Research Article

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Halloysite nanotubes in polymer science: purification, characterization, modification and applications

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Abstract: Halloysite nanotubes (HNTs) are natural tubular materials, which show a number of attractive advantages such as the unique micro-spatial structure, large length-diameter ratio, high lumen volume, nontoxicity and widespread. The development of HNTs-based polymer composites expanded their applications in the fields of energy, catalysis, biomedicine, environmental protection and many others. This review will briefly summarize the purification, characterization and modification methods upon HNTs, in which the preparation and application of the HNTs-based polymer composites are emphasized. This paper may be beneficial for the development of novel strategies for the preparation of new libraries of HNTs-based polymer composites and the exploration of their applications.

Keywords: halloysite nanotube; clay; polymer science

1 Introduction

In recent years, an increasing number of research efforts were under way to develop organic–inorganic nanocomposites [1–4]. Generally, tubular micro- or nano- materials usually exhibit better processability, hydrodynamic properties and aerodynamic peculiarity than those of nanospheres [5, 6]. Numerous excellent research results and high-quality reviews focus on carbon nanotubes (CNTs) have been conducted in the past decades [7–11], while the high cost and poor water dispersibility significantly restrict their practical uses. Like CNTs, halloysite nanotubes (HNTs) exhibit a similar structure but many attractive advantages including higher biocompatibility, better solubility in water, environmental friendliness, as well as widely spreadable performance. It has been reported HNTs exist in in many countries and regions including China, US, Australia, Russia, etc.

HNTs are natural aluminosilicate clay minerals ($Al_2Si_2O_5(OH)_4$ $n$$H_2O$) with similar chemical composition to kaolinite [15, 16]. When he HNTs are in a hydrated status, the value of n in the above chemical formula is equal to 2. We can name the nanomaterials as HNTs-10 Å. After heating under ca.110°C, the moisture between the layers was evaporated to form HNTs-7 Å [17, 18], in which n is equal to 0. Generally, the multilayer tubule walls include 15-20 layers. HNTs usually have an outer diameter of ca. 50 nm and a length ranging from 500 to 1000 nm [13, 19]. Benefiting from the curled-up structure, HNTs exhibit different chemical characters between the internal (Al-OH) and external surface (Si-O-Si) [13, 20]. Thanks to its unique hollow morphology and large cavity, HNT can be empolyed as an ideal natural nano-carrier (details shown in Figure 1).

The word "halloysite" was first discovered by Berthier in the 1820s, but recaptured attention in recent years, especially after 2010, which can be owing to the growing interest of researchers in tubular nanomaterials in materials science and technology. A survey of publications involved with halloysite from 2010 to 2017 is conducted, in which the detailed data are shown in Figure 2 (based on Web of Science). The data clearly indicate that the halloysite has attracted a growing number of attention in recent years. In 2010, the literature related with halloysite was found to be less than 100 and only <50% was focused on its nanotubular character. While in 2017, the number of the publications related with halloysite rose by over 400% as compared to 2010, where the halloysite was used or re-

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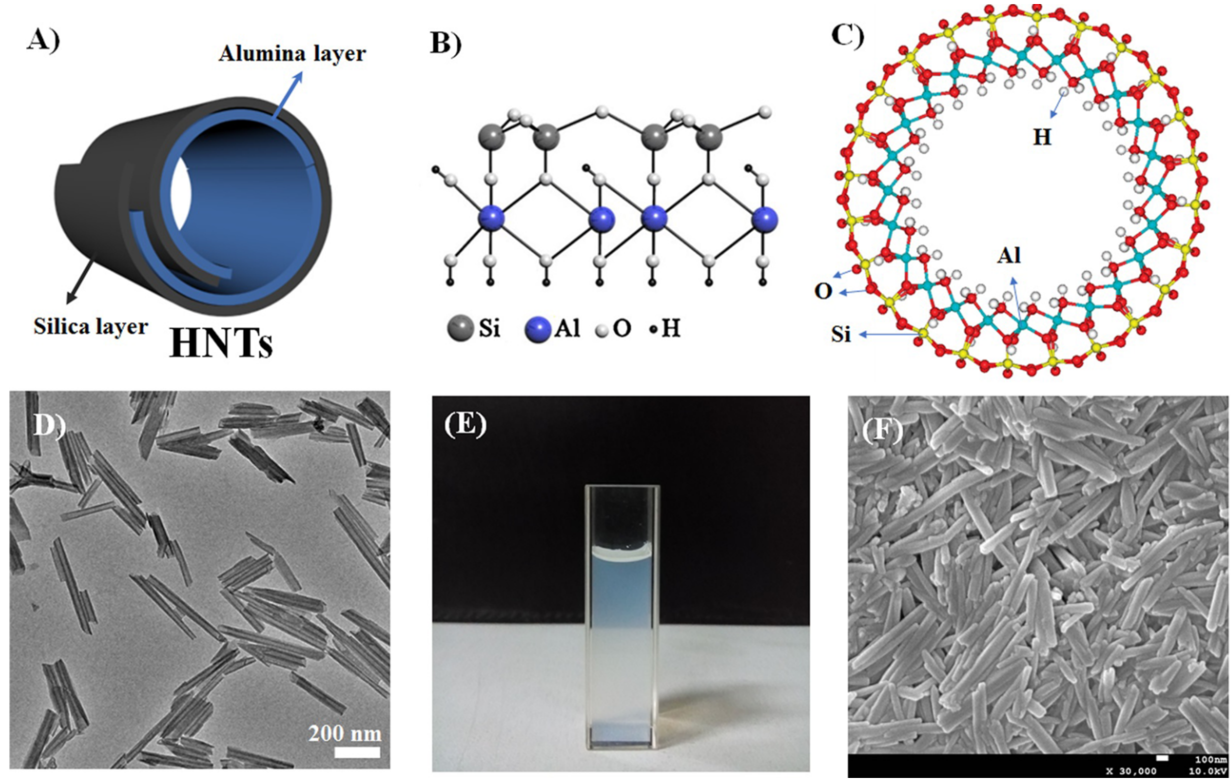


Figure 1: The structure of HNTs: A) the curly morphology of HNTs; B) schematic illustration of crystalline structure of HNTs [12]; C) cross section view of ideal single-walled HNTs calculated by Duarte *et al.* [13], D) the micromorphology of HNTs measured by transmission electron microscopes (TEM); E) the suspension of HNTs in water; F) the micromorphology of HNTs derivative measured by scanning electron microscopes (SEM) in the previous study [14]

garded as nanotubes for over 85%. Moreover, the number of the publications related with HNTs and polymer science was also dramatically growing from 2010 to 2017, in which the ratio of it to the sum of the publications related with HNTs increased to over 40% in the last years, implying the rapid growth of HNTs researches in the field of organic–inorganic nanocomposite materials. Despite some review papers based upon HNTs, which focus on their applications on catalyst, carriers, or some other aspects [21–25], a systematic and comprehensive review including purification, characterization, modification and applications is still in demand and rarely be reported. Here, the purification methods are summarized in this systematic review, which would be extremely favorable for the beginners in HNTs field. The physicochemical properties of HNTs are revealed based on the detailed characterizations conducted by our group, rather than simple summarizations. Some infrequently used but particularly applicable modification methods, such as the phosphoric acid, dopamine and arylboronic acid derivative-based modification methods, are included in this review. The applications, especially for the biomedical fields are emphasized; simultaneously, some applications that are less focused but with promising prospects are also included. We hope it will serve as a valuable resource for new and current researchers' interests in HNTs.

2 Purification

Nearly pure HNTs have been discovered in Utah, USA [26, 27]. In fact, the majority of the natural halloysite clay usually exists with some impurities, such as kaolin, illite, quartz, feldspar, chlorite, gibbsite, salts and metals, in which the size distribution of nanotubes ranges extensively. Therefore, the purification procedure is necessary for the study of HNTs in order to access further modifications and applications [28, 29].

Herein, a typical purification method was summarized as follows: Crude halloysite was mixed with sodium hydroxide in water in to get a suspension. The as-formed suspension was heated at 800°C for 4 h. Then the treated halloysite was poured into 40 mL of deionized water with constant stirring until completely dispersed. Then a gel can be formed, which was kept at 100°C for 4 h to make it slowly

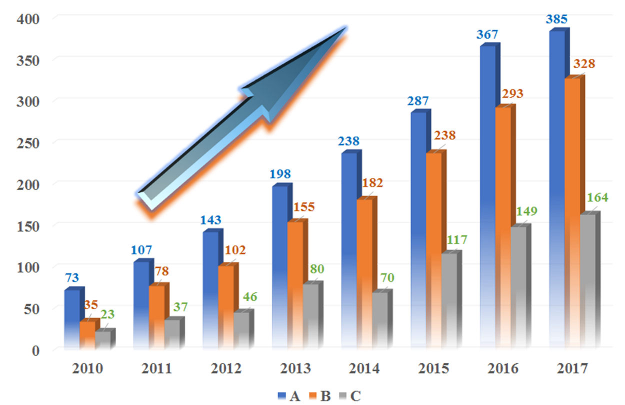


Figure 2: Comparison of the annual number of scientific publications focus on the halloysite from 2010 to 2017 (Data analysis of publications was done using the Web of Science search system. Section A represents the publication numbers with the term “halloysite”; Section B represents the publication numbers with the term “halloysite” and “nanotube”; Section C represents the publication numbers with the term “halloysite” and “polymer”)

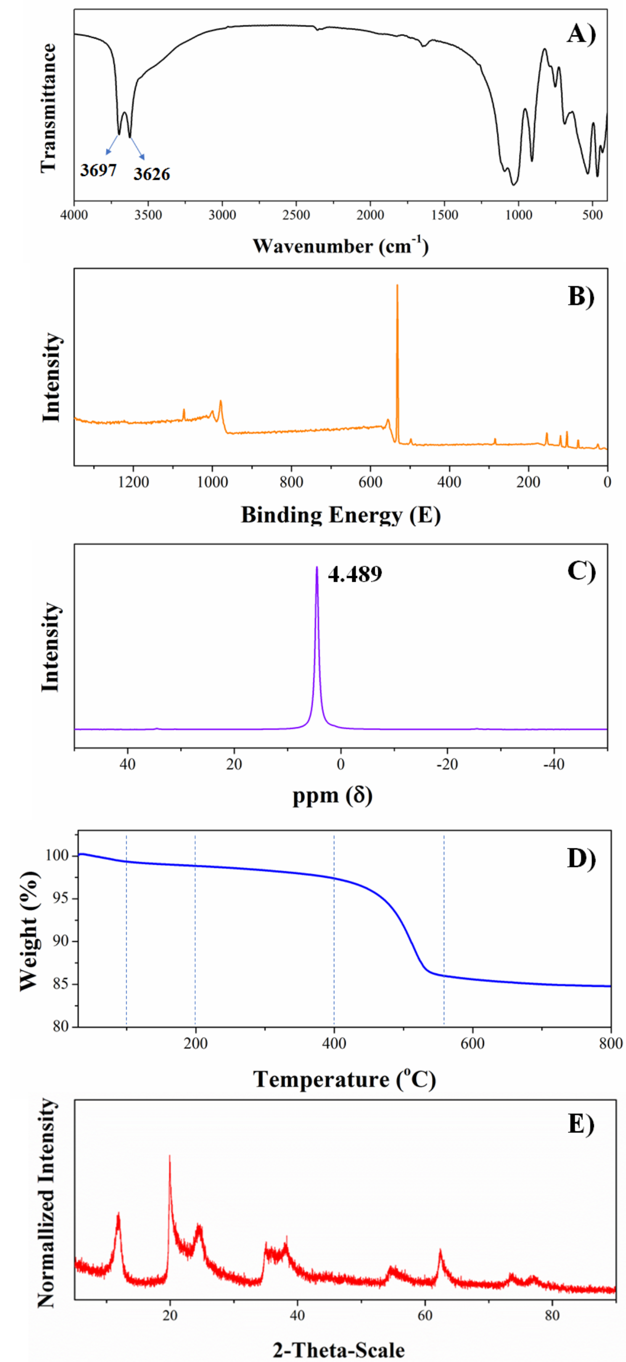


Figure 3: A) FTIR spectrum; **B)** XPS spectrum; **C)** SS ^{1}H NMR spectrum; **D)** TG curve; **E)** XRD spectrum of HNTs (the characterizations were conducted by our group)

crystallized. The obtained product was cooled down to about 25°C and washed with distilled water several times to give purified HNTs [30].

A base-treated purification method, in which the high temperature can be avoided, is being proposed. Crude halloysite and H_2O were mixed in a flask followed by the pH value adjusted to alkalescence. Dispersing agent was added to the solution and magnetically stirred for 6 h without any heating procedure. The highly purified HNTs can exist in supernate and collected by centrifugation or filtration [31, 32].

Owing the existence of some iron-containing impurities in some halloysite minerals, Sakiewicz *et al.* used multi-gradient magnetic separation technology to separate aluminum ferric silicate under weak magnetic field conditions [33]. Another way to deal with this problem is to treat the halloysite by hydrochloric acid, which is also beneficial for removing the other metal oxides impurities, *e.g.* copper oxides, calcium oxides, titanium oxides, etc. To further increase the purification efficiency, Rong *et al.* employed the ultrasound method to improve the dispersibility of the crude halloysite in aqueous phase [34].

3 Physicochemical properties and characterizations

The characterization methods, such as Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), solid-state nuclear magnetic resonance (SSNMR), thermogravimetric analysis (TGA) and X-ray powder diffraction (XRD), are commonly-used in the HNTs-associated studies, especially to reveal the changes on chemical composition for the HNTs-based polymer composites.

Here, the characterization data was summarized to reveal the inherent character of HNTs, in which the detailed spectra shown in Figure 3 were performed by our group [31, 35, 36]. Figure 3A revealed the IR spectrum of HNTs. There are two obvious peaks at 3697 and 3626 cm^{-1}, which can be ascribed to the stretching vibrations of Al-OH in the lumen and the curled layer, respectively. The stretching vibration around 1036 cm^{-1} is the characteristic band of in-plane Si–O–Si. Vibration peaks around 500 cm^{-1} can be attributed to the presence of Si-O and Al-O groups. The XPS spectrum (Figure 3B) of original HNTs showed the existence of aluminum (Al 2s and Al 2p) and silicon (Si 2s and Si 2p), matching well with the components in aluminosilicate clays. ^{1}H SSNMR of HNTs is shown in Figure 3C. The ^{1}H SSNMR spectrum of HNTs has only a signal peak at 4.489 ppm, which is the signal peak of the proton in the Al-OH group in the HNTs. HNTs don't display any resonances in the ^{13}C, ^{11}B [35] and ^{31}P SSNMR spectra, in which the ^{31}P SSNMR spectrum was performed by Lvov's group [19].

TG curve of HNTs was depicted in the Figure 3D. The slight weight loss less than 100°C is due to the evaporation of the adsorbed water on the surface of HNTs. The crystal water in the sheet of HNTs gradually lost between 200°C and 400°C. The weight loss from 400 to 600°C is due to the condensation reaction of Al-OH groups. The position of the characteristic peak of the XRD pattern (Figure 3E) of HNTs is about 11.9°, which is consistent with the basic spacing of the layer space. In addition, the diffraction signals at ca. 62.3°, 54.9°, 38.2°, 35.1°, 24.6° and 20.0° are also in accordance with that described in other documents [37, 38].

4 Modification of HNTs

Owing to the presence of the abundant Al-OH groups, HNTs cannot achieve a desirable dispersibility in polymer matrix [39]. Therefore, the modification of HNTs is the essential precondition to open a broader application, which can be divided into two major categories: physical method and chemical modification.

4.1 Physical method

Halloysite is a natural nano-inorganic material that can be used as a good inorganic filler to mix with polymers for producing materials with better mechanical properties. The improvement of the dispersion and the interface interaction were viewed as two crucial factors in preparation methods. The polymer matrix with HNTs as modifiers via the physical method is a significant topic which has been reviewed in many latest papers [8, 40, 41]. In this section some commonly-used physical methods are briefly introduced.

4.1.1 Solution process

Owing to convenient operation and simple process, solution processing is the most common strategy to prepare HNTs-based polymer composites [8]. In this method, HNTs and the polymer are uniformly dispersed in a suitable solvent by magnetic stirring or ultrasonic treatment, and then fabricated into films, fibers or gels by some special treatment. The purpose of sonication is to increase the dispersion of halloysite in the polymer but well-dispersed HNTs will reassemble together in the polymer during drying, so dispersion should be investigated initially before the practical process [42].

By referring to the literatures, latex rubber [43], poly (vinylidene fluoride) [44] polyethylene glycol [45], hydroxypropyl cellulose [46], potato starch [47], pectins [42], chitosan [48, 49] and polyvinyl chloride [50] can be used to prepare HNTs-based polymer composites by following such a simple solution process and can be further developed as membrane materials.

4.1.2 Melt process

Sometimes, solution process cannot be applied for polymers when they are difficult to be dissolved in solvent; in addition, the residue solvent usually brings troublesome problems in purification procedure. Under these circumstances, melt process is an alternative way that is specifically applicative for thermoplastic and rubber. On the other hand, as compared with solution process, melt process is more applicable for standard industrial facilities, which can be regarded as the most promising method to produce HNTs-based polymer composites in industrial manufacture. Melting process may subject polymers to unintended accidental degradation, oxidation at high temperatures, resulting in unexpected degradations. So, the thermostability is an essential factor in this case. In general, melt process is to mix the polymer in a molten state with HNTs by shear force with special tools. A majority of the composites of thermo-plastics, rubbers and biopolymers with HNTs have been prepared by the melt process (Table 1), in which the enhanced properties were highlighted.

Table 1: HNTs-polymer nanocomposites prepared by melt processing and the main properties enhancement [8]

Polymers	Proportion of HNTs	Associated properties				
		Mechanical	Thermal	Flame-retardant	Flammability	Rheological
NR-butadiene rubber blend [51]	3 wt.%	✓				
Butadiene-acrylonitrile rubber [52]	5 wt.%			✓		
Wheatstarch [53]	0–8 wt.%	✓	✓			
Soy protein [54]	0–10wt.%	✓			✓	
Poly (ϵ-caprolactone) [55]	0–10wt.%	✓	✓			✓
Polyethersulfone [56]	0–16 wt.%		✓		✓	
Polylactide [57, 58]	0–23 wt.%	✓	✓			
Fluoroelastomers [59]	0–23 wt.%	✓	✓			
Polyamide 6 [60]	0–30 wt.%	✓	✓			✓
Natural rubber [61, 62]	0–30 wt.%	✓	✓			
Polypropylene [63–68]	0–30 wt.%	✓	✓			
Linear low density polyethylene [69]	0–30 wt.%	✓		✓		

4.2 Chemical method

Benefiting from the presence of -OH groups, HNTs are more easily to be modified especially by chemical modifications than CHNTs. Generally, the pristine CHNTs are constructed by the sheets of hexagonal-shaped carbon atom without any active functional groups. The carboxylate or hydroxylate procedure is usually adopted to explore the CHNTs-derivative easily to be modified. Chemical modification of the HNTs surface is usually proceeded without the carboxylate or hydroxylate procedure in CHNT and can be directly used to immobilize the certain groups on the surface of HNTs [19]. The chemical modification can expand their applications as a nanocontainer [70], an inorganic admixture and also create some new applications such as stimuli-responsive materials, catalysis with high selectivity, drug delivery systems, biosensors, etc. [12, 19, 71]. As a result, the development of chemical modification upon the HNTs has attracted increasing attention. The chemical modification of halloysite can be divided into two major categories: non-covalent modification and covalent modification.

4.2.1 Non-covalent modification

4.2.1.1 Electrostatic interaction

The inner cavity of HNT is positively charged (ζ = +24 mV) and the outer surface is negatively charged (ζ = −35 mV), so selective modification can be afforded by utilizing the potential difference [7, 72]. Following this way, negatively charged molecules, such as anionic surfactants and negatively charged proteins, can be attached on the internal surface of the HNTs [28]. Lvov *et al.* mixed negatively charged proteins with HNTs and selectively fixed them on the inner surface of the lumen of HNTs [73]. The thermal stability and temporal biocatalytic abilities of immobilized negatively charged proteins have been enhanced compared with free enzymes in solution. Similarly, Yan *et al.* [74] fixed a negatively charged protein lipase to the lumen of HNTs, and then mixed the enzyme-nanotube compound with chitosan to prepare an enzymatic membrane, which can hydrolyze lipids without losing enzymes. Cavallaro *et al.* [75–78] reported that anionic surfactants (decyltrimethylammonium bromide, sodium perfluorinated anionic surfactants and dodecanoate) can be used for modifying inner surface. The usage of anionic surfactant to modify HNTs is believed to expand its applications in gas and oil storage, and also to stabilize the dispersion of HNTs in water and control its distribution between water and oil phases.

4.2.1.2 Enlargement of HNTs lumen

HNTs have similar chemical structure with kaolin but differ in possessing a multilayered hollow tubular structure. This special hollow structure makes it possible to become a nano-scale container for loading various drugs and particles. But many applications of halloysite are restricted by its lumen size. The enlargement of the cavity volume by acid treatment has already been presented. Lvov *et al.* [79] enlarged the lumen of halloysite clay nanotube through etching aluminum oxide selectively, which greatly increased the efficiency of tube loading rate, in which the enlarged cavity is available for loading silver acetate and anticorrosion benzotriazole (shown in Figure 4). Daniel *et al.* [80] assessed the effects of different acid treatments on the morphology and chemical composition of HNTs. Li *et al.* [81] etched HNTs' cavity by sulfuric acid to expand the capacity to improve the drug loading rate of ibuprofen.

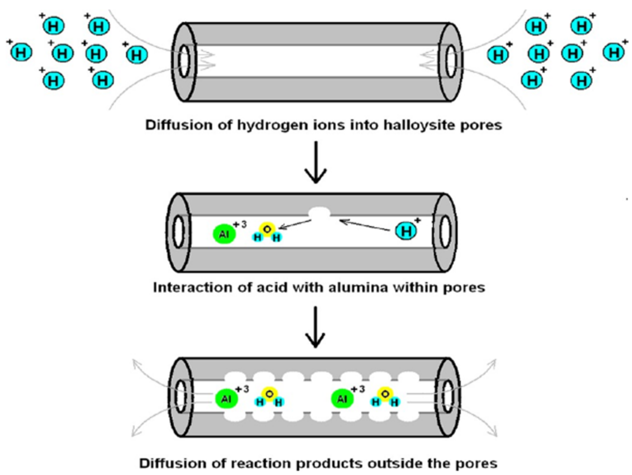


Figure 4: Acid etching of alumina inner layers from halloysite lumen demonstrated by Lvov *et al.* [79]

4.2.2 Covalent modification

Due to the higher length-diameter ratio, lower hydroxyl density and higher distribution of charge on the outer surface, as well as weaker hydroxyl hydrogen bonding, HNTs are more likely to be dispersed in the polymer matrix than other conventional nanoparticles such as carbon nanotubes, while the dispersion is still not good enough [39]. Therefore, it is necessary to modify HNTs in the preparation of halloysite nanotube composites. Additionally, the modified HNTs are more conducive to grafting polymers for further functionalization. The following is a brief summary of the covalent modification methods for HNTs.

4.2.2.1 Silane coupling agent

Silane coupling agent is a large class of low molecular weight organosilicon compounds with special structure, which generally contains two organosilicon compounds a with different chemical. The silane coupling agent can be represented as R-SiX_3. R is a non-hydrolyzable group, and is generally a reactive functional group having affinity or reactivity with a polymer, such as vinyl group, amine group, thiol, epoxy group, azide group, an isocyanate group, etc. X is a hydrolyzable group, including chloride, methoxy, ethoxy, trimethylsiloxy and acetyl groups, etc. Due to this special structure, the silane coupling agent molecule has a reactive group capable of chemically bonding with an inorganic material (silica, iron oxide, etc.), meanwhile has a functional group capable of chemically reacting with an organic molecule (organic small molecules and polymers). It has been reported in the literatures that silane coupling agents can condense with oxides or hydroxyl groups in the surface structure of HNTs. The modification of silane coupling agents can increase the dispersion of HNTs in the polymer matrix, also can significantly improve the mechanical properties of HNTs-based polymer composites [82].

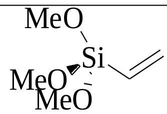
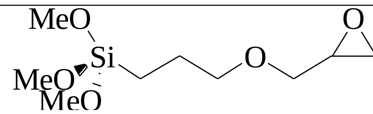
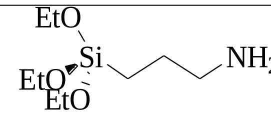
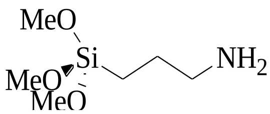
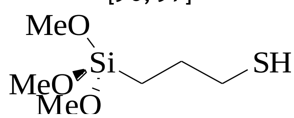
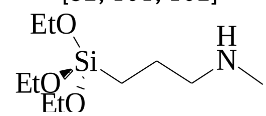
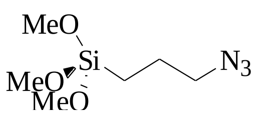
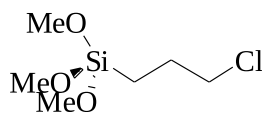
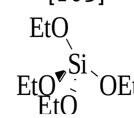
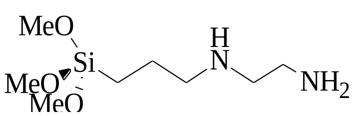
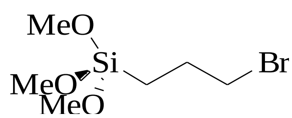
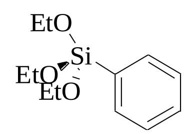
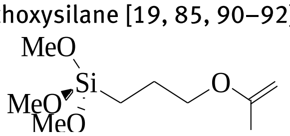
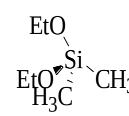
In the past decades, researchers have developed a lot of silanes to HNTs in order to modifying and recombining nanomaterials with well-defined structures (Table 2), in which methoxy silane coupling agent was more likely to be used as compared to ethoxy analogues. Following this way, amino-, azido-, epoxy-, vinyl-, bromo- groups were immobilized onto the HNTs surface.

Kepert *et al.* [82] demonstrated a modification of HNTs by using γ-aminopropyltriethoxysilane, in which the silane coupling agent can be used for preparing various high-performance halloysite nanotube-based organic-inorganic composite materials. Yang *et al.* [86] used 3-aminopropyltrimethoxysilane to generate an amination of HNTs, and then the modified HNTs was treated with 2-bromoisobutyl bromide. The product can be used as initiators for atom transfer radical polymerization (ATRP). Massaro *et al.* [105] used γ-mercaptopropyl trimethoxysilane to prepare amino modified HNTs by a microwave-assisted method. Then the modified HNTs reacted with cysteic acid salt to form aminated halloysite nanotubes containing sulphate (S-S) groups. The amine group in the HNTs can react with the β-diketone unit in the curcumin structure by dehydration synthesis, thus immobilize curcumin on the surface of HNTs. Since the S-S bonds can be degraded in acidic environment, the release of curcumin shows a pH-responsive behavior [106].

4.2.2.2 Phosphoric acid derivative

Phosphoric acid can react with aluminum oxide to produce aluminum phosphate, aluminum hydrogen phosphate, and other products. The surface modification of nano-alumina particles using phosphoric acid can improve the stability of the nano-alumina, thereby improving the heat resistance [107, 108]. In view of the fact that the surface structure of HNTs is similar to nanoalumina, Tang *et al.* [109] improved the fracture toughness of epoxy resin

Table 2: The chemical composition of silanes used for modification of HNTs [83]

Methoxy silane coupling agent		Ethoxy silane coupling agent
 Vinyltrimethoxysilane [84, 85]	 γ-glycidoxypropyltrimethoxysilane [96, 97]	 3-aminopropyltriethoxysilane [82, 101, 102]
 3-aminopropyltrimethoxysilane [86–88]	 3-mercaptopropyltrimethoxysilane [98, 99]	 [3-(methylamino)propyl]tri-methoxysilane [103]
 3-azidopropyltrimethoxysilane [89]	 3-chloropropyl-trimethoxysilane [100]	 Tetraethoxysilane [81]
 [3-(2-aminoethylamino)propyl]trime-thoxysilane [19, 85, 90–92]	 3-bromopropyltrimethoxysilane [85]	 Phenyltriethoxysilane [85]
 3-(trimethoxysilyl)propyl methacrylate [93–95]		 Diethoxy diethylsilane [104]

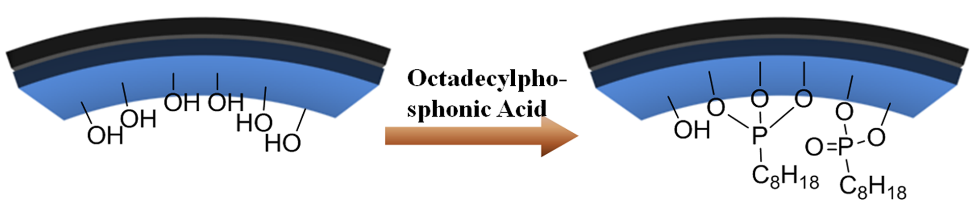


Figure 5: Selective modification of the inner surface by octadecylphosphonic acid proposed by Lvov *et al.* [19]

significantly through doping phenyl phosphonic acid modified HNTs into epoxy resin. Lvov *et al.* [19] modified the HNTs with octadecylphosphonic acid (shown in Figure 5), while the octadecyl phosphoric acid did not react with the outer wall of HNTs. Therefore, the outer wall of HNTs modified by octadecyl phosphate still has a hydrophilic structure, and the inner cavity is a hydrophobic structure. This special structure allows the modified HNTs to form stable micelles in water.

4.2.2.3 Transesterification

Halloysite contains a large number of hydroxyl groups and is easily dispersed in water, which provides conditions for the transesterification reaction to take place. Based on this point, Hakkarainen *et al.* [50] placed HNTs in a solution of dimethyl adipate to esterify the hydroxyl groups in HNTs with a small amount of free acid in dimethyl adipate solution. The HNTs modified with dimethyl adipate can react with 1, 4-butanediol, thereby enable the polybutylene adipate to be grafted on HNTs. The modification im-

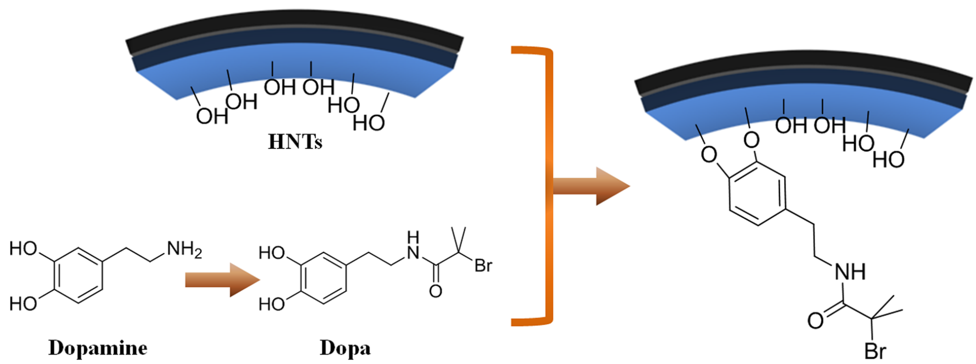


Figure 6: Dopamine derivative for selective modification of the inner surface of HNTs demonstrated by Takahara *et al.* [12]

proves the interfacial adhesion properties between HNTs and polyvinyl chloride.

4.2.2.4 Ring-opening metathesis polymerization

Ring-opening metathesis polymerization (ROMP) is based on the ring-opening polymerization of cyclic olefins. Carbene complex was used to catalyze the cleavage of the cyclic olefin double bond and then connects the fragmented materials in an end to end manner, which is a special method for synthesizing polymer materials and modified nanomaterials in recent years. HNTs was developed as an initiator in the ring-opening metathesis polymerization through immobilizing norbornene-based molecules on the surface of HNTs using Grubbs II as catalyst. Then the functional norbornene-based monomers were polymerized onto HNTs by the ROMP method followed by the semi-product was used to immobilize trivalent iron nanoparticles to prepare ferromagnetic HNTs derivatives.

4.2.2.5 Dopamine derivative

Dopamine (4-(2-aminoethyl)-1, 2-benzenediol) is a key neurotransmitter with high biocompatibility in the human hypothalamus and pituitary gland [110]. The pyrocatechol in its structure can dehydrate and condense with hydroxyl group. Takahara *et al.* [12] reported that the amine-modified HNTs was prepared by the dehydration condensation of aluminium hydroxyl groups in HNTs with catechol groups in dopamine (show in Figure 6). Meanwhile they proved that the modification occurred only on the inner cavity surface and the outer wall structure of HNTs was not affected. Then the ATRP initiator unit was introduced onto the in order to initiate a surface polymerization of methyl methacrylate (MMA) to give a HNTs-PMMA composite. Lin *et al.* [111] also modified the HNTs with a dopamine derivative containing an ATRP initiator, and then grafted polyphenyl sulphonic acid into the HNTs. Due to the fact that the product has good compatibility with polyether ketone, the ion exchange membrane prepared by combining HNTs with polyether ketone has good mechanical properties and separation performance.

4.2.2.6 Arylboronic acid

Early research upon alcohol affinity molecules showed that arylboronic acid can react with diols through dehydration condensation. The reaction of arylboronic acid and pinacol is one of the most organic chemical reactions. Yildirim *et al.* [112] employed the reaction of vicinal diols with boronic acids to expand the interlayer distance of graphene oxide, and improved the ability to adsorb gas. Our group have shown that arylboronic acid can also be covalently attached to the inner surface of HNTs, rather than the outer surface, to give the product with fluorescent characteristics [35] (shown in Figure 7).

4.2.2.7 Supernormal valence transition-metals

Supernormal valence transition-metals were proven to be capable of reacting with hydroxyl groups in organics and then generating radicals (-C· or -O·) that may be able to initiate the polymerization. This redox system has been employed to perform the surface grafting polymerization on a library of polymers. As a number of -OH groups existing on the surface of HNTs, it encouraged us to explore a redox system made by supernormal valence transition-metal and -OH groups on HNTs.

Following this way, poly(triethyl(4-vinylbenzyl)phosphonium chloride) (poly(Et-P)) were grafted on the surface of HNTs by using Ce(IV) as the initiator, which was conducted by our group. The product showed good stability and can be used to construct a uniform hydrogel by mixing with sodium alginate. [113].

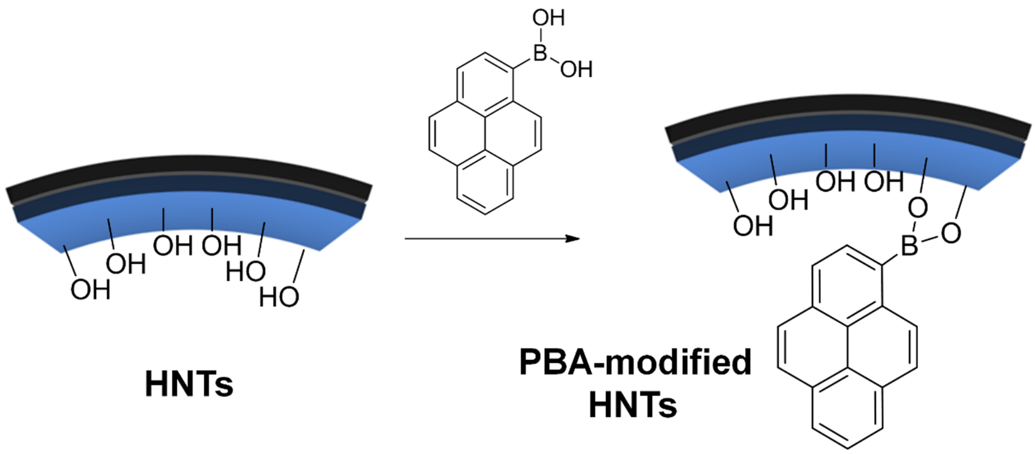


Figure 7: Selective modification of the inner surface by 1-pyrenylboronic acid conducted by our group [35]

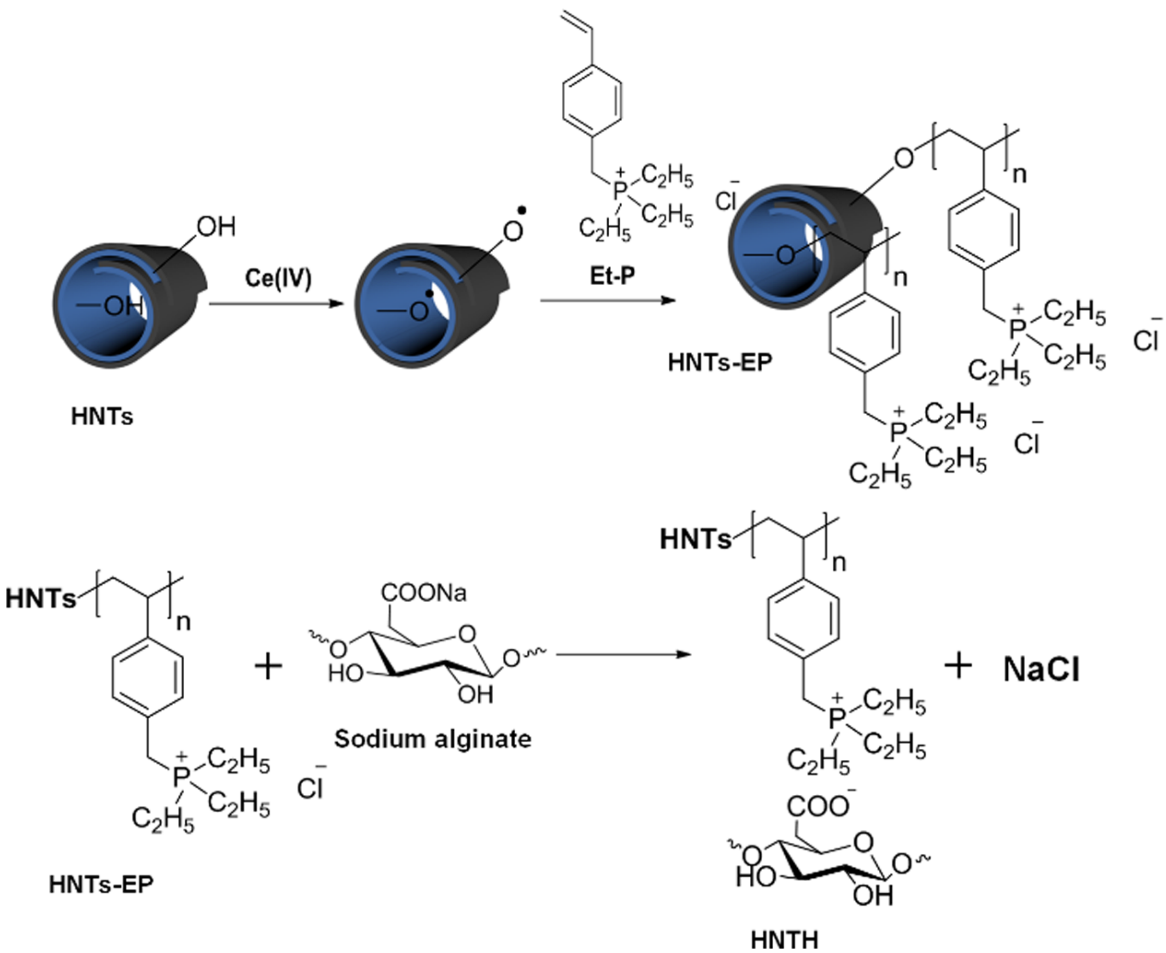


Figure 8: Grafting poly(triethyl(4-vinylbenzyl)phosphonium chloride) onto HNT by a redox system consists of Ce(IV) and -OH groups located on HNTs and the preparation of a hydrogel [113]

5 Applications

Benefiting from the semblable tubular structure with CHNTs, HNTs also possess some similarities in many fields, especially in the carrier materials. It should be noted that the HNTs show superior character peculiarities when using as drug carrier or zymophore owing to the larger cavity volume and higher biocompatibility. Moreover, the higher thermostability and polyhydroxy character make the HNTs a desirable candidate in heat protection material fields. It is a bit regret that the lack of p-conjugate component makes the HNTs cannot serve as a good candidate in photoelectric material field.

5.1 Biomedicine

HNTs has been demonstrated to be served as a biocompatible and non-toxic material in some latest literatures upon cell cultures [7], bacteria [90], invertebrate models [114], which is very suitable for applying in the field of biomedicine once modified. The application in biopharmaceutical fields is described as follows.

5.1.1 Sustained drug delivery

The use of HNTs for sustained drug release has a great advantage because of its hollow tubular structure. Compared with the drug in pristine form release behavior dissolved in water or other solvents, the drug molecules loaded in the cavity of HNTs usually manifest much longer release time.

Veerabadran *et al.* [115] loaded the drugs such as furosemide acid, dexamethasone and nifedipine into the HNTs cavity, in which the drug-loading rate was regulated by changing the pH value and alcohol / water ratio. After loaded in HNTs, the release behavior of the drugs was significantly slower than in original state and a completely release can be achieved in 10h. Forsgren *et al.* [116] prepared drug-loaded microspheres containing fentanyl with HNTs and microcrystalline cellulose as base materials. Compared with the ordinary fentanyl loaded microspheres, the fentanyl loaded microspheres prepared by the above method have obvious sustained release effect under the intestinal environment, which is expected to reduce the patients' dependence on opioid by eliminating the frequency of fentanyl administration. Zhong *et al.* [81] prepared a novel hydrophobic organosilane-enlarged HNTs (EHNTs@OS) hybrid nanocomposite for sustained release of ibuprofen. Compared with original HNTs, the modification of HNTs lumen was helpful for higher loading rate (25%) and longer releasing time (100 h). The mechanism and drug release curve are shown in Figure 9. Zhang *et al.* [117] prepared HNTs loaded with antimicrobial metronidazole, then doped with cellulose for spinning film processing. Compared with drug-loaded HNTs, the drug release behavior of the halloysite-doped membranes has more obvious sustained release effect. The results of cytotoxicity test and antibacterial test show that the drug-loaded membrane has good compatibility towards L929 mouse cells and is able to prevent the colonization of fusobacteria.

5.1.2 pH responsive drug delivery

The pH-sensitive polymers have raised a lot of attention in bio-medicine field [118]. As a typical pH-responsive polymer, poly (*N, N*-dimethlaminoethyl methacrylate) (PDMAEMA) has many attractive properties including biocompatibility and antibacterial activity. Hemmatpour *et al.* [119] functionalized HNTs with PDMAEMA and use it as drug container for loading diphenhydramine hydrochloride (DPH) and diclofenac sodium salt. The polymer chains on the HNT surface can act as barriers which significantly reduce the release amount, while a much higher release rate can be reached at a pH value<1.2 (show in the Figure 10).

5.1.3 Thermoresponsive drug delivery

A release mechanism of thermosensitive prodrug is based on the temperature-sensitive properties of the grafted polymer onto HNTs. As similar to the grafting of PDMAEMA can cause a pH-responsive release, the introduction of thermosensitive polymer—poly-*N*-isopropyl acrylamide (PNIPAAM) on the halloysite surface can result in a thermosensitive release manner of loaded drugs. Following this way Cavallaro *et al.* [120] used the modified nanocontainer to store the curcumin at 25°C, whereas a triggered release can be achieved at 37°C in a simulated gastrointestinal system (show in Figure 11).

5.1.4 Smart H_2O_2-Responsive drug delivery

Our group introduced a novel H_2O_2-responsive chemical hydrogel based on the B-C bond in the as-formed matrix, which can be degraded into B-OH and C-OH groups after the addition of H_2O_2. Then the cavity of HNTs was employed to load drugs to give the H_2O_2-responsive drug loading hydrogel. The as-formed hydrogel show little release behavior with the absence of H_2O_2, while a completely release can be achieved in H_2O_2 solution [36].

Our group also prepared another type of H_2O_2-responsive chemical hydrogel with a "turn-on" fluorescence character upon H_2O_2, which was also used to afford more intelligent H_2O_2–responsive drug delivery system (show in Figure 13) [121]. The drug release can be

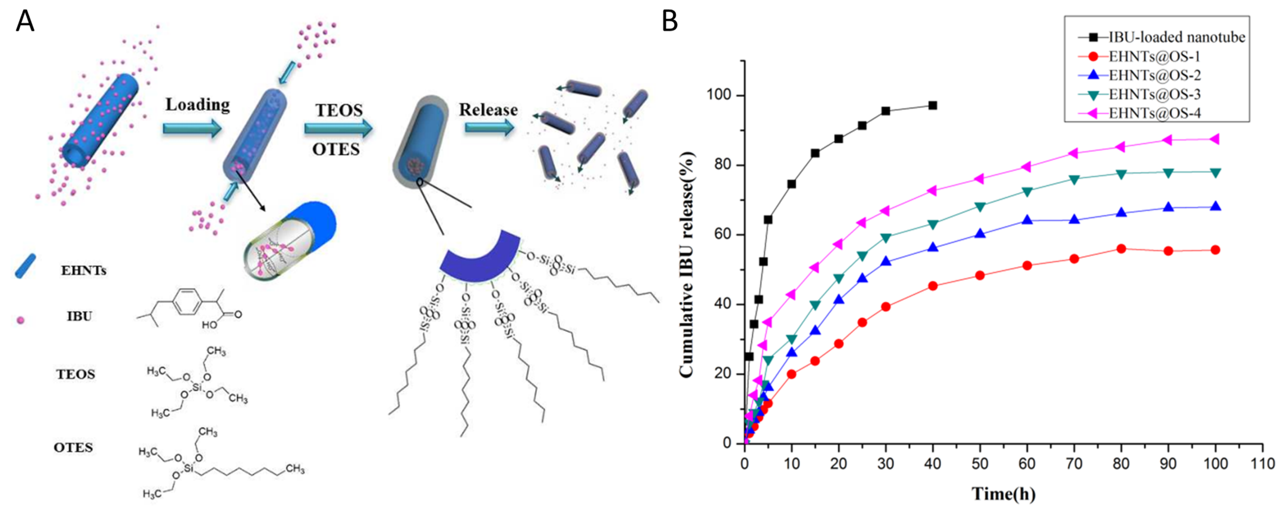


Figure 9: Schematic representation of IBU loading, modification, and drug-release process (A). Release profiles of IBU from the EHNTs@OS with different compositions (conducted) by Zhong *et al.* [81]

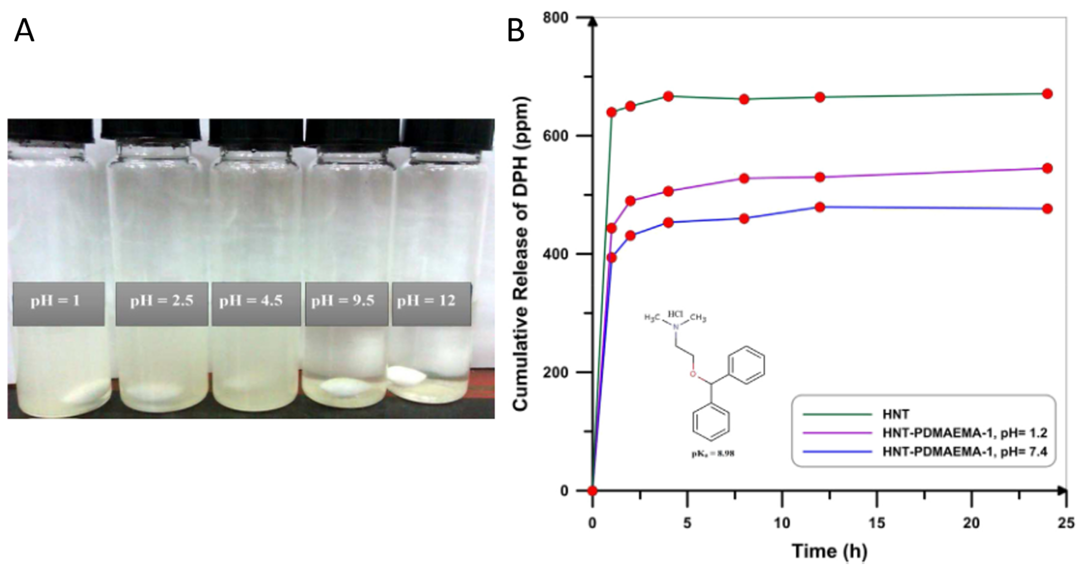


Figure 10: Sensitivity of HNT-PDMAEMA aqueous solutions with concentration of about 0.2 mg/mL to pH just 2 h after sonication (A), cumulative release of DPH from HNT and HNT-PDMAEMA-1 at two different pH values (B) demonstrated by Hemmatpour *et al.* [119]

achieved under overexpressed H_2O_2 concentration. Moreover, the drug release behavior can be monitored by the arising of fluorescence.

5.1.5 Synergistic effect

A synergistic effect can be achieved by fill the drug into the cavity of HNTs-based prodrugs. For examples, the HNTs modified with triazole units on the external surface was found to have a synergic effect with cardanol or curcumin, which is an ideal carrier for anti-cancer therapies which was proved by some tumoral cell lines [89, 122]. Massaro *et al.* [123] prepared a HNTs-based prodrug by immobilizing cyclodextrin derivatives onto the surface of HNTs, which is a suitable nanocontainer for the co-delivery of silibinin and quercetin that could achieve synergic effects in anti-cancer activities.

5.1.6 Antibacterial

The microscale of HNTs makes them difficult to penetrate the skin when used as external preparations. Generally,

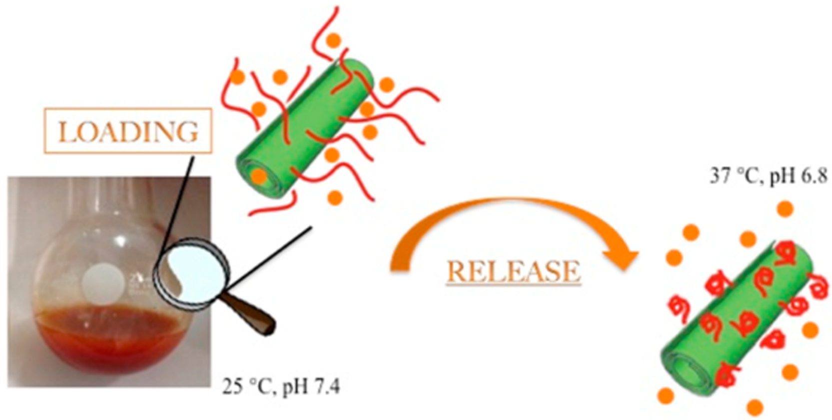


Figure 11: The release mechanism of curcumin was drew by Cavallaro *et al.* [120]

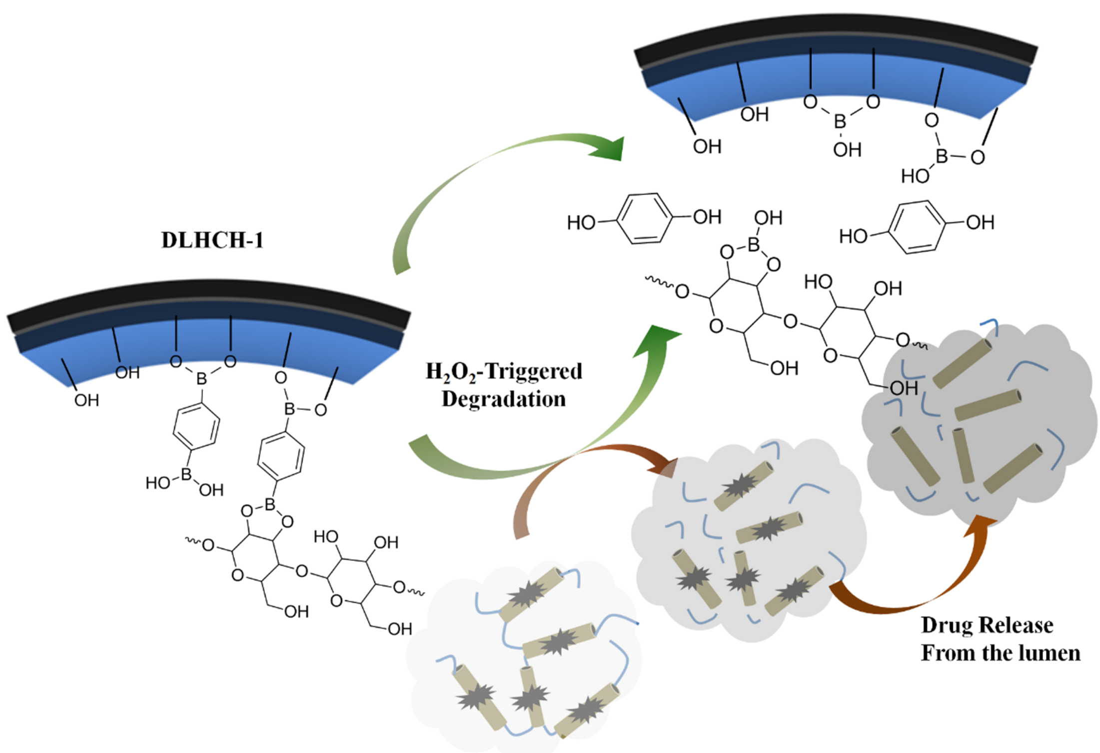


Figure 12: The procedures of H_2O_2-responsive drug delivery system conducted by our group [36]

loading drugs or special particles can endow antibacterial/antimicrobial activity to HNTs.

5.1.6.1 Loaded drugs

Drug and release features in the HNTs-based drug delivery system was made into a form (show in Table 3).

Triazoles and their derivatives have always played a very important role in the pharmaceutical industry, which has been verified to possess a library of bio-activities [89, 124]. Lazzara *et al.* [122] demonstrated the selective functionalization of triazolium salts on the external surface of HNTs. The introduction of triazole moieties on HNTs triggered an increase in the anti-tumor activities of the HNT-triazolium prodrug.

It has been reported that PDMAEMA has peculiar antibacterial activity. Hemmatpour *et al.* [119] have grafted PDMAEMA on HNTs successful by surface-initiated ATRP method. The HNTs-based product can also be used to load some other antibacterial to achieve a synergistic antibacterial effect.

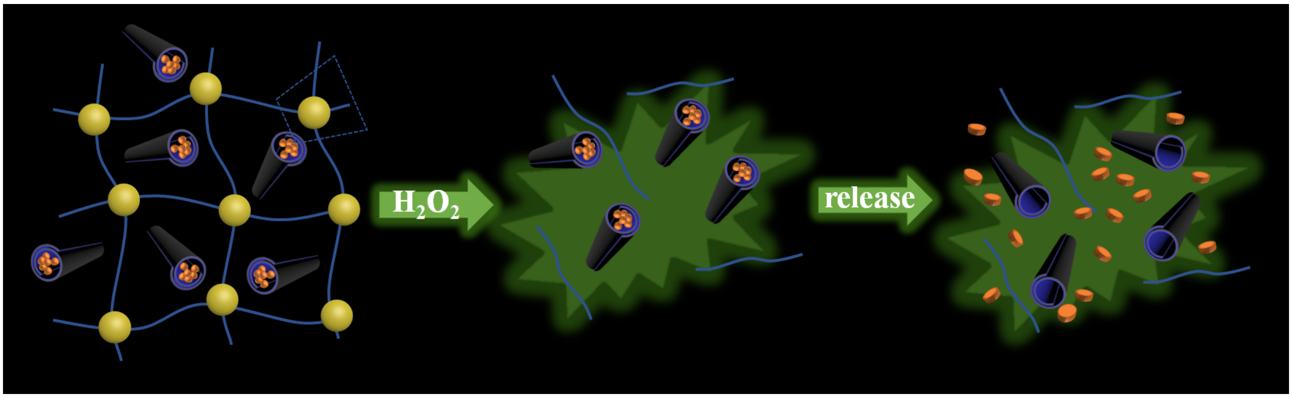


Figure 13: H_2O_2-responsive release mechanism of DHNTs@PVA@PA [121]

Table 3: Drug and release features in the HNTs-based drug delivery system

Drug name	Release feature	Drug efficacy
Ibuprofen	Sustained	Anti-inflammatory [101]
Dexamethasone	Sustained	Anti-inflammatory [115]
Aspirin	Sustained	Anti-inflammatory [102]
Diclofenac sodium salt	pH-sensitive	Anti-inflammatory [119]
pentoxifylline	H_2O_2-sensitive	Anti-inflammatory [36]
Oxytetracycline HCl	Sustained	Antibacterial [126]
Polymyxin B	Sustained	Antibacterial [125]
Ofloxacin	Sustained	Antibacterial [127]
Ciprofloxacin	Sustained	Antibacterial [125]
Curcumin	Sustained, pH-sensitive and thermosensitive	Anticancer [106, 128, 129]
Khellin	Sustained	Vasodilator [126]
Nicotinamide adenine dinucleotide	Sustained	Coenzyme [126]
Furosemide	Sustained	Diuretic [115]
Doxorubicin	Sustained	Antitumor [130]
Diphenhydramine hydrochloride	pH-sensitive	Anti-allergy [119]
Quercetin	Sustained	Antioxidant [131]
Silibinin	Sustained	Antioxidant [123]

Ciprofloxacin is the third generation of synthetic quinolone antibacterial drugs, while the anti-bacterial activity can be significantly enhanced by combined with other kinds of antibitic. Zhang *et al.* [125] developed a co-delivery antibacterial elastic nanocomposite, which show significant antimicrobial activity against both gram-negative and -positive bacteria by mixing ciprofloxacin and polymyxin B sulfate-loaded HNTs in gelatin.

5.1.6.2 Loaded particles

It has been reported that some nanoparticles showed desirable antibacterial effects, which cause little systemic toxicity when used as external preparations. Jana *et al.* [132] immobilized silver (Ag) nanoparticles (NPs) on HNTs by a wet method. The samples exhibit bactericidal effect for *E. coli* bacteria (show in Figure 14), which shows light sensitivity).

5.2 Biomacromolecule carriers

Biological macromolecules generally refer to various organic molecules with a molecular weight of more than 10000 Da, which existed in human, animal and plant bodies. Commonly used biological macromolecules mainly include proteins, nucleic acids and carbohydrates with high molecular weight, etc. As for proteins, the size of protein generally ranges from 3 to 8 nm. It should be a feasible route to load the protein into the HNTs lumen, in which

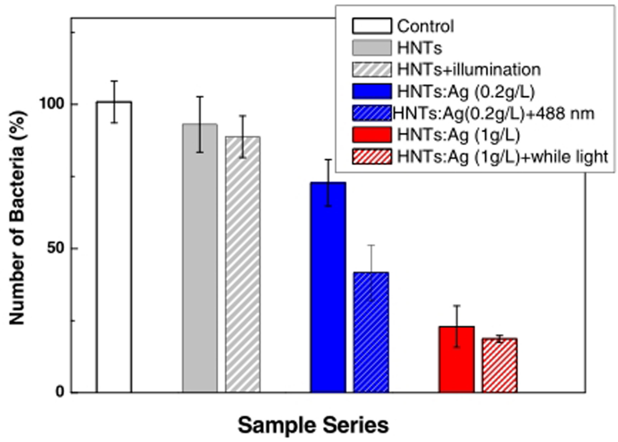


Figure 14: Relative number of E. coli bacteria after incubation without (control) and with bare HNTs (1 g/L) in darkness (grey bars) and under illumination (pattern grey bars) as well as with HNTs (0.2 g/L) covered by Ag NPs (blue bars) in darkness and under illumination at 488 nm (blue pattern bars), and HNTs (1 g/L) covered by Ag NPs (red bars) in darkness and under illumination with white light (red pattern bars) (conducted by Jana *et al.*) [132]

the inner diameter ranges from 15 to 20 nm. Lvov *et al.* [7] show that negatively charged biological macromolecules, such as deoxyribonucleic acid, are more likely to interact with the cationic charges carried by the lumen of nanotube, thereby increasing the load efficiency and avoiding adsorption of these biomacromolecules on the outer wall of the tube effectively.

Price *et al.* [126] successfully loaded urease, a protein molecule with a weight average molecular weight of about 480,000 Da, into the cavity of HNTs. Based on the price's studies, Shchukin *et al.* [28] developed the urease-loaded HNTs as nano reactors in which the loaded urease can catalyze the transfer from to carbonic acid and thereby synthesized calcium carbonate in the lumen of HNTs (show in Figure 15). Chen *et al.* [133] loaded the worm laccase into the cavity of HNTs by utilizing dopamine as a medium and the load rate up to 17%. The catalytic activity of worm laccase immobilized in HNTs to the phenolic compounds can retain up to 90% after five cycles. The employment of HNTs as enzyme immobilization carriers has the advantages of low cost, high biocompatibility, multi-cycle use and be able to retain the original catalytic activity of enzymes. Zhang *et al.* [134] utilized glutaraldehyde to immobilized a natural biological macromolecular—chitosan on the HNTs and fixed the horseradish peroxidase on the modified HNTs. HNTs loaded with biomacromolecules can be used to purify hydrogen peroxide, sodium hypochlorite and other impurities in tap water.

5.3 Catalysis

As compared to traditional catalyst, nanoscale materials have larger surface area, better stability and thereby higher activity [23, 135, 136]. It has been reported that the hydroxy groups in the halloysite nanotube structure can provide acidic active sites and thus can catalyze petroleum cracking, esterification, etc. Rong and Xiao investigated the catalytic activity of HNTs in heavy oil cracking reactions. The results indicated that their catalytic activity is higher than those of kaolin and dickite and other clay inorganic materials [22]. Zatta *et al.* [21] used HNTs to catalyze the esterification of methanol and lauric acid. The conversion rate is up to 95% in the presence of HNTs, which is significantly higher than the conversion rate (76%) without HNTs.

HNTs can also be employed as carriers for other nanocatalyst. As shown in the first paragraph of Section 5.3, HNTs have been introduced to prepare nano-catalysts by immobilized enzyme technology in the cavity. The large cavity volume of HNTs endows them desirable carriers for inorganic metal, as well as drug carriers. Liu *et al.* [137] loaded nano-silver particles with 10 nm in diameter into HNTs by using in-situ reduction method, which can be used to catalyze the reduction reaction of *p*-nitrophenol with sodium borohydride (the TEM images was show in Figure 16). Chen *et al.* [138] immobilized TiO_2 nanoparticles in HNTs by an one-step method, which can be used in the degradation of organic pollutants under the photocatalytic conditions. Sanchez-Ballester *et al.* [139] immobilized copper-nickel alloy nanoparticles (2 ~ 3 nm) in the HNTs cavity. The modified HNTs loaded with copper-nickel alloy nanoparticles are able to catalyze the reaction of nitric oxide and carbon monoxide to generate nitrogen and carbon dioxide. Under the immobilization behavior, the aggregation of the copper-nickel alloy nanoparticles can be effectively avoided and the copper-nickel alloy nanoparticles are uniformly dispersed in the HNTs cavity. As compared to the original state the catalytic performance of the copper-nickel alloy was significantly improved. Nitric oxide and carbon monoxide are the main components in automobile exhaust, as well as the major causes of haze formation. In this study, the composite prepared by HNTs and copper-nickel alloy nanoparticle shows a bright application prospects in the field of environmental protection.

5.4 Adsorbent

Adsorbent is a solid substance usually possessing a large surface area, suitable pore and specific surface structure,

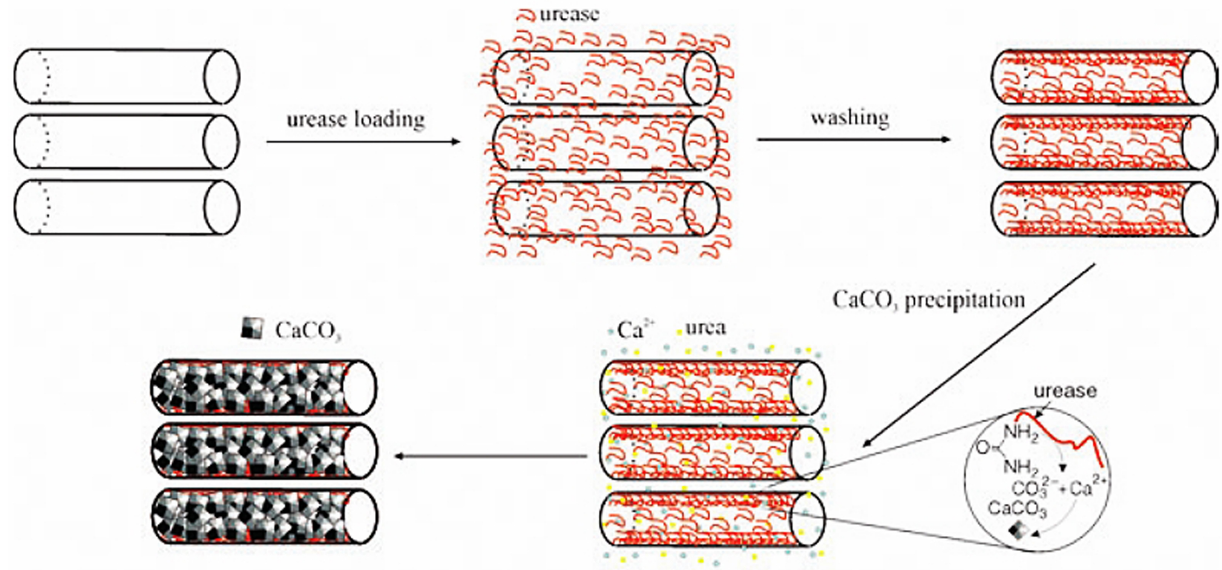


Figure 15: Schematic of the urease-catalyzed synthesis of $CaCO_3$ inside HNTs demonstrated by Shchukin *et al.* [28]

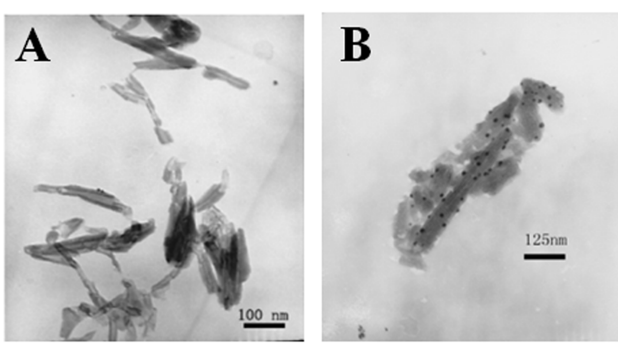


Figure 16: TEM images of HNTs (A) and Ag/HNTs (B) conducted by Liu *et al.* [137]

which can effectively adsorb specific components from gas or liquid. Furthermore, it has a strong adsorption capacity of adsorbate and does not react with adsorbates or a medium [140–142]. A good adsorbent also needs to meet the requirements of manufacturing convenience, such as: easy regeneration, low cost and should desirable mechanical properties. The inner and the outer walls of HNTs have positive and negative charges, which can adsorb molecules or ions with negative charges or positive charges, respectively. The literature suggests that the HNTs has a porosity of about 60 cm^2/g, the pore size of HNTs treated with strong acid or alkali can reach 6-7 times of the normal range. It can be concluded from the facts that HNTs are expected to be developed as ideal adsorbent materials [143].

An adsorption test demonstrated that halloysite had better adsorption capacity upon Rhodamine 6G and anionic Chrome azurol S as compared to kaolin. As for Chrome azurol S, higher pH value and temperature contribute to lower adsorption capacity. As for Rhodamine 6G, the adsorption capacity increases with the enhancement of ionic strength and temperature [143].

Cavallaro *et al.* [144] changed the charge of HNTs lumen surface from hydrophilic to hydrophobic, which endow it a strong adsorption effect on hydrophobic compounds such as hydrocarbons and aromatics. As a result, liquid or gas of such impurities can be effectively removed. Kilislioglu and Bilgin found that HNTs can adsorb uranium, a pollutant in water, and the adsorption mechanism and kinetics were investigated in detail. The results show that the adsorption reaction can be intensified at higher temperature [145]. Liu *et al.* [146] prepared a magnetic composite consist of Fe_3O_4-HNTs, which maintain a high adsorption capacity for methyl violet.

5.5 Energy storage

Nowadays, energy storage has become an attractive topic in social development, in which numerous nanomaterials have been developed as energy storage materials [147–149]. Owing to the widely spread properties, unique tubular structure, large surface area and high polarity of the internal surface HNT is a promising candidate in the field of energy storage. It has been reported that the maximum hydrogen capacity of HNTs can reach 2.8wt%, and the higher adsorbability can be achieved by altering the mesoporous or surface structures. Ohashi *et al.* [150] investigated the

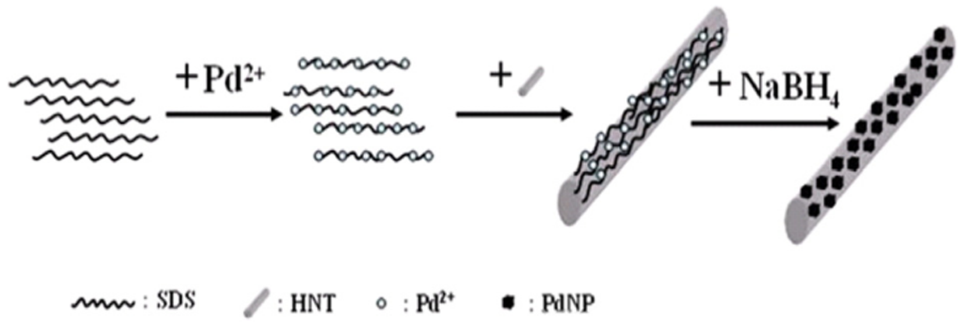


Figure 17: Schematic procedure of the synthesis of PdNPs-HNTs nanostructures demonstrated by Zheng *et al.* [157]

storage capacity of HNTs towards methane. In which the storage capacity is about 50.6 mg/ml. HNTs have the potential to be used as high-energy storage materials, while the enlargement of the lumen may be essential.

5.6 Biosensors

Biosensors are a library of instruments or devices or that are sensitive to biological substances, which can convert their concentration to electrical signals and thereby for visible detection [151–153]. Biosensors are a kind of analysis system that generally consist of a bio-sensitive material, a suitable transducer, an associated signal amplification device and so on. The introduction of nanotechnology result in a dramatically increase of the sensitivity and the reduction of economized detection time, which lead to the application of high-throughput real-time detection and analysis [154–156]. Zheng *et al.* [157] prepared the Pd nanoparticles (NPs)-HNTs, which was doped into a glassy carbon electrode by sodium dodecylsulfate (SDS) (show in Figure 17). The results show that the HNTs-based sensor has high accuracy and specificity in measuring the glucose solution. In addition, Zheng's group also reported a HNTs-based sensor with a detection limit of 0.3μM against hydrogen peroxide. The biosensors show attractive characteristics of high specificity, high sensitivity, short detection time, as well as, enhanced mechanical properties [158].

5.7 Gel

Gels, including hydrogel, aerogel, ionic gel, etc., are a non-fluid colloidal networks or polymers, which have promising applications in many fields [159–166]. Polymer hydrogel is mainly formed by chemical cross-linking between polymer chains. Some commonly known drawbacks include poor mechanical properties and increased brittleness after swelling limited their practical application. It has been reported the introduction of nanomaterials into the hydrogel network would integrate the rigidity, dimensional stability and thermal stability [167–169].

Liu *et al.* [170] also verified that the addition of HNTs can significantly enhance the mechanical toughness tensile modulus and tensile properties of hydrogels. Haraguchi *et al.* [171] synthesized poly (*N*-isopropylacrylamide) hydrogels with HNTs as cross-linkers. Compared to traditional poly (*N*-isopropylacrylamide) hydrogels synthesized by organic cross-linkers, the HNTs-crosslinked poly (*N*-isopropylacrylamide) hydrogel show much more excellent mechanical properties. Liu *et al.* [172] also prepared HNTs-based aerogel by using 1, 4-phenylene diisocyanate-modified HNTs and silica microparticals as raw materials, which compressive strength is up to 1.45 MPa, and the thermal conductivity can achieve 0.025W/m K. Our research group explored how to prepare halloysite nanotube-based hydrogels [173] (show in Figure 18) and the application of halloysite nanotube-based hydrogels in drug loading [121].

5.8 Flame retardant

Flame-retardant materials are able to inhibit or delay the combustion and in great demand in the defense, aerospace, fire and other fields [174–176]. Benefiting from the hollow structure and the inorganic character, HNTs show good heat blocking and the modification effect. On the other hand, the hydroxyl groups in tubular structure would undergo dehydration condensation reaction under high temperature and thereby beable to generate water vapor to achieve a cooling effect [177]. Schiraldi *et al.* [178] have developed aerogel composites consist of HNTs, Poly (vinyl alcohol) (PVOH), nanoscale silica, montmorillonite (MMT) and laponite. The results show that the flame-retardant ability of the HNTs-based aerogel are sig-

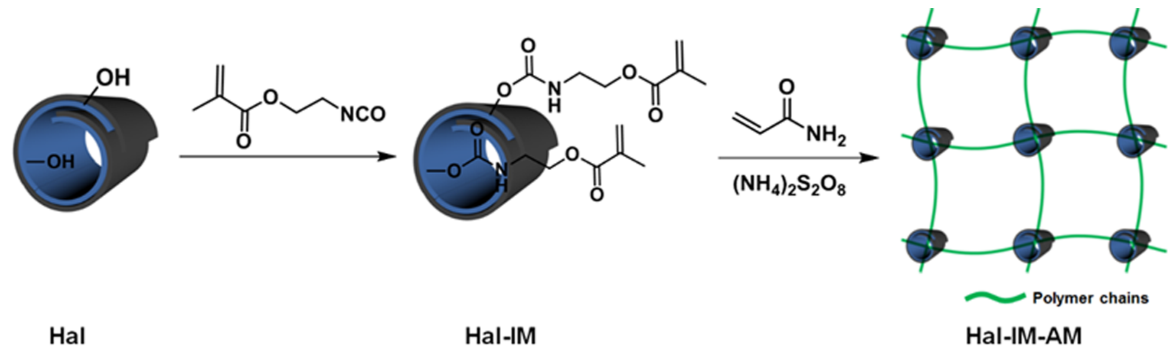


Figure 18: The modification of Hal by 2-isocyanatoethyl methacrylate (IM) and the preparation of Hal-IM-AM hydrogels [173]

nificantly higher than the other flame retardant materials. The above attractive property enables HNTs to be widely used in the field of flame retardant possible.

In summary, HNTs, have attracted much attention in the field of drug carrier, biological macromolecular carrier, catalysis, adsorption, energy storage, biosensors, gel preparation, flame retardant materials, etc. Moreover, some literatures have shown that HNTs also have broad prospects for application in the biomimetic materials, medical imaging and other fields [179–182]. It is still of great significance to expand the application field of HNTs.

6 Prospect

Despite of the increasing number of the publications upon HNTs, some fundamental research work is still in strong demand. i) a quality standard for HNTs including purity, size, length-diameter ratio, inner/outer diameter, electric potential and surface structure should be established, which is the precondition for large-scale processes; ii) the relationship of the size with hydrodynamic radius (R_h) should be illuminated, which is in extremely demand for the investigation of the permeability of HNTs against cytomembrane and skin tissue; in addition, Rh is associated with the intravascular accumulation and the enhanced permeability and retention (EPR) effect which is a critical factor for the passive-targeting preparations in antitumor fields; iii) the interaction of HNTs with other biomacromolecules, especially for the proteins, is a puzzling topic that cannot be ignored; iv) the exploration for a self-assembly method to achieve a head-to-tail ligation HNTs chains is very promising, which may pave a path for the HNTs-based conductor or sensor materials; v) the selectively modification of the outer Si surface is rarely studied, which would be beneficial to develop a new generation of smart delivery systems; vi) for HNTs-based polymer composites, more facile approach, the best is the one-step surface initiation, should be explored, which would be beneficial to achieve variety of smart delivery systems.

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