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Halloysite nanotubes as a new drug-delivery system: a review

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ABSTRACT: New drug-delivery systems have remained a challenge for pharmaceutical scientists due to the use of expensive polymers and the low loading capacity of prepared nanoparticles. There is pressure to develop formulations that contain not only cheaper materials but also have controlled-release properties. Halloysite nanotubes (HNTs) are a naturally occurring clay mineral similar to kaolin, possessing a special particle shape in the form of an ultramicroscopic multilayered hollow cylinder. Its uses encompass a wide range in anticancer therapy, sustained- and controlled-release drug-delivery systems, cosmetics, delivery of proteins, vaccines and genes. These advantages are due to its biocompatibility, significant mechanical strength and natural availability. The surfaces of the tubules can be modified by coating different polymers for application in the drug-delivery system. This review is focused on the various aspects of HNTs such as structure, properties, loading methods, applications and characterizations.

KEYWORDS: halloysite nanotubes, drug-delivery carrier, vacuum method.

The name 'halloysite' is derived from that of Omalius d'Halloy – the mineral was named in his honour by Berthier who discovered the mineral in Angleur, Liege, Belgium and the name was first used in 1882 (MacEwan, 1947). Halloysite nanotubes occur naturally in weathered rocks and soils of wet tropical and subtropical regions and particularly those from volcanic ash and tephra in a range of climates and can also be formed through hydrothermal alteration of various types of rocks (Robertson, 1955). Natural deposits of HNTs are found in New Zealand, China, Korea, Japan, USA, Brazil, Turkey and France. A number of companies in the USA, New Zealand, China and Turkey provide thousands of tons of halloysite. Halloysite nanotubes are naturally occurring aluminosilicate clay minerals which have the empirical formula $Al_2Si_2O_5(OH)_4nH_2O$. Halloysite nanotubes have the same chemical structure as kaolinite but physically have a single layer of water molecules which distinguishes halloysite from kaolinite. A HNT consists of the four main constituents of Al, Si, O and H. Based on crystalline and geographical conditions, particles of halloysite can adopt a variety of morphologies including short tubular, spheroidal, fibrous, onion-like, prismatic, rolled, crinkly, walnut-meat like, cylindrical, spherulitic, irregular laths with rolled edges, crumpled lamellar, scrolls and platy. However, a hollow elongated tubular shape is most common (Levis & Deasy, 2002; Joussein *et al.*, 2005; Lvov *et al.*, 2014; Yuan *et al.*, 2015).

Halloysite nanotubes are classified into two groups on the basis of hydration. One group is hydrated HNTs with a crystalline structure of 10 Å d_{001} spacing and the second group is dehydrated HNTs with 7 Å d_{001}

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spacing. Upon dehydration, the d_{001} spacing of halloysite nanotubes changes from 10 to 7 Å and this change is irreversible. Sometimes, the dehydrated state is referred as 'meta-halloysite'. Halloysite consists of two types of hydroxyl groups: inner and outer hydroxyl groups. Inner hydroxyl groups are located between the layers and outer hydroxyl groups are located on the surface of HNTs. Surface hydroxyl groups of HNTs have a low density compared to other silicates (Brigatti *et al.*, 2006; Du *et al.*, 2010). Some authors have claimed that HNTs have a two-layered structure (Veerabadran *et al.*, 2009). The outer surface of halloysite is composed of a tetrahedral (SiO_2) sheet with a negative charge under most natural pH conditions and the inner core or lumen is composed of an octahedral ($Al(OH)_3$) sheet with a positive charge under these conditions. The different inner/outer surface chemistries are suitable for encapsulation of negatively charged molecules inside the nanotubes at low pH. This chemistry also allows the selective modification of halloysite (Veerabadran *et al.*, 2009; Abdullayev & Lvov, 2011). Halloysite cylindrical tubes are tiny, with varying diameter and length depending on the deposits. The outer diameter varies from 50 to 100 nm, the internal diameter of the lumen ranges from 10 to 50 nm, while the length of the tubules ranges from 1 to 2 μm. Halloysite is found in a white colour in its pure form but sometimes traces of transition metal ions are present as impurities which replace the Si and Al atoms and give rise to different colours varying from yellowish to brown and sometimes to green. The most common impurity is Fe oxide while other traces are Fe^{3+}, Cr^{3+}, Ti^{4+}, *etc*. These impurities also affect the layer rolling of halloysite (Shchukin *et al.*, 2005; Abdullayev & Lvov, 2010, 2011).

Because of its special properties as a drug carrier, halloysite has been doped with many drugs (Price *et al.*, 2001), antiseptics (Wei *et al.*, 2014), proteins (Singh *et al.*, 2013) and enzymes (Zhai *et al.*, 2010). The pioneering work of loading drugs into halloysite was done by Price, Gaber and Lvov by encapsulating in HNTs oxytetracycline dihydrochloride, khellin and nicotinamide adenine dineculotide, and the release of these compounds from HNTs has been studied (Price *et al.*, 2001). Since that 2001 study, many researchers have evaluated HNTs as carriers for others drugs such as diltiazem HCL and propranolol HCL due to its biocompatible and non-biodegradable nature. Because of its non-biodegradability, it cannot be injected intravenously. Assessment of the biocompatibility of HNTs is a key requirement for the employment of halloysite as a biomaterial in clinical applications. The biocompatibility of halloysite was shown by Kommireddy *et al.* (2006) in cell-growth experiments (Levis & Deasy, 2003; Kommireddy *et al.*, 2006; Abdullayev & Lvov, 2011; Lvov & Abdullayev, 2013). Vergaro and co-workers also showed that halloysite is non-toxic up to concentrations of 75 μg/mL by using various cell cultures (Vergaro *et al.*, 2010).

The present review highlights previous research on halloysite as a drug-delivery system. After a brief introduction to the characteristics of halloysite which make it suitable for use in drug delivery and describing the characterization and methods for loading of drugs into HNTs, the review describes their applications in different fields as drug-carrying vehicles.

CHARACTERISTICS OF HNTs AS DRUG CARRIERS

Halloysite nanotubes are used widely as drug-carrying vehicles in drug-delivery systems due to their unique characteristics as a natural, non-toxic and biocompatible material (Vergaro *et al.*, 2008, 2010; Chiriaco *et al.*, 2014). The fine particle size, large surface area and good dispersion have made HNTs convenient for use in the controlled delivery of active agents (Kamble *et al.*, 2012). The large cation exchange capacity (Cornejo-Garrido *et al.*, 2012) and protection of the encapsulated drug, within the lumen, from the external environment due to a high mechanical strength have made HNTs suitable for the delivery of both lipophilic and hydrophobic drugs (Price *et al.*, 2001). Many other properties such as the chemical and physical nature, prolonged release time, increased duration of action and the need for reduced frequency of administration gave them unique properties. Relatively high loading capacities compared to other carriers, high aspect ratios, high porosity and their non-swelling nature, regeneration ability and high efficiencies of HNTs are also reported in previous literature (*e.g.* Kamble *et al.*, 2012). Halloysite also exhibits anti-inflammatory and anti-bacterial activities (Cornejo-Garrido *et al.*, 2012; Cervini-Silva *et al.*, 2013).

METHODS FOR LOADING DRUGS IN HNTs

Due to different inner and outer-surface chemistries of halloysite nanotubes, a wide variety of substances can be loaded. These substances may interact with halloysite nanotubes by various mechanisms including adsorption, intercalation and tubular entrapment.

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Adsorption

In this process, the drug (adsorbate solute) and halloysite nanotubes (solid sorbate) are mixed by stirring for almost 30 h. This period of mixing is sufficient to make sure that equilibrium has been attained between the drug adsorbate and the drug in solution. The adsorbate (drug-loaded halloysite) is obtained by filtration and dried in an oven at ~50°C. This equilibrium absorption process is usually illustrated through an isotherm (Aguzzi *et al.*, 2013). Adsorption of cationic surfactant from solution onto the solid surface of layered clay minerals (halloysite and kaolinite) occurs following the Langmuir isotherm, demonstrated by Lee & Kim (2002). In another study, Krejčová *et al.* (2012), by applying the same procedure, showed adsorption of diclofenac sodium by halloysite. In that case, the theory of Langmuir sorption is not always satisfied completely, principally when a minimum concentration of drug solution is used. The binding curve of diclofenac sodium has shown an unusual shape demonstrating that multilayer adsorption or two different concentration-dependent adsorptions take place (Krejčová *et al.*, 2012).

Intercalation

Halloysite nanotubes can intercalate a number of organic and inorganic substances in the interlayer spaces. In this process, molecules enter the interlayer space and cause expansion of these layers. This expansion increases the d_{001} spacing between the layers. Compounds that consist of -OH or -NH_2 groups, *e.g.* glycerol, have a tendency to intercalate with HNTs. In a recent study, Krejčová *et al.* (2012) demonstrated that dehydrated halloysite does not show an intercalation reaction. The phenomenon of intercalation is associated with the presence of interlayer water molecules. Water molecules between halloysite wall layers must be present for intercalation to occur (Krejčová *et al.*, 2012; Lvov& Abdullayev, 2013).

Tubular entrapment (vacuum method)

Tubular entrapment is known as the vacuum method and this method was introduced by Kelly *et al.* (2004). It can be performed in two ways (methods 1 and 2) and is the most important and most widely used method for loading of HNTs (Levis & Deasy, 2003; Kelly *et al.*, 2004; Ward *et al.*, 2010). Method 1 uses an excess of drug solution, which is blended with ground, sieved and dried HNTs. Then vacuum is applied to the suspension and, after the appearance of bubbles on the surface of the suspension indicates that occupied air inside the lumen of individual HNTs has been removed from tubes, the vacuum is released and the air is replaced by drug solution. This process is repeated at least two to three times to fill the tubes with drug solution completely. After the vacuum cycle is completed, the mixture is centrifuged, decanted and HNTs are dried within the vacuum. Method 2 also uses drug solution but not in excess and it is mixed with HNTs in equal portions by weight. The resultant mixture is a thick paste, not dispersion. The mixture is again placed inside the vacuum and atmospheric pressure restored. Once again, this process is repeated two to three times. The mixture is dried directly inside the vacuum. The advantages of the second method is that no wastage of drug or drug solution takes place and the amount of drug which is added to HNTs can be determined directly without analysis of the supernatant (Price *et al.*, 2001; Levis & Deasy, 2003; Kelly *et al.*, 2004; Tan *et al.*, 2014).

USE OF HNTs AS A DRUG-DELIVERY VEHICLE

Drug-loaded HNTs have been developing as new drug carriers in drug-delivery systems (Table 1) due to easy availability, low toxicity, biocompatibility and their hollow tubular structure. Halloysite nanotubes therefore have great potential for use in this field.

Halloysite nanotubes used in anti-cancer therapy

A micro-scale flow device which captures the circulating tumor cells (CTCs) from the patient's blood is used in cancer treatment. A microtube is functionalized internally with HNTs which enhance its performance in capturing and killing cancer cells (Hughes & King, 2010; Hughes *et al.*, 2012; Mitchell *et al.*, 2012; Dong *et al.*, 2013). Halloysite nanotubes also have potential for use as ultrasound contrast agents for clinical echo graphic imaging (Soloperto *et al.*, 2013; Di Paola *et al.*, 2014). Lack of specificity in terms of neoplastic tissues and selectivity in terms of the mechanism of the action, a low therapeutic index, molecular weight and solubility, a significant tendency towards degradation and strong chemoresistance are some limitations of current chemotherapy which can be overcome by using engineered nanocarriers (Vergaro *et al.*, 2011).

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Table 1. HNTs with different carriers used for drug loading.

Class of drug	Carrier + carrier modifier	Loading method
NSAIDs		
5-Amino salicylic acid	HNTs	Adsorption
5-Amino salicylic acid	HNTs + Starch, plasticizer	Vacuum
Diclofenac	HNTs	Vacuum
Diclofenac Sodium	HNTs + APTEs, BiBB, PMDAEMA	Adsorption
Ibuprofen	HNTs + 3-APT	Adsorption
Antimicrobials		
Metronidazole	HNTs + Polyprolactone-gelatin matrix	Vacuum
Tetracycline HCL	HNTs + PVA, PMMA	Vacuum
Tetracycline	HNTs + PLGA	Vacuum
Ofloxacin	HNTs + Chitosan, Fe_3O_4	Adsorption
Oxytetracycline HCL	HNTs + Epoxy Quitol 651	Vacuum
Anti-hypertensives		
Diltiazem HCL	HNTs + PVP, Glutaraldehyde,alkyl-2-cyanoacrylate, PEI, Poly-iso-butyl-cyanoacrylate	Vacuum in all cases
Propranolol HCL	HNTs + PVP, Glutaraldehyde, alkyl-2-cyanoacrylate, Polyethyleneimine, Poly-iso-butyl-cyanoacrylate	
Anti-cancer		
Resveratrol	HNTs + Polyelectrodes	Vacuum
Doxorubicin	HNTs + Folic acid with magnetite particles	Adsorption
Curcumin	HNTs + Triazolium salt	Vacuum
Methotrexate	HNTs	Adsorption
5-Forouracil	HNTs + Chitosan	Intercalation
Miscellaneous		
Brilliant Green	HNTs + Benzotriazole-Copper	Vacuum
Amoxicillin	HNTs	Vacuum
Fentanyl	HNTs + MCC	Adsorption
Dexamethasone	HNTs + PAH, PEI,PAA, PSS and Chitosan	Vacuum
Diphenhydramine HCL	HNTs + APTES, BiBB, PDMAEMA	Adsorption

In previous studies, resveratrol (a polyphenolic compound) has been loaded into HNTs and the effect of resveratrol on the growth of human breast-cancer cells examined. Its release time was 48 h. A functionalized halloysite with layer-by-layer (lbl) polyelectrode was loaded with resveratrol which killed the MCF-7 cells after degradation under physiological conditions. Halloysite nanotubes stabilize and protect resveratrol from degradation and enhance its bioavailability in biological systems which are limited due to its hydrophobic nature (Vergaro *et al.*, 2012; Aras *et al.*, 2014). A short half-life, rapid metabolism and incomplete absorption are some drawbacks of 5-florouracil (antimetabolite) in cancer treatment. Therefore, a controlled-release system developed by intercalation of 5-florouracil into clay may help in minimizing its drawbacks. The maximum plasma concentration was at a safe therapeutic level after 48 h of oral administration into rats. This reduces the risk of hepatotoxicity which can be developed due to plasma concentrations which are greater than tolerance levels (Chrzanowski *et al.*, 2013).

In another study, halloysite nanocomposite hydrogel was synthesized for the treatment of colon cancer. This pH-sensitive and time-dependent carrier prevented the exposure of 5-FU to the gastric region and avoided the systemic side effects; there was also a greater release of drug in the intestinal region and in a controlled manner

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over a 70 h period (Rao *et al.*, 2014). Halloysite nanotubes decorated with folic acid and magnetic particles were loaded with doxorubicin and cytotoxicity to HeLa cells was observed after pH-responsive release. The doxorubicin-loaded FA-Fe_3O_4@HNTs could be used for therapeutic purposes (Guo *et al.*, 2012).

HALLOYSITE NANOTUBES USED IN SUSTAINED AND CONTROLLED DRUG DELIVERY

Drug delivery systems which keep chemical agents for a long time and release them on demand in response to external signals are very attractive because of the healing effects which occur over a long period without an excess drug dose (Abdullayev & Lvov, 2011). Previous studies showed that naturally occurring halloysite nanotubes are good candidates for the sustained and controlled release of drugs (Price *et al.*, 2001; Levis & Deasy, 2003; Veerabadran *et al.*, 2007; Forsgren *et al.*, 2010; Yuan *et al.*, 2012; Tan *et al.*, 2013, 2014; Wang *et al.*, 2014; Hemmatpour *et al.*, 2015), antiseptics (Wei *et al.*, 2014), proteins (Lvov & Abdullayev, 2013), enzymes (Machado *et al.*, 2008; Zhai *et al.*, 2010) and anti-inflammatory drugs (Viseras *et al.*, 2008, 2009).

Entrapment and release of oxytetracycline HCL (a hydrophilic antibiotic), khellin (a lipophilic vasodilator) and nicotinamide dineculotide (NAD, a co-enzyme) from loaded halloysite has been carried out by Price *et al.* (2001). Release of oxytetracycline HCL from loaded halloysite was completed in 30 h while that of hydrophobic khellin was completed in 92 h. The NAD was released in 5 h. The Price *et al.* (2001) study showed that both hydrophilic and hydrophobic active agents may be entrapped in pre-treated halloysite. Veerabadran *et al.* (2007) demonstrated the sustained release of dexamethasone, furosemide and nifedipine from halloysite tubes at different pH ranges and alcohol/water ratios. The results showed that drug release from halloysite tubes was over a much longer period than that from the microcrystal. The nifedipine release time was 25 times longer from halloysite than from the crystal and in the case of furosemide and dexamethasone, 75 times longer (Veerabadran *et al.*, 2007). In one previous study, one highly water-soluble drug, diltiazem HCL and one less water-soluble drug, propranolol HCL was loaded in a biocomposite of halloysite, and both drugs showed a sustained release effect. Further delay of release rate can be achieved by applying layers of different polyionic polymers on halloysite (Levis & Deasy, 2003).

Sustained release of antiseptic brilliant green, a commonly used antiseptic, was achieved by loading into halloysite nanotubes. Surface coating of halloysite with benzotriazole copper provided increased loading efficiency of antiseptic and more sustained release from 50–200 h. Wei and co-workers used bacterial cultures to demonstrate the sustained release of brilliant green, amoxicillin and iodine from HNTs (Wei *et al.*, 2014). To reduce the risk of dose dumping and to avoid frequent dosing, a ceramic drug delivery vehicle was developed for oral administration of the highly potent opioid. A negative zeta potential of halloysite at pH > 2 facilitated the absorption of basic fentanyl base from the halloysite. Binding of the basic nitrogen atom of fentanyl with the de-protonated −OH group of the halloysite surface in the pH range 2.0–8.1 has been helpful for the sustained release of fentanyl. The release kinetics of intact and crushed pellets of fentanyl was studied. Intact pellets showed ∼3–4 h of sustained release while crushed pellets showed ∼2–3 h of sustained release of the drug (Forsgren *et al.*, 2010).

HNTs USED IN COSMETICS

Due to their elongated hollow tubular structure, HNTs have been attractive to many researchers from the cosmetics field for potential application in skin-care products. For cosmetics, various types of active agents such as glycerol as a moisturizing agent (Suh *et al.*, 2011), glycerin and vitamins (A, E, C) and fragrance (rose water) have been loaded in HNTs for daily use. These active agents can be used to improve skin elasticity, skin moisture and to maintain skin softness, smoothness, shininess and firmness, to treat wrinkles and age spots and to discontinue the signs of ageing. In addition to these active ingredients, any other active materials which improve or treat skin conditions can be loaded into halloysite nanotubes for use in cosmetic treatments (Suh *et al.*, 2011; Ghodke *et al.*, 2015). In its tubular shape, halloysite causes irritation to the skin. Halloysite nanotubes can be cut into the desired shape by applying high pressure to achieve microtubule halloysite nanopowder which is more suitable for cosmetic use (Suh *et al.*, 2013).

HNTs USED IN THE DELIVERY OF PROTEINS

Proteins are good candidates for use as therapeutics in various diseases. Proteins have some limitations such as large size, short half-life, susceptibility to enzymatic degradation, ion permeability, and immunogenicity,

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Table 2. Characterization and techniques used for identifications of halloysite nanotubes.

Characterization	Studied parameter	Technique (Used)
Physical	Surface morphology	TEM, SEM
	Size distribution	Dynamic light scattering
	Surface charge	Electrophoresis
	Electrical surface potential	Zeta potential analyzer
	Phase behaviour	DSC
	Entrapment efficiency (%)	Centrifugation
	Drug release (%)	Dissolution apparatus
Chemical	Elemental composition	X-ray photoelectron spectroscopy
Biological	Animal toxicity	Mouse fibroblast/osteoblast cell lines (ATCC)
	Human toxicity	Cervical adenocarcinoma (HeLa cells), breast cancer cells (MCF-7)

tendency to aggregate, adsorption, denaturation and uptake by the reticuloendothelial system due to their large size and accumulation in non-targeted organs. Moreover proteins have to cross many barriers to reach target sites. To overcome these disadvantages associated with protein drugs, nanocarriers are suitable for use as protein carriers. Proteins are encapsulated into ceramic carriers after changing their physiochemical properties by chemical modification (Singh *et al.*, 2013). Proteins have a large molecular size with a globular structure. 10–50 nm internal diameters of halloysite are suitable for encapsulation of proteins. Proteins have many functional groups which make bonds with the hydroxyl groups on the surface of halloysite so the release time of proteins from halloysite becomes longer. The release time of insulin from halloysite is 140 h. Negatively charged catalase and glucose oxidase have slow release as compared to positively charged haemoglobin due to the positively charged lumen of halloysite (Lvov & Abdullayev, 2013). Halloysite also provides thermal and storage stability to immobilized enzymes, urease and α-amylase, which retained their 90% enzymatic activity even after 15 days of storage (Zhai *et al.*, 2010). Similarly, enzyme-immobilized halloysite retained 80% of the catalytic activity of lipase compared to free lipase (Wang *et al.*, 2015).

HNTs USED IN THE DELIVERY OF VACCINES AND GENES

Halloysite nanotubes have been emerging as promising nanovehicles for delivery of vaccines and genes. Halloysite nanotubes with carboxyl functionalized multi-walled carbon nanotubes have undergone observation for the delivery of antigens to improve immune response against a recombinant LipL32 protein. Immunization using the HNTs and COOH-MWCNTs increased to a remarkable extent the rLipL32-specific IgG antibody titres of golden Syrian hamsters with leptospirosis disease (Hartwig *et al.*, 2015). Gene therapy is facing problems with use of viral vectors; in recent years, therefore, new non-viral gene carriers have attracted much attention. Zhang *et al.* (2010) studied HNTs as gene-delivery vehicles, in which antisense oligodeoxyneuclotide as therapeutic genes have been encapsulated in surface functionalized halloysite nanotubes for targeting survivin (an inhibitor of apoptosis protein) (Zhang *et al.*, 2010). Thus HNTs can be used as promising novel vectors for gene therapy application due to easy availability, biocompatibility, high mechanical strength and other structural benefits (Shi *et al.*, 2011).

CHARACTERIZATION OF HNTs

The formulation of HNTs and processing for any purpose are characterized to ensure their predictable *in vitro* and *in vivo* performance. The characterization parameters for the purpose of evaluation can be classified into three categories *i.e.* physical, chemical and biological parameters (Table 2).

CONCLUSIONS

Because HNTs are low-cost and found abundantly in nature, we can utilize simple and precise loading methods which are economical and affordable.

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Nowadays, HNTs are used as versatile carriers for the sustained and controlled delivery of drugs. With recent developments in this field, further work must be carried out to ensure the continued expansion and evaluation of halloysite products for drug delivery.

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