

# HALLOYSITE NANOTUBES: DESIGN, CHARACTERIZATION AND APPLICATIONS. A REVIEW

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## Abstract

Halloysite nanotubes (HNTs) have several exciting potential applications in polymer nanocomposites. These are naturally sourced nanomaterials obtained from the mines as a natural deposit. The hollow tubular nanostructure with biocompatibility, environmental friendly and low-cost possessing makes halloysite as trendsetter in green nanotechnology. These are composed of double-layered, aluminosilicate minerals with an ultra-tiny hollow tubular structure in submicron range. The specific characteristics of HNTs lead to plentiful range of applications in environmental sciences, dye removal, anticorrosive coatings, in cosmetics, flame retardants, forensic science, etc. HNTs display remarkable thermal stability, faster adsorption rates, tuneable release rates, excellent drug encapsulation, biocompatibility, mechanical properties and ease of availability, therefore with numerous pharmaceutical applications. Nanomedical applications are gene delivery, tissue engineering, cancer and stem cells isolation and bio-imaging. This review is focused on the detailing HNTs for its structure features, functionalization methods, drug loading and their versatile applications.

## Rezumat

Nanotuburile din haloizit (NHT) prezintă o serie de aplicații interesante cu potențial în domeniul nanocompozitelor polimerice. Acestea sunt nanomateriale naturale obținute din depozitele naturale miniere. Structura nanotubulară goală pe interior ce prezintă proprietăți biocompatibile, benefice mediului înconjurător și costuri reduse sunt principalele avantaje ale haloizitului ca și nanotehnologie verde. Acestea sunt compuse din minerale aluminosilicate bistratificate, cu o structură tubulară submicronică, goală pe interior și cu diametru mic. Caracteristicile acestora determină o gamă variată de aplicații în domeniul științelor mediului, pentru îndepărtarea coloranților, a învelișurilor anticorozive, în industria cosmetică, în domeniul produselor ignifuge, în criminalistică etc. Nanotuburile de haloizit prezintă stabilitate termică pronunțată, viteză de absorbție ridicată și eliberare rapidă ce poate fi potențată, excelente proprietăți de încapsulare a substanțelor medicamentoase, biocompatibilitate, bune proprietăți mecanice și biodisponibilitate, găsimu-și numeroase aplicații în domeniul farmaceutic. Utilizările nanomedicale se regăsesc în terapia genică, în domeniul ingineriei tisulare, în izolarea celulelor stem și a celor canceroase și în bioimaging. Articolul sintetizează cele mai noi informații referitor la nanotuburile de haloizit, respectiv a caracteristicilor structurale, a funcționalizării, a capacității de încărcare cu substanțe medicamentoase, precum și a utilizărilor versatile ale acestora.

**Keywords:** halloysite nanotubes (HNTs), biocompatible, cosmetics, gene drug delivery

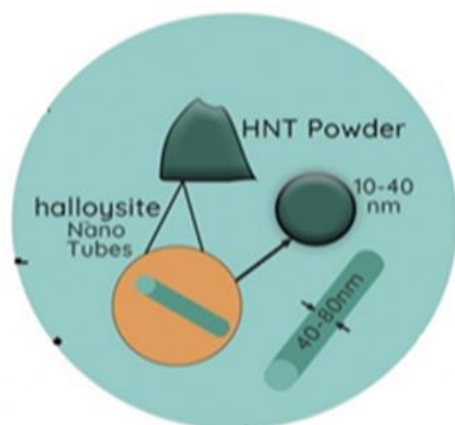
## Introduction

In the field of nanotechnology, various nanomaterials are used like carbon nanotubes, nanofluids, nano-emulsions, nanocapsules etc. Due to their harmful effects, these nano materials are not designed safe for individuals and for the environment as well [37]. Green nanotechnology is one of the promising technologies that aims in advancing environment safe and less harmful nanoproducts. HNTs, nanocomposites and nanopowders etc. are now emerging as trendsetter in green nanotechnology [14]. These are biocompatible and feasible carrier for the incorporation of biologically active molecules due to the hollow space inside the

tubular structure [8]. HNTs are novel 1D naturally occurring clay minerals having the similar chemical composition as kaolinite [30].

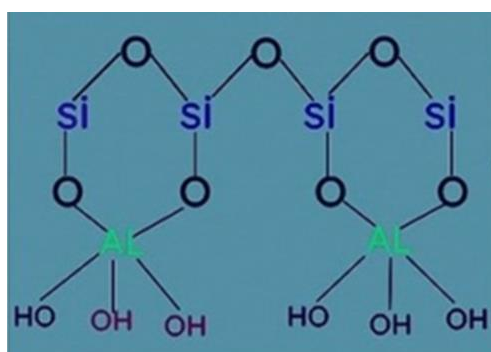
They belong to the class of aluminosilicate clays, with molecular formula  $(Al_2Si_2O_5(OH)_4 * 2 H_2O)$  exhibiting a hollow nanotubular structure [4] with their length ranging from 400 - 1000 nm, the inner and outer diameters of the nanotubes varying from 10 - 40 nm and 40 - 80 nm (Figure 1). The high aspect ratio (length/diameter) ranges from 10 - 50 nm [5]. HNTs are 1:1 phyllosilicates with six-membered rings, the atoms are arranged to form a structure of one octahedral and one tetrahedral sheet [45]. HNTs contain two types of hydroxyl groups, an inner one and an

outer one, which are placed between the layers, respectively on the surface of the nanotubes. The outer surface of HNTs is mainly formed by siloxane (Si-O-Si) groups, and the inner lumen surface is composed of aluminol groups (Al-OH) groups, making them Gibbsite-like highly hydrophilic (where Gibbsite-like already relates to the monoclinic crystallography and the prismatic aspect of the crystals), the edges of the HNTs consists of Al-OH and Si-OH groups [32], (Figure 2). Hence, the inner surface of HNTs is chemically active, whereas the outer surface is considered as non-reactive [6]. Taking into consideration the state of hydration, HNTs are broadly classified into two groups: hydrated HNTs with a crystalline structure of 10 Å  $d_{001}$  spacing and the dehydrated HNTs with 7 Å  $d_{001}$  spacing. As it has been reported, that the existence or the age of interlayer water in HNTs is one of the most significant features differentiating HNTs from kaolinite [12].



**Figure 1.**

Halloysite Nanotubular Structure  
(inner diameter = 10 - 40 nm; outer diameter = 40 - 80 nm)



**Figure 2.**

Molecular Structure of HNT  
HNTs consisting of Al-OH and Si-OH groups exhibiting the monolayer of water molecule

### Physicochemical properties of HNTs

Physical properties of HNTs are presented in Table I [29].

**Table I**

Physical properties of HNTs [29]	
Parameter	Values
Density	2.14 - 2.53 g/cm <sup>3</sup>
Average Pore Size	80 - 100 Å
Typical Surface Area	22.1 - 81.6 m <sup>2</sup> * g
Pore volume	1.25 mL * g
Aspect Ratio (L/D)	9 - 50 nm
Specific gravity	2.53 g/cm <sup>2</sup>
Cation exchange capability	0.1 - 0.7 mol * kg

### Chemical Properties [34]

The outer surface of the HNTs has the similar properties to SiO<sub>2</sub> having a negative charge at pH 6 - 7 (zeta potential -18 mV), whereas the inner cylinder core is related to Al<sub>2</sub>O<sub>3</sub> which is positively charged. The positive charge of the inner lumen urges the loading of HNTs with negative macromolecules within the void spaces. Negatively charged molecules are repelled by the negative charge present on the outer surface of HNTs.

### Advantages of HNTs

HNTs are natural, non-toxic, biocompatible, eco-friendly and low-cost material, and it is recognized as nanomaterials (EPA 4) by the Environmental Protection Agency [40]. They have fine particle size and elegant dispersion property in matrix [15]. HNTs are capable of inhibiting the release, unless triggered and tunable release rates are achieved [38]. They possess immense cation exchange capacity [12]. A halloysite nanotube is able to load multiple active agents simultaneously [50]. It maintains constant, sustained release rates and not requiring an initial over-dosage [11, 14, 38]. HNTs have high aspect ratio, immense porosity and non-swelling nature [11]. During harsh material processing, halloysite protects active agent within its lumen [14]. It has remarkable loading rates compared to other carriers [11]. Halloysite has regeneration ability and enriches the bone healing efficacy [38]. HNTs have fast adsorption rate and high adsorption capacity [11] and HNTs can be used in many forms such as powders, creams, gels, lotions and sprays [21].

### Solubility and Stability of HNTs

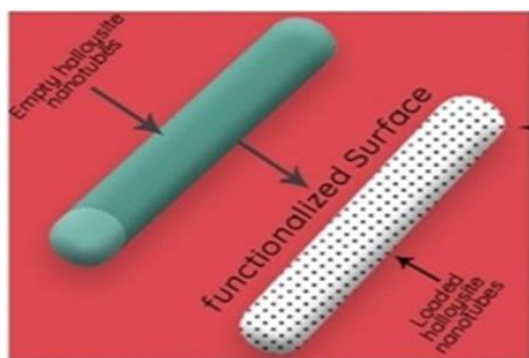
Solubilization and dispersion study of HNTs was performed by Mohtashim HS *et al.* without using organic solvents, to have a supramolecular product of HNTs and DNA [33]. A long-term stability study for natural HNTs was carried out at room temperature in three different solutions: strong acids (e.g., sulphuric acid, hydrochloric acid and acetic acid), strong base (e.g., sodium hydroxide) and distilled water. Both the acidic and basic environments reinforce the mechanism of nanotubes transformation to propose the dissolution of HNTs and precipitation of stable forms of amorphous Al (OH)<sub>3</sub> and SiO<sub>2</sub>, respectively [46].

*Functionalization of HNTs*

Among the various phyllosilicate nanomaterials (silicate based layer structure) such as kaolin and montmorillonite, halloysite has some prominent advantages. HNTs are composed of small tubes that allow removal of nanoparticles from a living organism. The active molecules can be incorporated into the lumen of an empty HNTs or even drug can be absorbed onto the outer surface of HNTs.

The chemical modification can be introduced into the external surface of the HNTs; whereas the lumen of the HNTs can simultaneously function by initiating supramolecular interactions of the drugs with the lumen of HNTs. The inner lumen is the most enticing feature of HNTs, with a diameter capable of entangling the chemical agents such as drugs, DNA, nanomolecules and nanodots and other chemically active agents e.g., anticorrosion for protective coating [31].

The optimized properties of nanocomposites are obtained by advancing the nano dispersion and stress transfer. The interfacial interaction between the nanotubes and the polymer, should be carefully governed [41]. In other respects, impoverished load transfer among the nanotubes and circumferential polymer chain may induce interfacial spillage and reduces the mechanical properties of the composites. Thus, the functionalization of HNTs is highly essential for processing and increasing the properties of HNTs polymer nanocomposites, (Figure 3). The modified polymer nanocomposites nanotubes reveal enhanced mechanical and thermal properties, as the functionalization advances the dispersal and stress transfer [24].



**Figure 3.**

Functionalization of HNTs

The functionalization of HNTs is achieved by two different processes, as follows.

*Covalent functionalization*

The inner surfaces and the edges of the sheets consist of hydroxyl group leading to the formation of multi-walled tubes that provide active sites for covalently adhering chemical substances.

The resulting outcomes are expected by adopting the relevant techniques.

Incorporation of hydrocarbons results in modification of chemical composition of HNTs surface, by minimizing the polarity of HNTs surface, safeguarding the surface hydroxyl group, and lastly, by generating the functional groups on the surface of HNTs. Poikelispaa *et al.* reported that the dispersion property of the HNTs can be enhanced in the solvents and polymers by booming their interfacial interactions [35].

*Modification of HNTs with 2-hydroxybenzoic acid* [23]. HNTs were modified by Li *et al.* in 2008, by dissolving 2.8 g of 2-hydroxybenzoic acid (HBA) in 100 mL absolute ethanol and 4.5 g of HNT-3-aminopropyltriethoxysilane (APTES) was suspended in a mixture with continuous heating and stirring, adding 4 g of N, N'-Dicyclohexylcarbodiimide (DCC) to the suspension and then kept at reflux for 48 h at 86°C. The obtained product was filtered and washed with absolute ethanol and dried in an oven for 12 h at 60°C.

*Silane Coupling.* By condensation process, the most common covalent modification of HNTs is to graft silanes between the surface hydroxyl group of halloysite and hydrolyzed silane. Modification of the internal surface is significant for immobilization and controlled release process, whereas the modification on the external surface and edges benefits the nanocomposite applications. Yuan *et al.* in 2008 modified halloysite clay nanotubes by grafting with  $\gamma$ -aminopropyltriethoxysilane (APTES) [48].

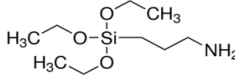
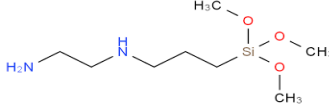
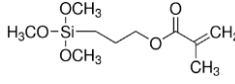
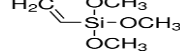
*Halloysite modification by Hexa-decyl-tri-methyl-ammonium bromide* [18]. HNTs were modified by Khunova *et al.* in 2013. A 5% solution of Hexa-decyl-tri-methyl-ammonium bromide (HEDA) was used for the treatment of purified HNTs at 80°C for 24 h, followed by filtration and drying of HNTs in oven at 60°C for 24 h to obtain the modified HNTs.

The numerous types of silanes used for modifications of HNTs are listed in Table II [22].

**Table II**

Silanes used for modifications of HNTs [22]

Silanes	Composition
$\gamma$ - Glycidoxypropyltrimethoxysilane (GPTS)	
3- Aminopropyltrimethoxysilane (APS)	

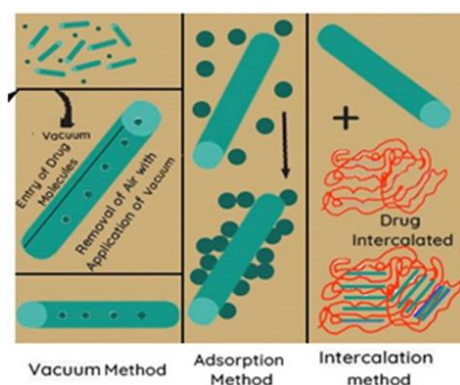
Silanes	Composition
3- Aminopropyltriethoxysilane (APTES)	
[3-(2-Aminoethylamino)propyl] trimethoxysilane (AEAPS)	
3-(Trimethoxysilyl)propyl methacrylate (MAPTS)	
Vinyltrimethoxysilane (VTMS)	

### Non-covalent functionalization

Non-covalent functionalization is the most efficient approach to disperse the tubes in aqueous and non-aqueous solvents without damaging their unique structure and thus retaining their intrinsic properties [47].

**Characterization of HNTs.** HNTs are characterized by using scanning electron microscope (SEM), scanning force microscope (SFM) and transmission electron microscope (TEM). As reported, these techniques explain that most of the samples have cylindrical tubes with 40 - 50 nm diameter and 0.5 - 2  $\mu\text{m}$  length. TEM images apparently illustrate the empty lumen of HNTs having a diameter of 15 - 20 nm [43].

**Loading techniques in HNTs.** There are few methods of loading drugs into HNTs and preferred methods are depicted in Figure 4.



**Figure 4.**

### Drug Loading Techniques of HNTs

**Adsorption.** The functional groups present on the surface of the HNTs such as Si-OH and Al-OH groups assist in determining the adsorption mechanism of HNTs. The surface charge of HNTs at pH 3 is positive, whereas above this pH it is negatively charged. An ionic pollutant does not possess high affinity for HNTs, as a result of negatively charged surfaces placed on the outer surfaces [19].

**Intercalation.** HNTs has the capacity to intercalate a wide number of organic and inorganic substances within the interlayer spaces. In this process, as the molecules penetrate the interlayer space, there is an

origin of enlargement of these layers, due to the integration of water in the inter-lamellar spaces. The enlargement of these layers contributes to increase in  $d_{001}$  spacing between the layers [20]. The main criteria for developing the intercalation process are to entrap the water molecules between the walls of halloysite layers [13].

**Tubular Entrapment.** The most extensive and widely used method for loading of drug into HNTs is tubular entrapment method. It is also commonly known as *vacuum* method. This method was proposed by Kelly *et al.* in 2004 [16].

### Applications of HNTs

#### Biomedical Applications of HNTs

**Tissue Engineering Scaffolds.** Tissue engineering scaffolds are components made of polymeric bio-materials to provide the structural support for cell attachment and subsequent tissue development [7]. HNTs are the rising materials in the field of tissue engineering, as they satisfy certain pre-requisites to be an ideal scaffold [26]. Zhou *et al.* in 2012 [25] fabricated halloysite-chitosan scaffolds by using freeze drying method. The halloysite-chitosan scaffold has revealed enhanced compressive strength, modulus, and thermal stability and has not induced any cytotoxicity as compared to pure chitosan scaffold. Hence, HNTs polymer nanocomposite shows great potential for applications in tissue engineering.

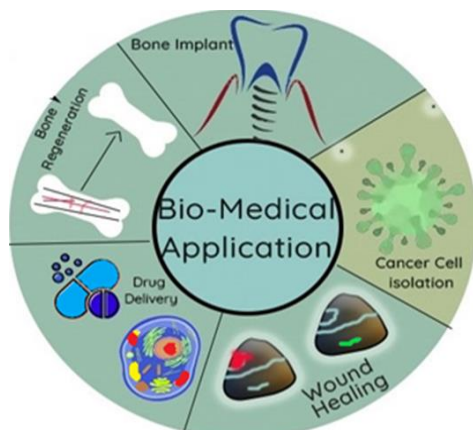
**HNTs as Wound Healing Sponges.** Properties such as mechanical strength, good biocompatibility and haemostasis of tubular HNTs makes them ideal candidate for wound healing applications. HNTs-based nanocomposite are tuned into dressings with wound healing properties. The porous and flexible chitosan composite sponges were fabricated by addition of HNTs which resulted in increased elastic modulus, compressive strength and toughness. Liu *et al.* have formulated chitosan-HNTs nanocomposite sponge by imposing freeze drying method. It was observed that the HNTs improved chitosan's blood clotting ability [27].

**HNTs for Bone implant/Bone cement.** Bone grafting is a surgical process which reinstates the missing bone in order to restore bone fractures. The most efficiently

available bone implants are dental implants and devices used in the improvement of damaged bones. The most extensively used bone cement is poly (methyl methacrylate) (PMMA) as it showed magnificent biocompatibility and mechanical properties for arthroplasty [39]. The bone cement is fabricated by incorporating the PMMA with gentamycin loaded HNTs. Thus, the PMMA/HNTs/gentamycin composite offered consistent sustained release up to 300 - 400 h and hence there by maintaining extended antibacterial protection [28].

**HNTs for Cancer Cell Isolation.** Curcumin is the most significant drug possessing the anti-inflammatory and anticancer properties and hence several methods have been adopted to load the curcumin into the lumen of HNTs. Massaro *et al.* in 2013 have reported that drug loading is carried out by functionalization of positively charged HNTs using tetrazolium salts. These HNTs-based carriers of curcumin were used as drug delivery for different cell line studies and were proved to be effective in many of cancer cells [36].

**HNTs as potential Drug delivery vehicles.** The most effective site for drug entrapment is the nanopore of HNTs [9]. The surface of drug loaded HNTs can be further coated with different polymers to achieve better delayed drug release rates [10]. Drugs, proteins and different substances can be loaded into the clay tube [2]. The chitosan and polyethyleneimine (PEI) coated HNTs reveal delayed release rates compared to uncoated HNTs [3], Figure 5.



**Figure 5.**

#### Biomedical Applications of HNTs

Halloysite nanotubes possess wide range of biomedical applications such as in tissue engineering (bone regeneration), drug delivery, wound healing, bone implant and cancer cell isolation

#### HNTs for Non-Biomedical Applications

##### Use of HNTs as Nanoreactors and Nanocontainers

Nanoparticles and nanowires can be formulated by employing HNTs as nanoreactors. Synthesis of enzyme-catalysed inorganic reaction can be carried out by using HNTs bio-mineralization reactors, whereas HNTs lumen behaves as biomimetic nanoreactor [1].

#### Nanocontainers

**Anti-Corrosion Coating with Benzotriazole.** Corrosion of metals is a crucial technical problem. HNTs are used as tubular sacs for benzotriazole which is considered as corrosion inhibitor [48].

#### Use of HNTs in the synthesis of silver nanorods

Silver nanorods were fabricated by thermal decomposition of silver acetate from its aqueous solution and loaded into the lumen of the halloysite, by employing the vacuum cycling process. The polymer composite of silver nanorods revealed antimicrobial activity and increased tensile strength [42].

#### Gold Nanoparticles

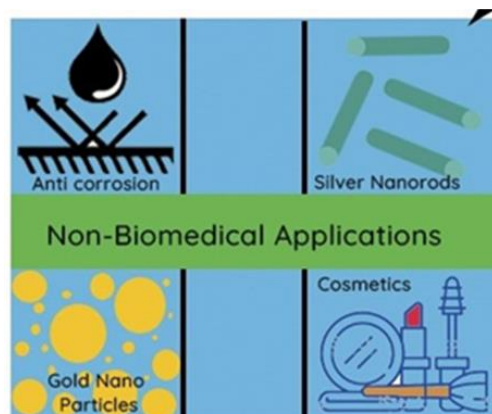
Gold nanoparticles were prepared by reduction of chloroauric acid ( $\text{HAuCl}_4$ ) using HNTs. Gold nanoparticles possess large surface area, which promotes high drug loading efficiency, biocompatible, and are freely accessible for the conjugation with biomolecules. These are non-cytotoxic to normal cells [17].

#### Application of HNTs for in situ chemical polymerization

The polyaniline (PANI) is laminated on the facet of the HNTs by adopting *in situ* soapless emulsion polymerization of anilinium chloride adsorbed on HNTs. Ammonium persulfate (APS), an oxidant, is used to roll out the HNTs in an aqueous solution of aniline with constant stirring and ultrasonic irradiation. The acidity of polymerizing media and adsorptivity of anilinium chloride on the surface of HNTs modify the structural characteristics of PANI/HNTs nanocomposites [51].

#### HNTs for Cosmetic Application

As a result of elongated hollow tubular structure and strong absorption capacity, HNTs can be availed as cleansing masks, which promote deep purification and clears the facial pores. The hollow HNTs can be loaded with a variety of active ingredients; particularly those used in cosmetics, household and personal care products [44], as shown in Figure 6.



**Figure 6.**

#### Non-Biomedical Applications of HNTs

Halloysite nanotubes have non-biomedical applications; therefore they can be used as anti-corrosive agent, cosmetics, in the fabrication of silver nanorods and gold nanoparticles

## Conclusions

This review highlights the structural features, functionalization, biomedical and non-biomedical applications of HNTs. HNTs display remarkable thermal stability, faster adsorption rates, tuneable release rates, excellent drug encapsulation, biocompatibility, mechanical properties, and ease of availability therefore with numerous pharmaceutical applications. The functionalization of HNTs is a main necessity for processing and promoting the properties of HNTs polymer composites. HNTs have also established prominent character in various fields of biomedical sciences such as tissue engineering, bone implants, fillers in bone cement, and cancer cell isolation. Apart from biological features, HNTs have played roles in the synthesis of silver and gold nanoparticles, nano-reactors and nanocontainers, cosmetics, and drug delivery. Thus, it can be concluded that HNTs have acquired promising anticipation in the development of new structural and functional materials to emerge as trendsetters for green nanotechnology.

## Conflict of interest

The authors declare no conflict of interest.

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