's outer surface through glutathione or pH-responsive bonds. Functionalized HNT surfaces with different types of polymers could produce novel materials with numerous applications like scaffolds for tissue engineering, biosensors, and drug-delivery systems. Further research with various surface modifications and potential therapeutic medicines will further enhance the utility of HNT in numerous therapeutic applications.

Data Availability

Data will be provided upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We thank the Department of Science and Technology (DST) (International Bilateral Cooperation Division), India, for financial support through "INDO-RUSSIA Project (File No. INT/RUS/RFBR/385)". AKS acknowledges the Science and Engineering Research Board (SERB) for funding through CRG/2021/001517. This project was supported by Researchers Supporting Project number (RSP-2021/383) King Saud University, Riyadh, Saudi Arabia.

References

[1] D. Rawtani, N. Khatri, S. Tyagi, and G. Pandey, "Nanotechnology-based recent approaches for sensing and remediation of pesticides," *Journal of Environmental Management*, vol. 206, pp. 749–762, 2018.

[2] M. Tharmavaram, D. Rawtani, and G. Pandey, "Fabrication routes for one-dimensional nanostructures via block copolymers," *Convergence*, vol. 4, no. 1, pp. 1–13, 2017.

[3] S. Saadat, G. Pandey, M. Tharmavaram, V. Braganza, and D. Rawtani, "Nano-interfacial decoration of halloysite nanotubes for the development of antimicrobial nanocomposites," *Advances in Colloid and Interface Science*, vol. 275, p. 102063, 2020.

[4] M. Barman, S. Mahmood, R. Augustine, A. Hasan, S. Thomas, and K. Ghosal, "Natural halloysite nanotubes/chitosan based bio-nanocomposite for delivering norfloxacin, an antimicrobial agent in sustained release manner," *International Journal of Biological Macromolecules*, vol. 162, pp. 1849–1861, 2020.

[5] M. Preethika and A. K. Sundramoorthy, "Humic acid/halloysite nanotube/flavin adenine dinucleotide nanocomposite based selective electrochemical biosensor for hydrogen peroxide," *Applied Surface Science*, vol. 488, pp. 503–511, 2019.

[6] Y. Lvov and E. Abdullayev, "Functional polymer-clay nanotube composites with sustained release of chemical agents," *Progress in Polymer Science*, vol. 38, no. 10-11, pp. 1690–1719, 2013.

[7] A. C. Santos, C. Ferreira, F. Veiga et al., "Halloysite clay nanotubes for life sciences applications: from drug encapsulation to bioscaffold," *Advances in Colloid and Interface Science*, vol. 257, pp. 58–70, 2018.

[8] M. Di Paola, A. Quarta, P. Pisani et al., "Surface coating highly improves cytocompatibility of halloysite nanotubes: a metabolic and ultrastructural study," *IEEE Transactions on Nanotechnology*, vol. 15, no. 5, pp. 770–774, 2016.

[9] X. Zhao, C. Zhou, and M. Liu, "Self-assembled structures of halloysite nanotubes: towards the development of high-performance biomedical materials," *Journal of Materials Chemistry B*, vol. 8, no. 5, pp. 838–851, 2020.

[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," *Microchimica Acta*, vol. 185, no. 1, pp. 1–33, 2018.

[11] Z. Jia, B. Guo, and D. Jia, "Advances in rubber/halloysite nanotubes nanocomposites," *Journal of Nanoscience and Nanotechnology*, vol. 14, no. 2, pp. 1758–1771, 2014.

[12] M. Liu, Y. Chang, J. Yang et al., "Functionalized halloysite nanotube by chitosan grafting for drug delivery of curcumin to achieve enhanced anticancer efficacy," *Journal of Materials Chemistry B*, vol. 4, no. 13, pp. 2253–2263, 2016.

[13] Y.-F. Shi, Z. Tian, Y. Zhang, H.-B. Shen, and N.-Q. Jia, "Functionalized halloysite nanotube-based carrier for intracellular delivery of antisense oligonucleotides," *Nanoscale Research Letters*, vol. 6, pp. 1–7, 2011.

[14] G. Pandey, D. M. Munguambe, M. Tharmavaram, D. Rawtani, and Y. K. Agrawal, "Halloysite nanotubes-an efficient 'nano-support'for the immobilization of α-amylase," *Applied Clay Science*, vol. 136, pp. 184–191, 2017.

[15] R. Price, B. P. Gaber, and R. Y. Lvov, "In-vitro release characteristics of tetracycline HCl, khellin and nicotinamide adenine dineculeotide from halloysite; a cylindrical mineral," *Journal of Microencapsulation*, vol. 18, no. 6, pp. 713–722, 2001.

[16] P. Botella and E. Rivero-Buceta, "Safe approaches for camptothecin delivery: structural analogues and nanomedicines," *Journal of Controlled Release*, vol. 247, pp. 28–54, 2017.

[17] C. Rizzo, R. Arrigo, F. D'Anna et al., "Hybrid supramolecular gels of Fmoc-F/halloysite nanotubes: systems for sustained release of camptothecin," *Journal of Materials Chemistry B*, vol. 5, no. 17, pp. 3217–3229, 2017.

[18] T. G. Shutava, R. F. Fakhrullin, and Y. M. Lvov, "Spherical and tubule nanocarriers for sustained drug release," *Current Opinion in Pharmacology*, vol. 18, pp. 141–148, 2014.

[19] G. Y. Kırımlıoğlu and Y. Yazan, "Development, characterization and in vitro release characteristics of rabeprazole sodium in halloysite nanotubes," *European International Journal of Science and Technology*, vol. 5, pp. 99–109, 2016.

[20] L. Lisuzzo, G. Cavallaro, S. Milioto, and G. Lazzara, "Halloysite nanotubes coated by chitosan for the controlled release of khellin," *Polymers*, vol. 12, no. 8, p. 1766, 2020.

[21] D. Tan, P. Yuan, F. Annabi-Bergaya et al., "Loading and in vitro release of ibuprofen in tubular halloysite," *Applied Clay Science*, vol. 96, pp. 50–55, 2014.

[22] P. Dramou, M. Fizir, A. Taleb et al., "Folic acid-conjugated chitosan oligosaccharide-magnetic halloysite nanotubes as a delivery system for camptothecin," *Carbohydrate Polymers*, vol. 197, pp. 117–127, 2018.

[23] L. Fan, J. Zhang, and A. Wang, "In situ generation of sodium alginate/hydroxyapatite/halloysite nanotubes nanocomposite hydrogel beads as drug-controlled release matrices," *Journal of Materials Chemistry B*, vol. 1, no. 45, pp. 6261–6270, 2013.

[24] Q. Wang, J. Zhang, and A. Wang, "Alkali activation of halloysite for adsorption and release of ofloxacin," *Applied Surface Science*, vol. 287, pp. 54–61, 2013.

[25] E. G. Bediako, E. Nyankson, D. Dodoo-Arhin et al., "Modified halloysite nanoclay as a vehicle for sustained drug delivery," *Heliyon.*, vol. 4, no. 7, article e00689, 2018.

[26] S. Patel, U. Jammalamadaka, L. Sun, K. Tappa, and D. K. Mills, "Sustained release of antibacterial agents from doped halloysite nanotubes," *Bioengineering*, vol. 3, p. 1, 2016.

[27] M. Massaro, R. Amorati, G. Cavallaro et al., "Direct chemical grafted curcumin on halloysite nanotubes as dual-responsive prodrug for pharmacological applications," *Colloids and Surfaces. B, Biointerfaces*, vol. 140, pp. 505–513, 2016.

[28] Y. Hu, J. Chen, X. Li et al., "Multifunctional halloysite nanotubes for targeted delivery and controlled release of doxorubicin in-vitro and in-vivo studies," *Nanotechnology*, vol. 28, no. 37, p. 375101, 2017.

[29] A. M. Yamina, M. Fizir, A. Itatahine, H. He, and P. Dramou, "Preparation of multifunctional PEG-graft-halloysite nanotubes for controlled drug release, tumor cell targeting, and bio-imaging," *Colloids and Surfaces. B, Biointerfaces*, vol. 170, pp. 322–329, 2018.

[30] J. Kurczewska, M. Cegłowski, B. Messyasz, and G. Schroeder, "Dendrimer-functionalized halloysite nanotubes for effective drug delivery," *Applied Clay Science*, vol. 153, pp. 134–143, 2018.

[31] Y. M. Lvov, M. M. DeVilliers, and R. F. Fakhrullin, "The application of halloysite tubule nanoclay in drug delivery," *Expert Opinion on Drug Delivery*, vol. 13, no. 7, pp. 977–986, 2016.