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Halloysite nanotubes: a green resource for materials and life sciences

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Abstract

Clay minerals are considered one of the materials of the 20th century for their peculiar physico-chemical features. Among them, halloysite nanotubes (HNTs) are an emerging nanomaterial with a particular tubular structure that makes them a low cost and valuable alternative to the most common carbon nanotubes. Due to their tubular morphology, HNTs are employed in several fields acting as nanocontainers for different compounds for applications in drug carrier and delivery fields, catalysis, and as filler for polymeric matrices. The modification of HNTs' surfaces allows to the synthesis of different nanoarchitectures that can improve the mechanical and thermal performance of polymer as well as they can enhance the use for the loading and release of chemicals. In this review, we summarize our recent results on halloysite functionalization, both supramolecular and covalent, and the application aforementioned fields.

Keywords Halloysite nanotubes · Covalent modification · Supramolecular interaction · Drug carrier and delivery · Catalysis

1 Introduction

Clay minerals are phyllosilicate present since the origin of the life with particular morphologies, and consequently, they are able to interact with molecules forming nanocomposites (Lazzara et al. 2017b).

Among them, halloysite nanotubes (HNTs) are aluminosilicates, of the kaolin group, which possess predominant hollow tubular morphology with chemical formula $Al_2Si_2O_5(OH)_4{\cdot}nH_2O$. HNTs are a dioctahedral 1:1 clay mineral present in soils, especially in wet tropical and subtropical regions and weathered igneous and non-igneous rocks, and it can be mainly found in USA, Australia, China, Mexico, Brazil, and New Zealand. By varying the deposit, it can be found HNTs with different hydration state, characteristic sizes, and purity grade.

Halloysite was discovered by the Belgian geologist Omalius d'Halloy from whom it was named by the mineralogist M. Berthier in 1826, and in the years, it has attracted attention in the scientific community (Fig. 1).

Generally, the halloysite is constituted of 10–15 bilayers, with a spacing of approximately 0.72 nm, and has a density of 2.53 g cm^{-3}. The external surface is composed of siloxane (Si–O–Si) groups, while the inner one consists of a gibbsite-like array of aluminol (Al–OH) groups, and Al–OH and Si–OH groups at the edges of the tube (Fig. 2). The sequence of the layers gives to the tubes' Si–O groups at the outer surface and Al–OH groups at the inner surface (Massaro et al. 2018c). According to the different chemical composition, HNTs present different surface charge depending on the pH (Bretti et al. 2016). In detail, the tubes show a positive charged inner surface and a negative charge on the external one.

Usually, the inner and outer diameters of the tubes are in the ranges of 10–30 nm and 40–70 nm, respectively, while their length is in the range of 0.2–1.5 µm (Abdullayev et al. 2013; Abdullayev and Lvov 2013) depending on the extraction site and purification processes. In some deposits, indeed, there were found halloysite tubes with length up to

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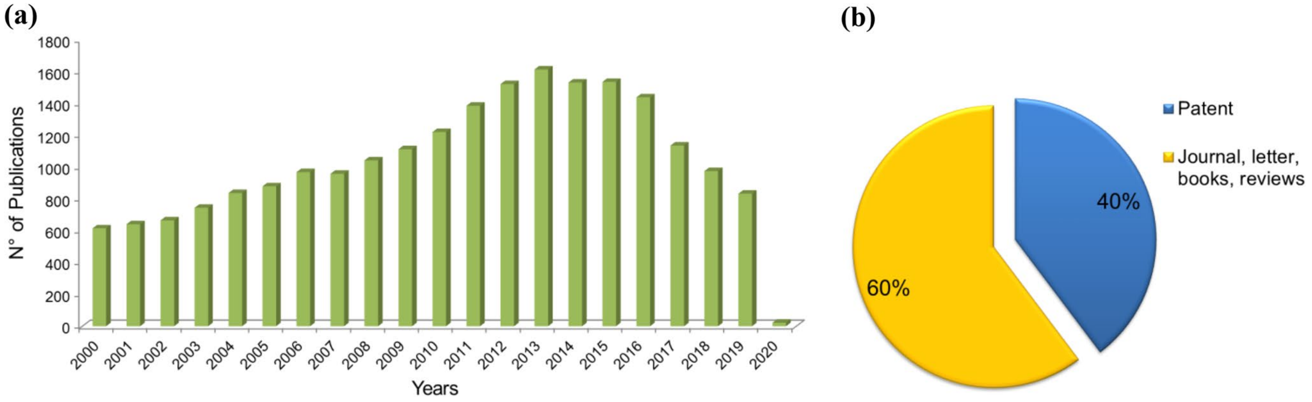


Fig. 1 Comparison of **a** the annual number of scientific publications and patents and **b** distribution (%) of scientific publications in "patent" and "journal" related to the term "halloysite" (data analysis of publications was done using the SciFinder Scholar search system with the term "halloysite", as on December 2019)

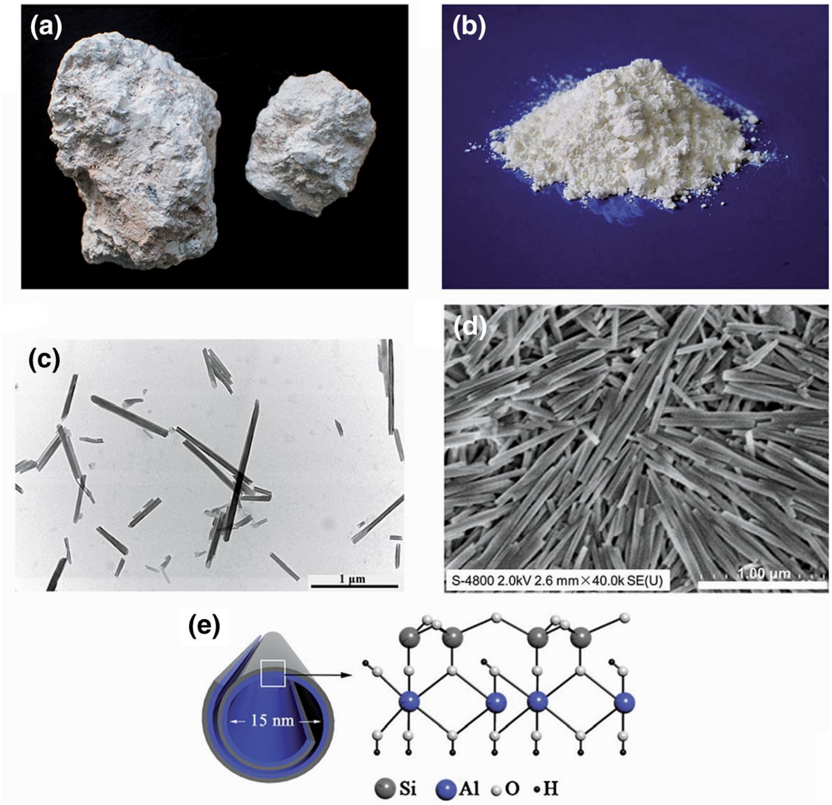


Fig. 2 **a** The raw halloysite and **b** ground halloysite; **c** TEM and **d** SEM photos of HNTs mined from Hunan Province, China; **e** schematic illustration of the crystalline structure of HNTs. Reproduced from (Liu et al. 2014) and (Yah et al. 2012) with permission from Elsevier and American Chemical Society

3–5 µm, but in the size distribution curve, they have a minor fraction. However, these shorter tubes are the most attractive from a biological point of view, since they are more suitable for composites with sustained delivery of chemicals and drug formulations with regards to the longer ones.

The main advantage of HNTs in comparison with other nanoparticles is its biocompatibility. So far, several studies present in the literature have shown that HNTs are not toxic materials both for living organism and plants (Fakhrullina et al. 2015; Lazzara et al. 2018). Halloysite is efficiently removed from organisms by macrophages. The toxicity of HNT was tested both in vitro and in vivo experiments. For example, in fibroblast and human breast cells, no toxicity was observed after 48 h of incubation (Vergaro et al. 2010); in addition, it may penetrate into the cell membranes disposing around the nucleus. It is important to highlight that in the human body are not present the biological mechanisms for the aluminosilicate degradation and intravenous injections cause thrombosis, so HNTs could be mainly used for oral administration or for the development of creams, implants which can afford a slow release of the loaded drugs for external medical treatment.

The oral toxicity of halloysite was also investigated by Wang et al. (2018) who studied the hepatic toxicity of purified halloysite in mice via oral route. It was found that the oral administration of halloysite stimulated the growth of the mice at low dose [5 mg kg^{-1} per body weight (BW)]. They showed that HNTs' toxicity is due to aluminum accumulation that induces oxidative stress as a consequence of hepatic dysfunction and histopathological abnormalities. Thus, this study highlights that the oral administration of halloysite should be controlled ensuring the oral administration limit at ca. 20 mg kg^{-1} BW.

Since plant membranes are very similar to the cellular ones, comparable results are found in phytotoxicity studies.

In this context, a study on *Raphanus Sativus* L has demonstrated that halloysite possesses positive effect on growth of seeds, showing no phytotoxic effects even at concentration of 1500 mg L^{-1} (Bellani et al. 2016). Furthermore, the analysis of chromosomal aberrations on root tips of low-vigor seeds revealed mild genotoxic effects, suggesting a sensitive and quantitative risk assessment model for analyses of the effects of novel NPs' conjugates on plant life.

2 Pristine halloysite nanotubes: nanocontainers for organic compounds

The presence of a positively charged HNT lumen makes that halloysite can be used mainly as nanocontainer for different compounds, which show a very low aqueous solubility, which benefit in terms of stability and protection.

The loading of compounds on halloysite lumen is mainly based on the electrostatic interactions between negatively charged molecules and the positive aluminum surface or hydrophobic effects in an aqueous regime.

It was demonstrated that the positive halloysite cavity is suitable to encapsulate chemically and biologically active molecules with a negative electron density such as isoniazid (Carazo et al. 2017), vancomycin (Kurczewska et al. 2017), norfloxacin (Fizir et al. 2017), salicylic acid (Aguzzi et al. 2013; Ghezzi et al. 2017), bovine serum albumin, α lactalbumin, and β-lactoglobulin (Duce et al. 2017). Pioneering work of Price et al. (2001) showed that halloysite cavity is efficient in the entrapment and controlled release of tetracycline HCl (a water soluble antibiotic), khellin (a lipophilic vasodilator), and nicotinamide adenine dinucleotide (a co-enzyme). Insulin was loaded on both HNT surfaces by maximizing the electrostatic interaction between the protein and the differently charged clay surfaces (Massaro et al. 2018b). The loading of insulin into HNT led to the synthesis of an efficient nanocarrier which allows a prolonged and sustained release of the protein over 7 days. Noteworthy, dichroism circular experiments highlight that the protein is released from the carrier in its native form.

3 HNT as filler for polymeric matrices

Halloysite nanotubes possess interisting features such as low cost, biocompatibility, environmental-friendliness and availability in terms of tons, high aspect ratio (lenght/diameter) (from 8 to 50) (Pasbakhsh and Churchman 2015), which increases filler-polymer interactions; therefore they represent a valuable inexpensive alternative to the most known carbon nanotubes and to silicate fillers for application in the polymeric field as reinforcing agents.

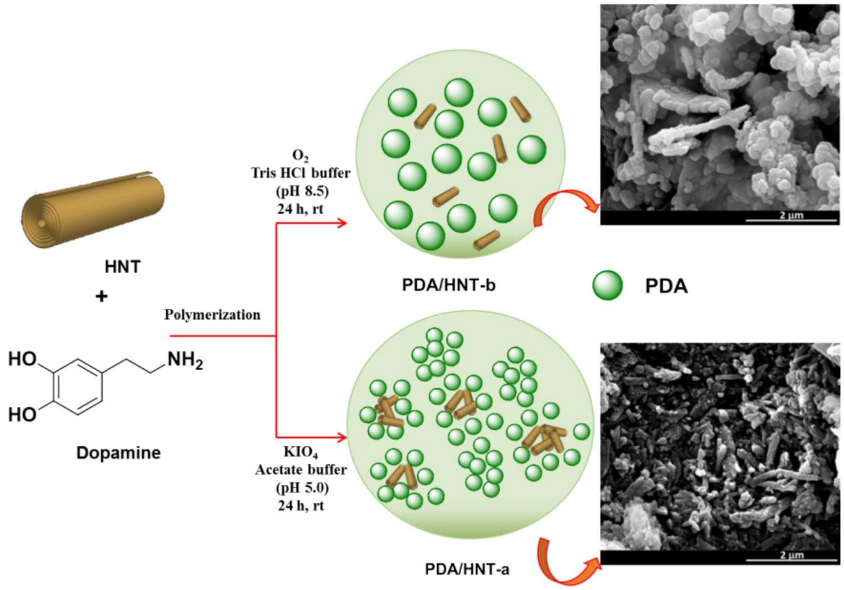
The introduction of HNTs in a polymeric matrix, indeed, causes an increase in the physico-chemical properties of the polymer leading an enhancement of its thermal and mechanical performance. Furthermore, due to the presence of an empty lumen, it is possible to load on HNTs chemically and biologically active substances, which can be introduced in polymer application-specific chemical inhibitors (antimicrobial, anticorrosion, flame-retardant, drugs, and microcrack self-healing).

In the years, several nanocomposites have been obtained using HNTs as filler for different kind of polymeric matrices (Palantöken et al. 2015; Xue et al. 2015).

Polydopamine (PDA) is a highly adhesive mussel-inspired eumelanin-type polymer widely used to form hydrophilic coatings for substrate-independent surface functionalization. Due its properties, PDA has found applications in several fields, from the material science to biology. Although several studies are focused on the development of PDA polymers with enhanced properties, there is still the need to found eco-compatible and low-cost strategies to manipulate them. Recently, HNTs were used as filler for PDA to obtain a novel nanocomposite with both thermal stability and adsorption capability towards organic pollutants compared to pristine PDA. PDA/HNT nanocomposites were obtained both under alkaline and acidic oxidation conditions, and were characterized from a physico-chemical point of view (Massaro et al. 2019a). Depending on the oxidation conditions, HNTs can interact in different way with the PDA; in particular at pH 8.5, the HNTs appear to be uniformly dispersed in the PDA matrix, looking as tubes covered by PDA, whereas in acidic medium, they seem to be more aggregated and wrapped by the polymer (Fig. 3).

Recently, it has been developed a novel carrier system based on HNT as filler for LAPONITE® (Lap) hydrogel, for the potential intraarticular delivery of kartogenin (KGN) (Massaro et al. 2019c). The introduction of halloysite filler, in Lap hydrogel, helps the gel formation with an improvement of the rheological properties as a consequence of electrostatic interactions between the negative HNT outer

Fig. 3 Schematic representation of the synthesis of PDA/HNT nanocomposites



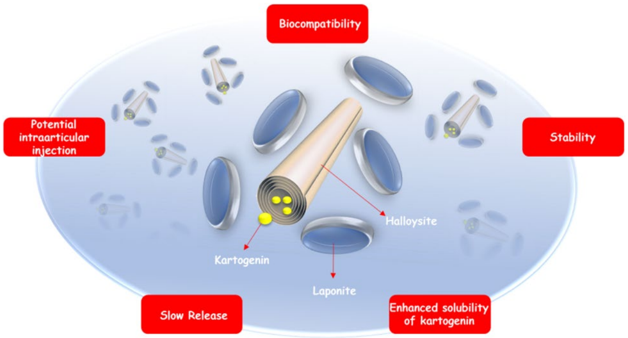


Fig. 4 HNT/KGN/Lap hydrogel for intraarticular injections. Reproduced from (Massaro et al. 2019c) with permission from American Chemical Society

surface and the Lap edge, which possesses a positive charge. The efficacy of HNT/Lap hydrogel as a carrier for KGN was proved by in vitro release experiments performed at pH 7.4 and in ex vivo synovial fluid at 37 °C, to simulate both the physiological conditions and the joint environment, respectively. The two components of the hybrid hydrogel system HNT/Lap act in a complementary way: the Lap acts as an inert carrier, since the gel matrix is dissolved in a physiological medium after 24 h and thus does not affect the KGN release; on the contrary, a sustained release of the drug was observed from HNT (Fig. 4). It was found that KGN has a slower release in synovial fluid than that of phosphate buffer at pH 7.4.

From a biological point of view, the most common developed bionanocomposite are that constituted by biopolymers and HNT (Lazzara et al. 2017a). For example, bionanocomposite films based on chitosan and pristine HNT were successful used for horseradish peroxidase (HRP) trapping to promote the direct electrochemistry of HRP and catalyze the reduction of H_2O_2 (Sun et al. 2010).

Ad hoc designed organic molecules, able to interact selectively with HNT lumen and to each other through suitable terminal groups, were used to develop an organic/inorganic hybrid filler for chitosan and hydroxypropyl cellulose biopolymers (Arcudi et al. 2014). The HNT lumen functionalization causes the formation of fibers and clusters in the micrometer range which are responsible of the enhancement of mechanical and thermal properties of both polymers.

A similar approach was exploited for the loading on both HNT surfaces, cucurbit[6]uril (CB[6] and cucurbit[8]uril (CB[8]) molecules (Biddeci et al. 2016; Massaro et al. 2016c). In this way, there were synthetized some nanosponges which can interact with different molecules for several purposes. The HNT/CB[6] nanomaterial was used for the loading of peppermint essential oil (PO) and used as filler for pectin for food packaging applications. The addition of the hybrid filler enhanced both the mechanical performances and the surface hydrophobicity of the pectin based film, while the thermal behavior is slightly affected. Both the kinetics and the extent of PO released into the simulant food solvent (50% v/v ethanol) are thermo-sensitive. Interestingly, the bionanocomposite film preserves a large amount of the incorporated active agent at refrigerated as well as room temperature. In addition, the film maintains relevant mechanical performance even after 120 h of exposure to the food simulant solvent (Biddeci et al. 2016). The bionanocomposite film showed a reliable antioxidant activity as evidenced by the large inhibition percentage (41%) of the free radical DPPH. As concerns the antimicrobial properties, in vitro experiments for *E. coli* and *S. aureus* isolated from food sources revealed that the composite biofilm is more efficient at higher temperatures confirming the PO release data.

On the contrary, HNT/CB[8] hybrid was used for remediation purposes, in particular for the hydrocarbon removal; for example, toluene (both in vapor and aqueous phases) and pyrene (Massaro et al. 2016c).

4 Covalent functionalization

The external HNT surface, constituted by siloxane groups with the presence of some structural defects in the form of silanol groups, is well suited for the grafting of organosilane to develop HNT hybrids covalently modified. Due to this, it can be envisaged both an expanding of the application field and the overcoming of the drawbacks often associated with the supramolecular linkage of compounds on HNT, first of all the weak interactions involved in the assembly of HNT/molecules hybrids (Aguzzi et al. 2007; Tan et al. 2014).

Among the different organosilane molecules which can be used to achieve the above objectives, the most used one is the 3-aminopropyltriethoxysilane (APTES). The presence of the amino group on the external surface of HNT was helpful in the increasing the performances of HNT with respect to pristine one.

Similarly, owing the strong interactions existing among amino groups and heavy metal ions, the APTES functionalized HNTs were widely used for wastewater treatments. In this context, Cataldo et al. reported the use of amino-functionalized halloysite for the removal of Pb^{2+} ions. They found that the adsorption ability of amino-functionalized HNT-NH_2 towards Pb^{2+} was considerable higher than that of p-HNT in the same experimental conditions and that the obtained nanomaterial showed a noticeable reuse capability (Cataldo et al. 2018).

Going further, the amino groups present on the HNT external surface can be exploited to attach polymers or small organic moieties on HNT by amide condensation mediated by DCC. In this context, several strategies have been proposed, to obtain nanocomposite with different features.

The introduction of polymers on halloysite was an easy strategy to modulate HNT properties depending on external stimuli. For example, by the covalent linkage of a thermo-responsive polymer, such as poly-(*N*-isopropylacrylamide) (PNIPAAM) (Cavallaro et al. 2015), which shows a low critical solution temperature (LCST) around 32 °C, after which the polymer brushes collapse on the HNT surface; it is possible to achieve a targeted release of a drug by changing temperature or catalytic systems with improved performances (Massaro et al. 2016e).

Recently, we proposed a similar system where two different curcumin species or curcumin and doxorubicin were simultaneously delivered and released for the treatment of breast cancer and acute myeloid leukemia (Massaro et al. 2020). The obtained results have showed that the cytotoxicity effects of the hybrids synthetized in this work are strictly correlated both to the nanoparticles size and to the release profile of the drug supramolecularly loaded on Hal surfaces (Fig. 5). The combination of the drugs allows us to obtain novel systems which possess enhanced antiproliferative activities even on multidrug-resistant cancer cells.

The amino-functionalized HNT serves as scaffold to introduce by covalent grafting, tartaric acid on the HNT external surface, which was used as carbon source to obtain highly fluorescent carbon dots by means of a microwave mediated pyrolysis in the presence of ethylene diamine as passivant agent (Fig. 6) (Massaro et al. 2018e). The obtained

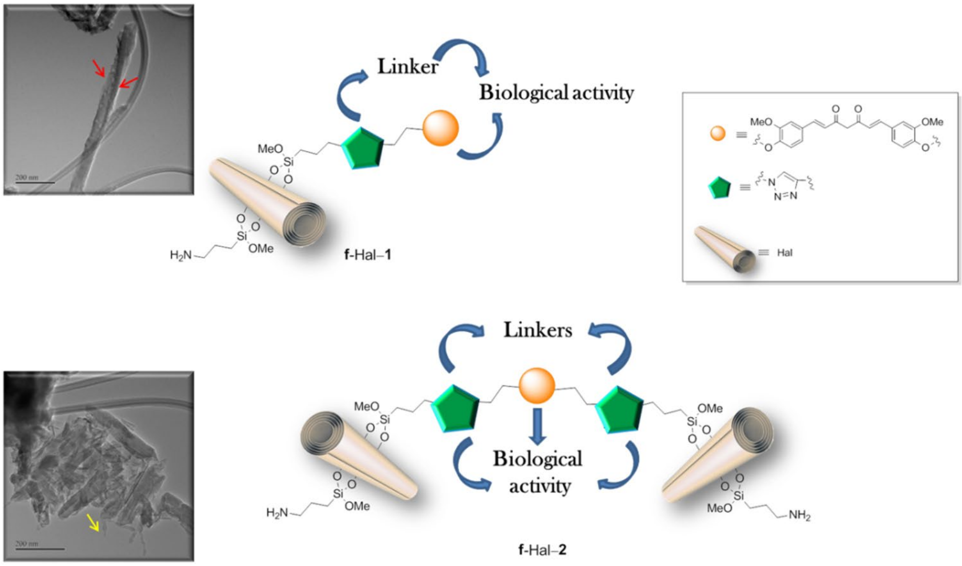


Fig. 5 Schematic representation of the halloysite–curcumin hybrid materials. Reproduced from (Massaro et al. 2020) with permission from Elsevier

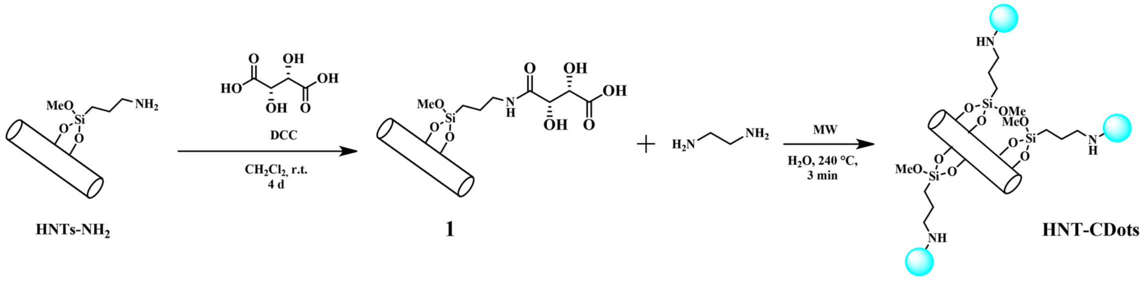


Fig. 6 Synthesis of fluorescent halloysite nanotubes

nanomaterials possess the peculiarity of both halloysite and carbon nanodots. In particular, it was demonstrated that the aqueous dispersion of halloysite hybrids showed a broad and bright visible light emission under UV illumination.

The HNT-CDots hybrid was used as non-viral vector for gene delivery (Massaro et al. 2019b). To achieve this aim, the interaction of the hybrid with calf thymus DNA, chosen as model, was investigated by means of fluorescence spectroscopy and circular dichroism. All investigations performed showed that the obtained HNT-CDots hybrid could be considered a multi-functional cationic non-viral vector, since, besides the potential gene delivery capacity, it has shown by tunable fluorescence studies intracellular tracking of the delivered molecules and promising in vitro antioxidant performances.

Another versatile functional group which can be grafted on HNT surface is the azido one. This allows to synthetize pH-sensitive HNT–triazolium salt carrier (HNT-triazo) (Massaro et al. 2015a; Riela et al. 2014) by means of a Cu-mediated Huisgen reaction. The obtained nanomaterials showed promising applications both in the drug carrier field and in catalysis (Massaro et al. 2015c).

As far as is regarding the biological utilization, the HNT–triazo hybrids were successful employed for the delivery of cardanol and curcumin (Massaro et al. 2015a; Riela et al. 2014). Due to the presence of the triazole moieties, known for their interesting biological properties, it has been overcame the low aqueous solubility of the biologically active molecules and it has been enhanced their cytotoxicity towards different cell lines.

The covalent linkage of ionic liquids on HNT opens up the possibility to obtain several supported for metal nanoparticles. In this context, imidazolium salts functionalized halloysite were employed for the immobilization of Pd nanoparticles and tested as catalyst in C–C cross-coupling reactions (Suzuki, Sonogashira, and Heck reactions) (Massaro et al. 2014a, b, 2018d). Also in this case, the functionalized halloysite showed enhanced catalytic performances if compared to other inorganic solid supports.

Since halloysite present an empty cavity, the functionalized HNTs can be further functionalized by loading on functionalized HNT other molecules with complementary properties.

Starting from the APTES-HNT, we have introduced on the external HNT surface, an antioxidant molecule, namely trolox, by means of amide bond. To enhance the antioxidant properties of the synthetized hybrid, a co-antioxidant (quercetin) was loaded into the lumen (Massaro et al. 2016d).

A similar approach was used to link on HNT an amino-acid functionality, the Fmoc-phenylalanine, to obtain an hybrid filler which can be easily dispersed in an Fmoc-Phe hydrogel (Rizzo et al. 2017).

The obtained material was employed as carrier system for camptothecin. The experimental results highlight that the functionalized HNT can release the drug in its active form, preventing the hydrolysis of the lactone ring.

Conversely, thiol functionalized HNT was used for immobilization of gold nanoparticles. The hybrid obtained was tested as catalyst in the p-nitrophenol reduction showing excellent catalytic performances reaching remarkable TOF values (up to 2,204,530 h^{-1}). Due to its high catalytic activity and recyclability, the HNT-SH@Au system was also used as stationary phase in a chromatographic column to obtain a packed continuous-flow reactor for industrial applications (Massaro et al. 2019d).

Halloysite prodrug systems were obtained by grafting on the thiol functionalized halloysite, the cysteamine molecule, by means of a disulphide linkage (Massaro et al. 2016a). Afterwards, curcumin molecules were chemically conjugated to the amino end groups of halloysite via Schiff's base formation. The so-obtained system showed both a pH and redox stimuli responsive linkage which can envisage some interesting application in the biomedical field.

The thiol groups linked on HNT external surface are interesting starting point for the development of more complex HNT hybrid with two or more cavities (Fig. 7). In the years, to achieve this goal, several cyclodextrin derivatives (CD) were covalently linked to HNT by means of a thiol-ene reaction between the SH functionality and some allyl groups.

These systems were used for the delivery of a single drug, such as clotrimazole (Massaro et al. 2018a) and curcumin

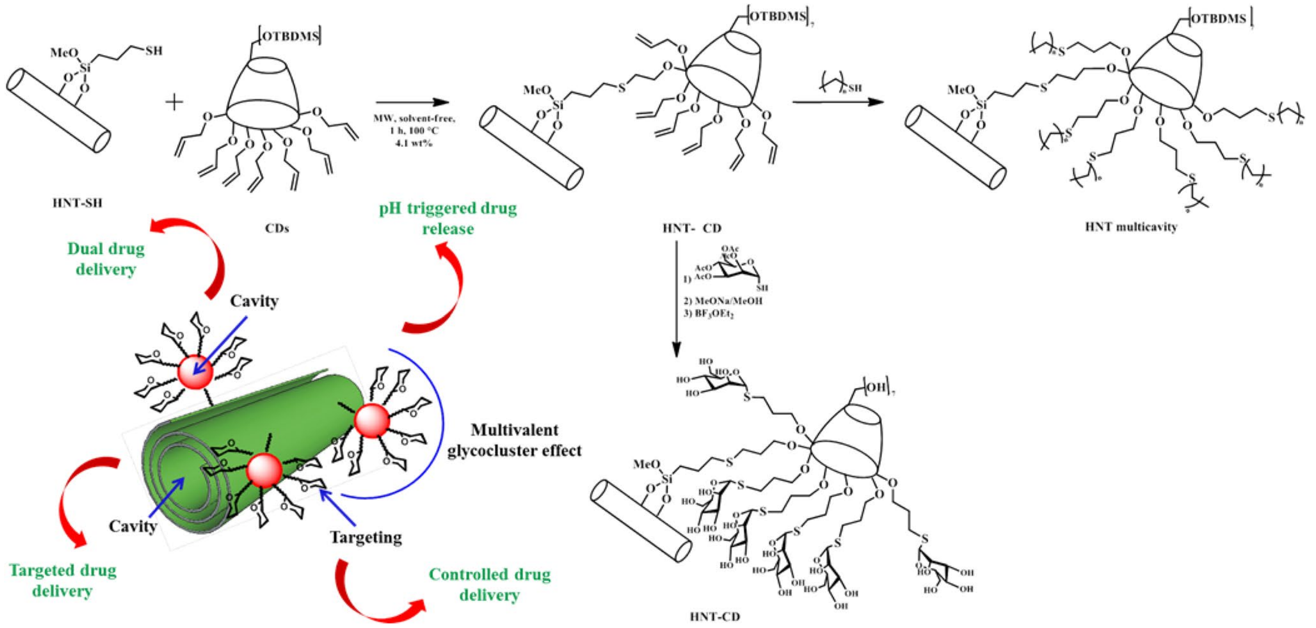


Fig. 7 Schematic representation of the different HNT-CD multicavity systems. Reproduced from (Massaro et al. 2016b) with permission from The Royal Society of Chemistry

(Massaro and Riela 2018; Massaro et al. 2014c), or for the co-delivery of two different molecules with synergistic effects for cancer treatment (Massaro et al. 2015b). Moreover, the CD core allows the introduction of some sugars moieties, obtaining halloysite glycocluster hybrids with enhanced cellular uptake (Massaro et al. 2016b).

By mixing the thiol functionalized halloysite with different molar ration of allyl cyclodextrin it was synthetized a halloysite nanosponge with a hyper-reticulated network (Fig. 8a) (Massaro et al. 2017).

The nanomaterial so-obtained has shown promising activity as organic dye removal for environmental purposes.

The feasibility of the material as a decontaminant of wastewater was investigated by studying its adsorption capacity toward an organic dye, Rhodamine B. Adsorption experiments evidenced that the adsorption capacity is strictly influenced by the pH of the medium, and the presence of cyclodextrin in the hybrid enhances the adsorption ability of halloysite. The performance of the hybrid nanosponge was also evaluated toward different cationic and anionic dyes, and the obtained results showed that HNT-CDs nanosponge hybrids are good nanoadsorbents for selective adsorption of cationic dyes with respect to the anionic ones in a wide pH range (Fig. 8b).

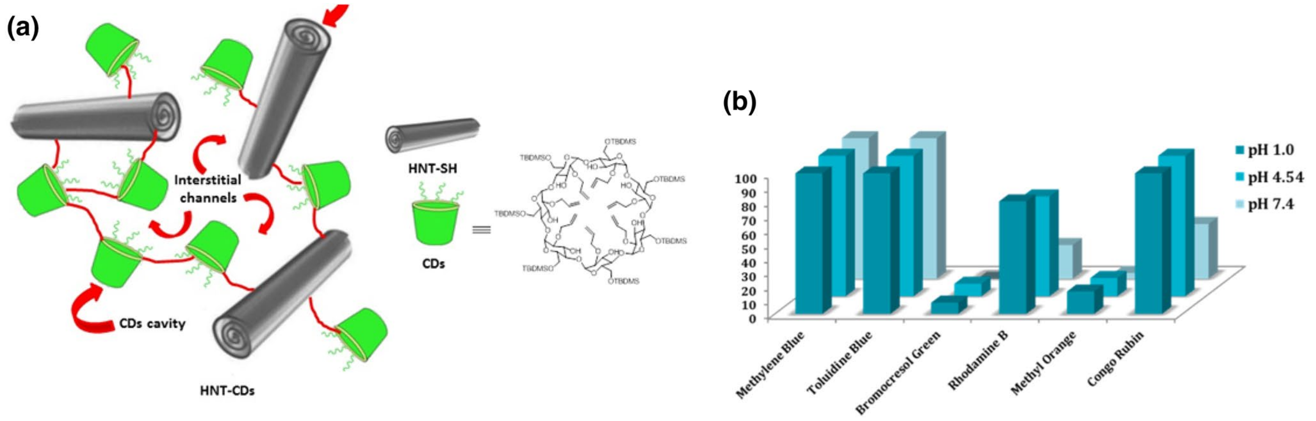


Fig. 8 **a** Cartoon representation of the HNT-CD nanosponge; **b** adsorption efficient of the obtained nanosponge towards different organic dyes in three different pH media. Reproduced from (Massaro et al. 2017) with permission from American Chemical Society

5 Conclusions

In conclusion, halloysite nanotubes are a versatile material that possesses several advantages over other kinds of nanoparticles. This aspect is testified by the growing interest on this research as shown by the number of patents and publications of the last few years.

Among the different uses of HNTs, in our opinion, the most interesting one is the development of smart drug carrier and delivery systems. Halloysite used as carrier for biologically active molecules, indeed, could have an advantage due to the biocompatibility, low cost, and natural resources of the material and the simple methods used to prepare dosage forms. These characteristics should allow for quick industrial scale-up. The goal should be to increase the use of halloysite clay nanotubes in biomedical treatment suitable for different routes of administration.

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