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ORIGINAL ARTICLE

Halloysite nanotubes and halloysite-based composites for biomedical applications

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Abstract Novel biomaterials for diagnostics and therapeutics of biomedical issues have been considered using biomedical science and health care. Halloysite nanotubes (HNTs) are naturally occurring aluminosilicate clay. Because of their unique hollow tubular structure, biodegradability, mechanical and surface properties, they have drawn the attention of researchers to a variety of biomedical applications. HNTs are inorganic natural aluminosilicates that are tubular-shaped and nanosized. These are well-known nanofillers and nanocontainers used to develop composites for various biomedical applications to load bioactive molecules and therapeutic agents. HNTs-polymer nanocomposites, their characterizations, properties, and applications in biomedical fields are all covered in this review paper. The current article provides an overview of HNTs and their

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applications in medical and biomedical settings, focusing on individualized HNTs and drug loading methods and biomedical applications, which may aid researchers in developing novel biomaterials for biomedical engineering and health care.

1. Introduction

Clay minerals are phyllosilicate minerals with unique microstructures that make chemical modification challenging. Furthermore, their mixture at the micro or nanometric scale can create attractive artificial nanocomposites for various applications from industry to biomedical engineering. The tubular structure of aluminosilicate halloysite is mostly hollow (Massaro et al., 2018; Massaro et al., 2021). Nanotechnology is an advanced research area with numerous applications in science and technology, and other fields. This field has a bright future ahead of it, with wide-ranging research done to expand the range of its applications. Tissue engineering, wound healing, and the sustained release of therapeutic agents are just a few nanotechnology applications in biomedical science (Khan et al., 2021c; Khan et al., 2020d; Ramos et al., 2017). Other significant applications include synthesizing nanomaterials to develop smart hydrogels, scaffolds, polymeric composite materials, etc. Many different nanomaterials can be synthesized from natural or synthetic occurring materials artificially via top-down and bottom-up techniques (Al-Arjan et al., 2020; Aslam Khan et al., 2020; Khan et al., 2021a). Halloysite nanotubes are nanomaterial with various functions that can be found in abundance in nature as mineral clay. These mesoporous tubular particulates have significant adsorption and loading capacities. These are made from geologically rolled alternative silica layers and alumina. The physicochemical properties of HNTs have thoroughly explained, demonstrating their potential applications from catalysis nanomedicine (Rashid et al., 2018; Satish et al., 2019).

Furthermore, as resources dwindle and the global climate deteriorates, a broader range of eco-friendly and environmentally friendly materials is required (Hu et al., 2020; Wu et al., 2017; Zahidah et al., 2017a). These materials, which include cellulose, lignin, and starch, have gradually replaced traditional petroleum-based materials. HNTs as fillers have become essential components in most synthetic elastomers. Structure nanofillers, size, specific surface area, and surface groups are important factors (Chen et al., 2019; Zahidah et al., 2017b). These variables impact the final mechanical properties and curing behavior of elastomer composites (Hu et al., 2020; Lazzara et al., 2018; Wu et al., 2017).

HNTs are naturally occurring and low-cost materials available abundantly in natural deposits. These are widely used as nanofillers and nanocontainers to sustain and control biomolecules, drugs, or bioactive substances (Abdullayev and Lvov, 2013; Kushwaha et al., 2021; Lvov and Abdullayev, 2013; Wu et al., 2019). The effectiveness of medication and therapy is significant in medical treatment, and healthcare and HNTs play a vital role in improving medicine and healthcare in biomedical applications (Danyliuk et al., 2020; Veerabadran et al., 2007). The nanosized, green, and inorganic nature of HNTs makes them different from many other materials. Nanocomposite materials and polymeric composites are synthesized from HNTs due to several available functional groups. These synthesized materials are antibacterial, biocompatible, nontoxic, hemocompatible, and sustained release of therapeutic agents in biomaterial engineering (Can et al., 2021; Cavallaro et al., 2018; Cavallaro et al., 2020; Gaaz et al., 2015). HNT has been used as nanocontainers for biomolecules and nanofillers in polymer composites because of their exceptional characteristics. Polymers are widely applied as composite matrices due to their wide range of compositions and forms, as well as their ease of fabrication (Aslam Khan et al.; Cavallaro et al., 2020; Hameed et al., 2015).

Moreover, polymer matrices could act as a reservoir for drugs. Thus, as the polymer degrades, the drugs can be released. Likewise, the polymers' low cost, soft, ductile, biodegradable, and biocompatible properties put it as the material of choice. As a result, HNT-based composites are becoming potential materials for advanced research to develop biomaterials such as drug delivery vehicles in nanomedicine. Its nanocomposites for implants and scaffolds, surgical instruments and fixtures, and therapeutic medications due to their outstanding properties. This review highlights the findings that can be used to determine the potential of HNTs in biomedical applications using various polymer matrices. This comprehensive article will discuss HNT for biomedical applications and its drug loading methods and focus on numerous studies of HNT polymer composites in medicine and health care delivery.

2. Halloysite nanotubes

These consist of a hollow tubular double-layer of aluminosilicate clay. It has a chemical formula, $Al_2Si_2O_5(OH)_4nH_2O$, with an outer diameter (50–80 nm), lumen diameter (10–15 nm), and length (1 μm). Halloysite was named after Omaliusd Halloy, the first person to discover the mineral in Belgium, and Berthier was the first to describe it in 1826 (MAcEwAN, 1947). These are economical, naturally abundant, and can be found in tens of thousands of tonnes in natural deposits. HNTs are chemically similar to kaolin, another clay mineral. The alumosilicate sheets in HNT are rolled into tubes, whereas platy particles dominate kaolin (Rawtani and Agrawal, 2012). HNTs have two key functional groups on external (Si-O-Si) and eternal (Al-OH) surfaces. These two functional groups have different surface charges and pH. The tubule lumen is positively charged with pH $\leq$ 8.5, and the outer shell is negatively charged with pH $\geq$ 1.5 (Bugatti et al., 2017). Negatively charged molecules such as Dexamethasone, Nifedipine, and Furosemide drugs can be explicitly loaded inside the lumen due to the charge difference on the surface. It prevents them from adhering to the tubules' negative outer surface (Veerabadran et al., 2007). HNTs are nanocontainers because of the different functional groups on their inner and outer surfaces. These nanocontainers can be used for loading bioactive molecules (including drugs and enzymes) into polymers for controlled release over time (Kamble et al., 2012; Price, 2001). Molecules can be loaded into HNT through various mechanisms, including adsorption, intercalation, and tubular entrapment (Abdullayev and Lvov, 2011; Lvov and Price, 2007; Shchukin et al., 2005). The structure and chemical composition of HNT has shown in Fig. 1.

3. Methods of loading molecules into halloysite nanotubes

3.1. Adsorption

A typical adsorption process involves stirring the drug and HNTs for nearly 24 h to ensure that the loaded and free drug

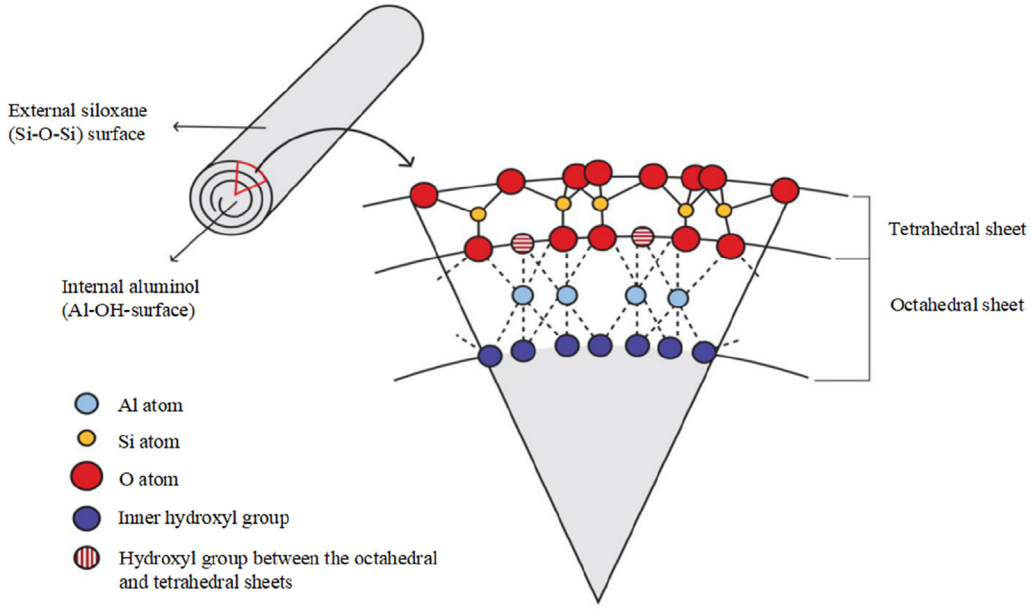

Fig. 1 Structure and chemical composition of HNT.

molecules are in thermodynamic equilibrium. Centrifugation and oven drying procedures are used to obtain drug-loaded halloysite (Guo et al., 2012; Lee and Kim, 2002). An isotherm is commonly used to depict the equilibrium absorption rate (Khalil et al., 2013; Viseras et al., 2009; Viseras et al., 2008). The loading drug (cationic drug) via adsorption phenomena over HNT and it obeys Langmuir isotherm (Lee and Kim, 2002; Zhang et al., 2009). Diclofenac sodium is a cationic drug and exhibited substantial adsorption over the polyionic mineral surface (Krejčová et al., 2013). On the other hand, the Langmuir adsorption theory is not always accurate, especially when using a low drug solution concentration. The binding curve for diclofenac sodium is unusually shaped, indicating that adsorption occurs in multiple layers of HNTs. Several experiments have been carried out to demonstrate the adsorption phenomena on the surface of HNTs. It works as a nano-adsorbent to treat waste water by adsorbing cationic pollutants (Luo et al., 2010; Zhao and Liu, 2008).

3.2. Intercalation

Since HNTs are interlayer material and can intercalated different bioactive molecules of organic/inorganic. These bioactive molecules enter the interlayer space during this process, causing the d001 spacing between the layers to expand by 0.3–0.5 nm. HNTs are intercalating materials that interact with silica and tetrahedral silicon sheets, forming significant dipole interactions and hydrogen bonds. On the other hand, anionic functional groups interact with alumina layers and intercalated into HNTs (e.g., amides, aniline, dimethyl sulfoxide, formamide, hydrazine, potassium acetate, etc.) (Lvov and Abdullayev, 2013; Rawtani and Agrawal, 2012). At higher temperature, the HNTs are dehydrated that cause low intercalation capability due to minimum, or no as strong hydrogen bonds exist between layers (Levis and Deasy, 2002; Luo et al., 2010; Lvov and Abdullayev, 2013). The intercalation phenomenon is linked to interlayer water; intercalation necessitates the exchange of water molecules between HNT wall layers. The disadvantage of this method is that the limited space between HNT wall layers prevents higher molecular weight substances from being loaded. As a result, it could be helpful in applications that use smaller substances like corrosion inhibitors and drugs (Lvov and Abdullayev, 2013).

3.3. Tubular entrapment

Tubular entrapment, known as the vacuum method, is the most prominent loading HNT (Kelly et al., 2004; Levis and Deasy, 2003; Ward et al., 2010). Unlike intercalation, this technique allows storing any material to the lumen of HNT. Tubular entrapment can be done in two methods. The first method's general procedure is as follows: First, dried HNT is stirred with a highly concentrated solution of the targeted molecules. Solvent To provide excellent solubility for the molecules and wet HNT walls, the solvent must have low viscosity. Specifically, water is a suitable solvent for the loading of most biomolecules, while acetone and ethanol are desirable for organic compounds (Lvov and Abdullayev, 2013; Ward et al., 2010). A substantial amount of drug loading for negatively charged bioactive molecules has been observed due to the high dielectric constant of the solvent. The hydroxyl groups of the HNTs-walls are ionized, stabilizing a uniform suspension of HNTs to improve bioactive molecules loading in the lumen (Abdullayev and Lvov, 2010).

The vial suspension is shifted to vacuum-jar to make a homogeneous mixture from the suspension by evacuating several times via vacuum pump. During vacuum, a minor solution fizzing is a sign of lumen air removed from suspended HNTs. The suspending media should be remained under vacuum for 10–30 min before being returned to atmospheric pressure to replace the removed air with the desired molecules. To ensure that the lumen is filled with the molecule solution, this process is repeated two to four times. Typical 10–15 wt% bioactive molecule loading has been reported into HNT lumens with

15 nm diameter, and it is very near to theoretical estimates (Abdullayev and Lvov, 2010; Lvov and Abdullayev, 2013). Following the vacuum cycle, the HNT suspension is centrifuged to remove weakly attached bioactive molecules. The washing procedure was repeated two times to ensure that HNTs are fully loaded with desired bioactive molecules.

Meanwhile, the targeted bioactive molecules are mixed in equal parts by weight with HNT in the second method. Instead of dispersion, the resultant mixture in this method is a thick paste. Two to three times, the mixture is cycled between vacuum and atmospheric pressure. The obtained mixture is vacuum dried to have bioactive molecule-loaded HNTs. To avoid bioactive molecules or solution wastage are outcomes of the latter method and maximum loading of targeted bioactive molecules into HNTs. That can be determined without examining supernatant (Kelly et al., 2004; Levis and Deasy, 2003; Tan et al., 2014).

4. Applications of halloysite nanotubes

One of the outstanding attributes of HNT is its biocompatibility, which makes them favourable for applications in cosmetics (Suh et al., 2011), drug delivery (Leporatti, 2017; Lvov and Price, 2007), and medical implants (Wei et al., 2012). Moreover, studies have shown that HNT has a low to absent toxicity level (Lai et al., 2013; Vergaro et al., 2010). Recent research has been conducted to compare the cytotoxicity of HNTs and multi-walled carbon nanotubes (MWCNs) against human umbilical vein endothelial cells (*in-vitro*) and blood vessels of mice (*in-vivo*) assays (Lai et al., 2013). The results conclude that HNT is more biocompatible than multi-walled carbon nanotubes (MWCNs) to blood vessels. Therefore, HNTs are suitable candidates for biomedical applications, including anticancer therapy. A micro-scale flow device enhanced with HNT coating is fabricated to capture the circulating tumor cells (CTCs) from the patient's blood. The utilization of HNT improved the performance of microtube's in capturing and killing cancer cells (Dong et al., 2013; Hughes and King, 2010; Hughes et al., 2012). In addition, HNT decorated with folic acid and magnetic particles loaded with doxorubicin were found to be toxic to cervical adenocarcinoma (HeLa) cells in a study. The HNT decorated anticancer agents are potential biomaterials to treat cancer due to sustained and targeted release of anticancer agents (Guo et al., 2012; Leporatti, 2017). The control drug release system has been developed by intercalation of 5-fluorouracil (antimetabolite) into HNT. It helps minimize drawbacks of 5-FU (e.g., shortened half-life, quick metabolism, and low absorption) for cancer treatment (Chrzanowski et al., 2013; Mazzaferro et al., 2012).

HNT also uses ultrasound contrast agents for clinical echographic imaging (Chrzanowski et al., 2013) and unique delivery systems such as transdermal patches and wound care (Di Paola et al., 2014; Soloperto et al., 2013). Furthermore, biomedical applications of HNT include the use for sustained and controlled release of antiseptics (Wei et al., 2014), proteins (Zhai et al., 2010), enzymes (Machado et al., 2008; Zhai et al., 2010), and drugs (Yuan et al., 2012). HNTs nano-carriers are also known as 'nano-bazookas' that load therapeutic agents like nano-bullets to targeted cancer cells in a sustained manner (Leporatti, 2017). HNTs are biocompatible but non-biodegradable and can be used for systemic administration because they are readily available (intravenously). The non-biodegradability of HNTs makes it potential material for the nano-cosmetic formulation, treating animals, preparation of nano-medicines, implants developments or plasters, etc. (Leporatti, 2017). Nonetheless, integration of HNT in polymer matrices can be considered for a broad range of applications.

5. Halloysite nanotubes/polymer composite

Because of their unique properties, HNTs disperse more readily in polymeric matrices than platy clay (e.g., kaolin and montmorillonite) without exfoliation. These include easy surface modification, tubular structure, and surface hydroxyl groups readily available (Lvov and Abdullayev, 2013). HNTs are hydrophilic and uniformly disperse into polar polymeric systems, e.g., polyamides (Guo et al., 2009), poly(ethyleneimine) (Lvov et al., 2002), polyvinyl alcohol (Bediako et al., 2018; Liu et al., 2007), polymethylmethacrylate (Vuluga et al., 2018), and biopolymers including polysaccharides (Cavallaro et al., 2011) and proteins (Zheng and Wang, 2009). Surprisingly, they are also compatible with non-polar polymers like polypropylene (Du et al., 2006b) and polylactic acid (Venkatesh et al., 2019a) with the use of surface-compatible agents.

Several methods may be applied to prepare HNT/polymer composites. Melt-blending is a commonly used functional method. In this method, a polymer is allowed to melt and combine with the required quantity of intercalated clay via an extruder (Khan et al., 2020b; Rane et al., 2018). This process is conducted in an inert environment (argon, nitrogen, or neon). Another standard method is solvent casting, where the well-dispersed mixture of polymer. The HNTs are casting and dried to create composite films (Kelly et al., 2004). Another popular method is electrospinning, producing HNT/polymer composite nanofibers mats (Bulbul et al., 2020; Elumalai et al., 2020; Sabatini et al., 2020). Furthermore, HNT/polymer composites can be fabricated using hydrogel preparation (Zheng and Wang, 2009), coagulation (Liu et al., 2007), injection molding and compression molding (Wang and Huang, 2013), in-situ polymerization (Gaaz et al., 2017; Sabatini et al., 2020), and layer by layer deposition of HNT and polycations (Gaaz et al., 2015; Wang and Huang, 2013). Several economical methods have been reported to synthesize polymer-HNTs composites. The method selection was made to enhance HNT dispersion into a polymeric matrix with improved interfacial interaction (Gaaz et al., 2015).

Some of the basic properties are affected, such as microstructure and thermomechanical characteristics, including HNTs into the polymeric matrix. The uniform dispersion of HNT particles into the polymeric matrix promotes more microstructural features than aggregates (Gaaz et al., 2017). The morphological characteristic of HNT/polypropylene (HNT/PP) nanocomposites have been improved by prepared by water-assisted injection molding (WAIM) and compression molding (CM) technology (Wang and Huang, 2013). The results show that most of the HNT are well oriented into the PP matrix at a limited amount of HNTs (2 wt%). As the amount of HNT increased from 5 to 8%, larger aggregates were observed.

The increasing amount of HNTs into polymeric matrix acts as reinforcing that improve the mechanical behavior polymer-

HNTs composites (Gaaz et al., 2017). The increased mechanical characteristic is due to the increasing aspect ratio, intrinsic stiffness, and uniformed dispersion of HNTs into the polymeric matrix. The Young's Modulus of a single HNT is 130 GPa (Lu et al., 2011). The improved flexural and tensile modulus are observed when a uniformly HNTs dispersion is incorporated into polylactide (PLA) matrices (Wu et al., 2013). The improvement may be attributed to the stiffness enhancement of the nanocomposite by HNTs, allowing higher stress transfer at the interface. However, no significant improvement in tensile strength of the polymeric nanocomposites is observed due to weak interaction between PLA matrix and surface of HNTs (Wu et al., 2013). On the contrary, the desirable interface of HNT and PLA matrix is observed when using a quaternary ammonium salt treated HNT (modified-HNT). The tensile mechanical strength and Young's modulus of polymeric nanocomposite increased much higher than an unmodified polymeric composite of HNT/PLA (Prashantha et al., 2013). The enhanced mechanical behavior was observed with polyvinyl alcohol-HNT polymeric nanocomposites with increased tensile mechanical strength and elongation at break after loading HNT up to 7.5 wt% (Liu et al., 2008). Moreover, flame retardancy and thermal stability have been reported by reinforcing effects of HNTs with improved mechanical behaviors (Du et al., 2006a; Marney et al., 2008).

The versatility properties of HNTs as a nanocarrier for controlled delivery release and conductive filler expand new horizons of unique polymeric composites for biomedical applications. It also allows flexibility in the engineering and designing of biomedical products (Kamble et al., 2012). It has been reported that the use of polyacrylic acid (PAA) grafted chitosan/HNT hydrogel composites as an adsorbent to remove ammonium from wastewater (Aslam Khan et al., 2020; Marney et al., 2008). Furthermore, studies show that alginate/HNT hybrid beads are effective of to remove methylene blue. It indicates that this nanocomposite can be used for dye removal in practical applications (Khan et al., 2020b).

6. Biomedical applications of HNT/polymer composite

Due to the simple preparation process, improved mechanical and thermal properties, and good biocompatibility of polymeric-HNT composites. They have great potential as biomedical materials, including biosensors, nanomedicine, tissue engineering, wound healing, drug carriers, etc. HNTs have a high water-dispersion capacity and the synthesis process to produce polymeric composites used in biomedical applications. The HNTs can interact with the polymers through van Waal, electrostatic, and hydrogen bonding (H-bonding) interactions during the synthesis of polymeric composites. The interactions in the composites are of benefit for the formation of uniform dispersed composites and their improved properties.

6.1. Drug delivery

Due to its unique properties, like natural availability, non-toxicity, and biocompatibility, HNT has been widely used as drug-carrying vehicles (Khan et al.; Lisuzzo et al., 2021; Vergaro et al., 2008). Moreover, previous literature also reported relatively high loading capacities compared to other carriers, high aspect ratios, high porosity, and non-swelling nature (Soloperto et al., 2013). HNT also exhibits anti-inflammatory and anti-bacterial properties (Hanif et al., 2016; Lisuzzo et al., 2019). Furthermore, the tunable release characteristic of HNT enables them to release the stored molecules in their lumens in a uniform, sustainable, or controllable manner (Cornejo-Garrido et al., 2012; Hanif et al., 2016; Lisuzzo et al., 2019). HNT surfaces were modified with various polymers for drug delivery applications because they have an excellent dispersion characteristic. The drugs can exist on three distinct locations in the HNT/polymer nanocomposite: within the cylindrical cavity of HNT, in the outer surface of HNT, and interlayer spaces HNT (Fig. 3). There are various drugs for different treatments, and the classification of other drug delivery systems has been presented in Fig. 2.

6.1.1. Anti-cancer drug delivery system

Cancer is one of the world's leading causes of death and increasing mortality rates that kill millions of people every year. Chemotherapy is becoming a popular cancer treatment option (Fizir et al., 2018; Santos et al., 2019; Vergaro et al., 2011). Some limitations of current chemotherapy such as the undesirable side effects typically arising in the bone marrow and gastrointestinal (GI) tract, lack specificity in terms of neoplastic tissues and selectivity in terms of the mechanism of the action, a low therapeutic index, a significant tendency towards degradation and strong chemoresistance, can be overcome by using HNT-drug carrier with controlled-release behavior (Bertolino et al., 2020; Mock et al., 2015).

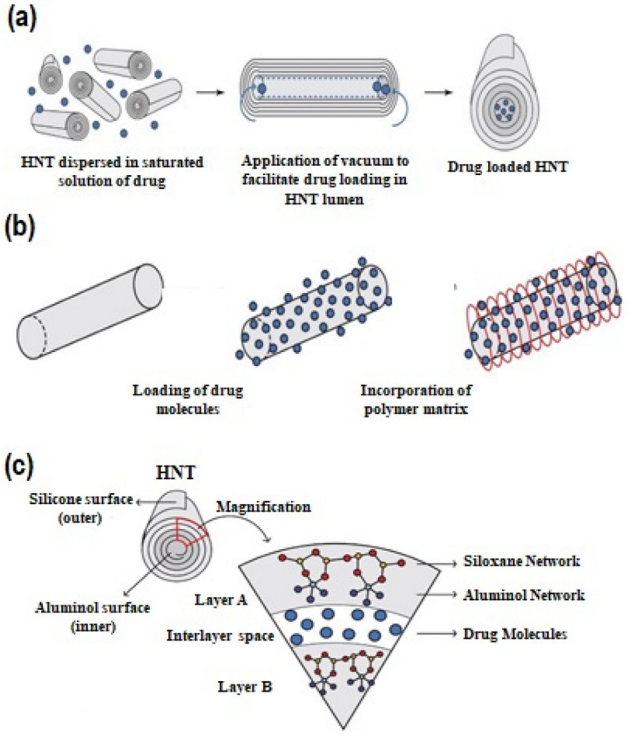

Fig. 2 Locations of drug-loaded in HNT: (a) within the cylindrical cavity of HNT, (b) in the outer surface of HNT, and (c) in interlayer spaces of HNT.

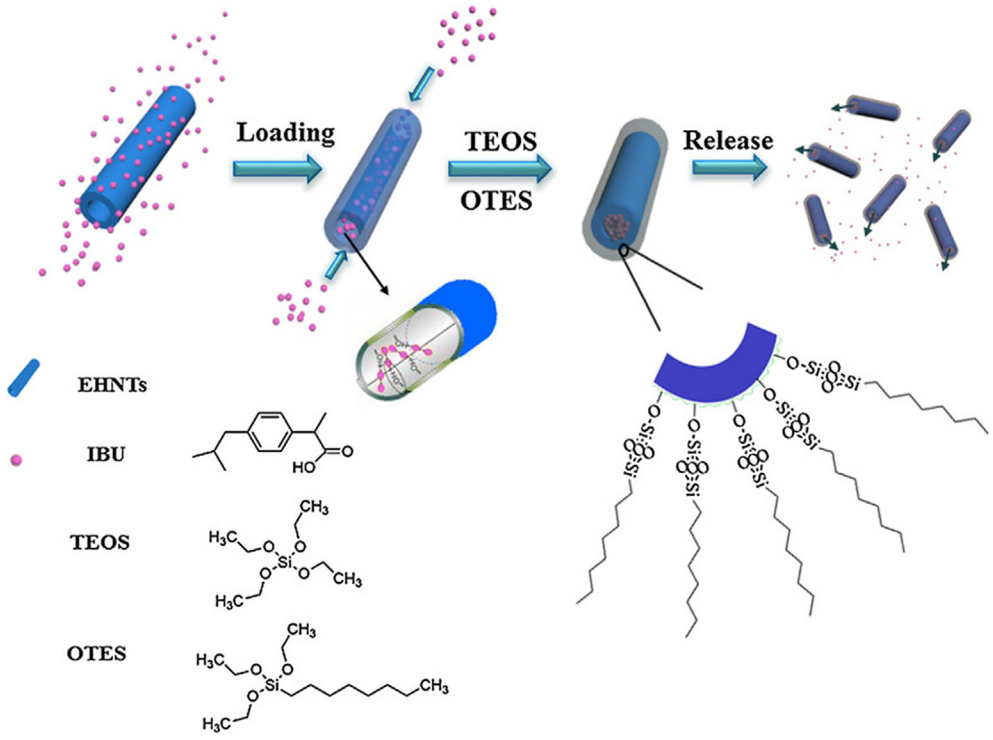

Fig. 3 Drug loading, modification and release process.

Curcumin, Doxorubicin, Paclitaxel, Resveratrol, Methotrexate, and 5-fluorouracil are antitumor drugs that have been loaded within HNT/polymer-based carriers. Curcumin (CUR), for example, is a naturally bioactive molecule - with exceptional anti-inflammatory, antioxidant, antiproliferative, and anticancer properties (Kerdsakundee et al., 2017; Khan et al., 2020a; Mock et al., 2015). Though, the therapeutic effect of CUR is hindered by its chemical instability and rapid metabolism. Besides, its poor solubility in aqueous media limits the oral administration of CUR. The oral bioavailability has been improved by designing a multifunctional nano-in-micro polymeric composite. The polymeric composite has been synthesized by HNT modification using mucoadhesive polymers. It has a mucoadhesive function that increases HNT interactions with intestinal cells to enhance drug penetration through monolayers of intestinal cells. CUR was then loaded onto the functionalized HNT. Microfluidics was used to encapsulate the loaded HNT in a pH-responsive polymer. According to in-vitro drug release and cytotoxicity studies, the cytocompatible composite materials are potential drug carriers. It enables drugs to withstand the harsh gastrointestinal environment while also allowing them to be released at a specific location in the small intestine (Cavallaro et al., 2015; Santos et al., 2019). The external surface of the HNTs is functionalized with polymer (N-isopropyl acrylamide) to load CUR into a thermoresponsive drug delivery system of HNTs (Cavallaro et al., 2015). In-vitro kinetic release system has revealed no release for the first 50 min in the gastro-imitated environment. It suggests a strong interaction between the CUR and the nanocarrier, followed by a low CUR release (ca. 2.5%). On the contrary, there was a higher level of release (ca. 10%). The drug delivery system allows for the controlled release of CUR without its degradation in acidic environment.

To treat breast cancer, researchers developed doxorubicin (DOX) drug carrier based on chitosan oligosaccharide-grafted (COS)-HNT. (Shah et al., 2016; Yang et al., 2016). Because COS has a lower molecular weight than chitosan, it was chosen for this study instead of chitosan. The multi-targeted approach of mitochondria and nuclei improves DOX efficacy. According to the research, the nanocarriers are highly biocompatible, have a low hemolysis rate, and have controlled drug release in vitro. This study builds on previous work by the same group, which used HNT–Carboxylic acid/-chitosan as a nanocarrier for curcumin release sustained over time (Liu et al., 2016). However, because the covalent functionalization of chitosan protected the surfaces of HNT, the surface areas and loading ability of HNT were reduced. HNT was coated with DNA for DOX delivery in another study (Lee et al., 2013). The carrier released DOX continuously for more than two weeks, with no initial burst of DOX. In addition, a novel folate-mediated and redox-based drug delivery system was developed for the treatment of cancer (Hu et al., 2017). DOX was first loaded into HNT, followed by thiol group modification of HNT. Afterwards, per-thiol-β-cyclodextrin was grafted onto functionalized HNT to behave like a control gate for drug release from the HNT lumen. These long-term stable nanocarriers have also been enhanced with folic acid and polyethene glycol to target the desired site (Hemmatpour et al., 2015). The surface of HNTs was functionalized through poly (methacrylic acid-co-methyl methacrylate) for sustained release of cancer therapeutic agent, i.e., Paclitaxel (PTX). Because of its ability to dissolve in basic media, the polymer PMMM was selected to quickly release

drug outflow in basic pH-media (intestinal fluid). The research showed that formulated polymeric composite might pass through harsh conditions of the stomach to release PTX into the digestive system (Yendluri et al., 2017).

HNT can be coated via a layer-by-layer method because it has a negatively charged surface. Sequential adsorption of positive and negative charges polyelectrolytes forms a polymer wall around HNT, allowing active molecules to be conjugated (Leporatti, 2017). In addition, the polycation/polyanion multilayer shell acts as a diffusion barrier. That also causes delayed delivery of bioactive molecules from multi-layered HNTs (Lvov and Abdullayev, 2013). In research, HNTs were supplementarily coated with poly (sodium 4-styrene-sulfonate) and poly (allylamine hydrochloride) to load resveratrol. The impact of resveratrol on human breast cancer cell growth was investigated. Under physiological conditions, the result showed breast cancer cells (MCF-7) after resveratrol degradation (Vergaro et al., 2012). Methotrexate (MTX), a drug used to treat osteosarcoma, was entrapped within the coating layers of HNT coated with polyvinylpyrrolidone and polyacrylic acid in another study. The system inhibited osteosarcoma cell differentiation and growth that has been used as a nanocarrier for sustained release of drugs to discourage tumor metastasis (Sun et al., 2016). 5-fluorouracil (5-FU) is an antimetabolic drug. It is commonly used to treat cancer. 5-FU is loaded into poly (L-glutamic acid) to load into multilayers of HNTs. It is coated with chitosan. This system had a slow 5-FU release and a 52.32% uptake capacity (Yan et al., 2011). Colon cancer has been treated with sustained release of 5-FU using a novel HNT-hydrogel. It contains sodium hyaluronate (SH) and poly (hydroxyethyl methacrylate) to develop the controlled delivery system. The pH-sensitive and time-dependent carrier prevented 5-FU from reaching the gastric region, where less than 10% release was observed. Meanwhile, over 70 h, maximum drug release was noticed in intestinal fluid in a sustained manner (Rao et al., 2014).

6.1.2. Anti-hypertension drug delivery system

A nanocarrier was synthesized for the controlled release of calcium channel blockers (e.g., diltiazem hydrochloride). Diltiazem hydrochloride is commonly used for high blood pressure treatment (Fizir et al., 2018). Self-polymerization of dopamine (PDA) was loaded on the outer surface of HNT and dispersed in alginate solution for synthesis of nanocarrier (Ganguly et al., 2016). In the study, in situ and post-loading drug loading procedures were used. In situ loading was found to have a better-controlled release feature than post-loading. A sequential degradation of polymer layers can be proposed as the mechanism for in situ loading. After some time, the coating layer of alginate was degraded and released the PDA successfully. It causes the delivery of bioactive molecules from the hollow HNTs' inner lumen in a slow and controlled manner.

6.1.3. Antibiotic and anti-bacteria drug delivery system

In the first study on the antibiotic sustained drug-delivery system, tetracycline (TC) was loaded to pristine HNT via vacuum process. The release of TC was observed during the first 10 h (Ganguly et al., 2016). G. Biddeci et al. have reported the synthesis of the edible film with thermoresponsive antioxidants/antibacterial activities. They have conducted antibacterial activities against Gram + ive and Gram -ive bacteria. They also conducted the morphological analysis of the synthesis schematic, as shown in Fig. 4. They have reported that these films are highly antibacterial and antioxidant (Biddeci et al., 2016). Since then, researchers have tested HNT as a controlled-release nanoparticle in antibiotics such as amoxicillin, ofloxacin, and norfloxacin. With the improvement of TC delivery, various efforts have been made. Solution casting, for example, was used to embed TC-loaded HNT in polyvinyl alcohol (PVA) and polymethyl methacrylate (PMMA) films (Khan et al., 2020b). The study found that TC was released in a controlled manner from PVA and PMMA films. After 220 min, 66% of the TC in TC-loaded HNT/PVA films was removed. This release lasts longer than pure TC/PVA film, which has a 100% TC release in 220 min. PMMA was fabricated using pure tetracycline, and 60% burst drug release was observed after 10 h. However, when the film is prepared with TC-loaded HNT, there is no burst effect, and the release rate is slower. TEM analysis with other illustrations have of HNTs have illustrated in Fig. 5. A novel nanofiber-based drug delivery system was developed by loading tetracycline hydrochloride (TCH) into HNTs and made a homogenized mixture with poly (lactic-co-glycolic acid) to fabricate composite nanofibers for controlled drug (Tohidi et al., 2016). The composite nanofibrous mats were found to act as a double-container drug delivery system, reducing the drug's initial burst release. TCH (32%) was released after 28 days, indicating that the system had a sustained release profile within a month.

The same fabrication method was discovered in another study. HNT loaded with amoxicillin (AMX) was incorporated into the PLGA solution. A hydrophilic composite nanofibrous mat was fabricated from AMX/HNT/PLGA/chitosan using two syringes. The syringe contains hydrophilic chitosan to enhance the hydrophilicity of the composite nanofibrous mat (Tohidi et al., 2016). The system's drug release analysis revealed that combining HNT with PLGA increased the drug release rate while decreasing initial burst release.

Magnetic microspheres were made by spray-drying 2-hydroxypropyltrimethyl ofloxacin/Fe3O4/HNT/ammonium chloride-chitosan glutaraldehyde for controlled delivery of ofloxacin (Wang et al., 2014). According to the study, the introduction of HNT to HACC/Fe_3O_4/OFL magnetic microspheres enhanced the surface roughness of the microspheres. It has a cumulative release ratio of 84% after 5 h, which means it speeds up the release of OFL in the stomach. Moreover, it has the potential to improve OFL bioavailability in the gastro-retentive drug delivery system. As a result, the nanocarrier system can be used for magnetically guided targeted and sustained release in the upper gastrointestinal tract.

A novel polymer grafted-norfloxacin (NOR) loaded magnetic HNT(MHNT) carrier is fabricated via surface-initiated precipitation polymerization from NOR-MHNT (nanotemplate) methacrylic acid (monomers), ethylene glycol dimethacrylate (cross-linker), and azobisisobutyronitrile (initiator) (Zhang et al., 2009). This system had a longer-lasting sustained release of NOR (>60 h) as NOR is a cationic drug and has strong interaction with monomers. As a result, this newly developed nanocomposite could be used in a targeted drug delivery system. NOR was incorporated into the HNT lumen by vacuum and sonication in a recent study, and the TEM result confirmed the loading of NOR in the HNT lumen (Li et al., 2016a). The NOR-loaded HNT was used to make an

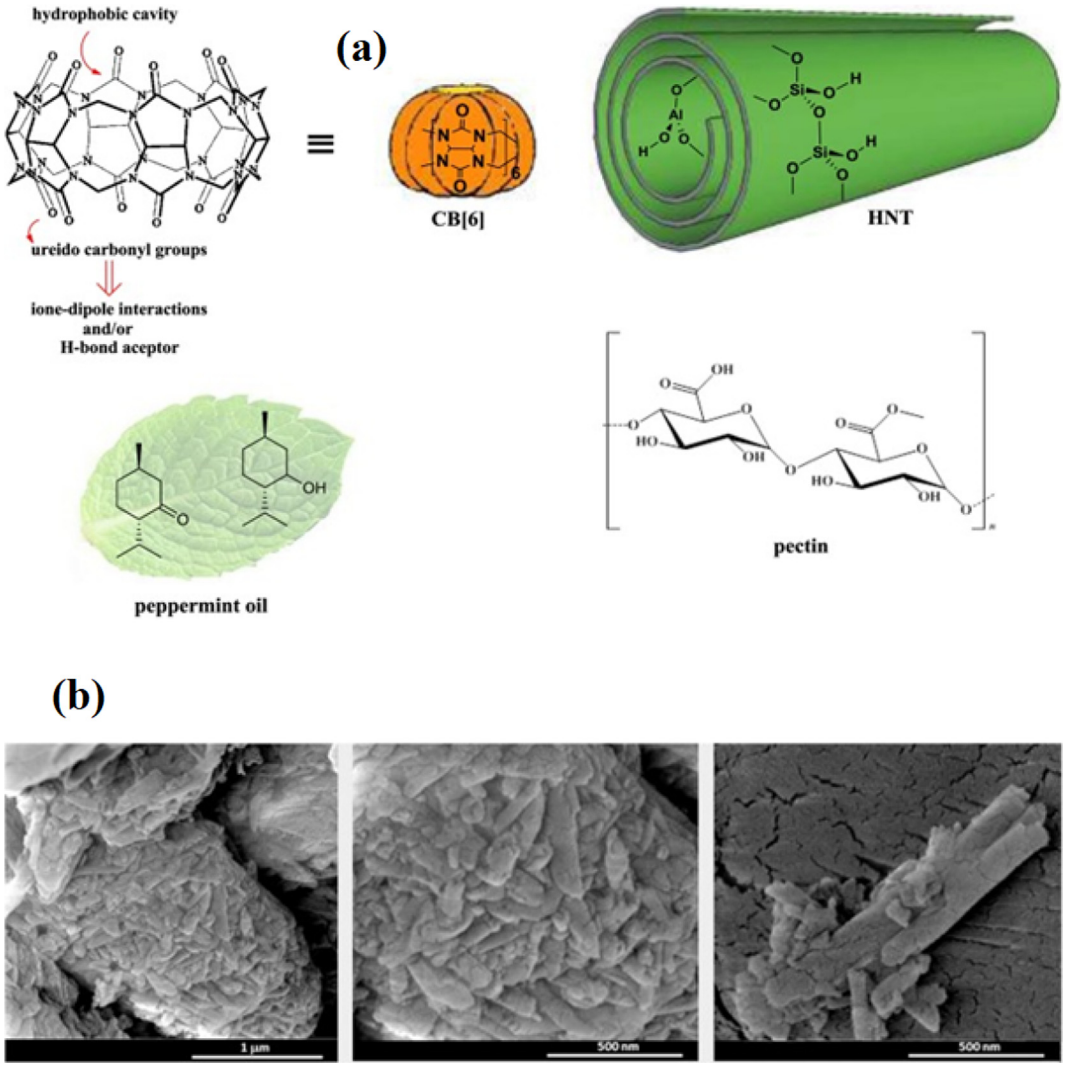

Fig. 4 (a) Schematic representation of the pectin films components (Biddeci et al., 2016) and (b) SEM images of HNT/CB nanofiller (Biddeci et al., 2016).

HNT/chitosan nanocomposite film using a solvent casting and freeze-drying technique. In a cytotoxicity study, the nanocomposites film demonstrated improved antibacterial activity and biocompatibility. The *in-vitro* delivery of NOR exhibited that HNT/chitosan polymeric nanocomposites keep the drug flowing.

6.1.4. Anti-inflammatory and analgesics drug delivery system

Ibuprofen, diclofenac sodium, and aspirin are examples of poorly water-soluble drugs with low bioavailability. Researchers have started developing an intelligent drug delivery system utilizing drugs encapsulated in nanoparticles to overcome drug bioavailability. A novel polymeric nanocomposite was synthesized by encapsulating functionalized ibuprofen (IBU) and loaded HNTs in polyelectrolyte solution using chitosan and sodium alginate (Li et al., 2016a). The suggested drug delivery system outperformed IBU in terms of sustained-release performance (115 h). The result indicated that PECs have reasonable storing and blocking effects. The ALG/CHI coatings create an additional barrier to molecular movement. As a result, the entrapped IBU release is difficult to be dissolved in media. The controlled release of IBU from IBU-AHNTs@PECs is due to the strong interaction between IBU and functionalized HNTs. The study also demonstrated that changing the pH of media the change in IBU from IBU-AHNT@PECs polymeric composite is a pH-responsive system.

The sustained release of diclofenac sodium (DS) through oral administration was achieved by sol–gel interaction of HNTs and sodium alginate, and 57.09 mg/g release was observed from the nanohybrid system (Fan et al., 2013). The controlled release of DS (10%) was observed from SA/DS beads within 5 h *in-vitro,* and that burst release is lower. The tubular structure of HNTs is an essential factor that enhanced drug loading and releases behavior. In-situ-formed HA nanoparticles limit the SA polymer mobility of chains.

The porous microspheres system of chitosan-coated HNT has developed water/oil microemulsion for controlled and sustained release of aspirin (ASP), and a substantial release of ASP (42.4 wt%) was observed than pristine (2.1 wt%) (Li et al., 2016b). The loading is 20 times higher, and lower release

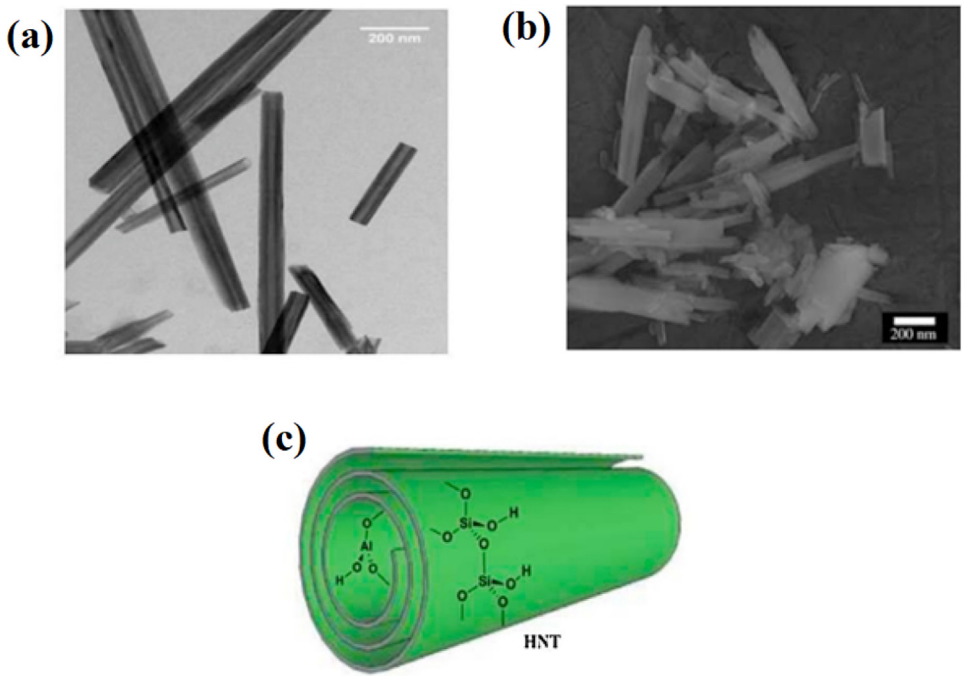

Fig. 5 (a) Precipitated TEM analysis of HNTs (Fakhrullin et al.; Yendluri et al., 2017), (b) SEM analysis of HNTs (Konnova et al., 2016) and (c) schematic illustration of HNTs (Biddeci et al., 2016).

was observed in harsh gastric fluid environments, whereas burst release was observed in intestinal fluid. As a result, the release of ASP in the intestine rather than the stomach would be preferable to maximize medical effectiveness while minimizing stomach side effects to the greatest extent possible. A novel nanocomposite-based drug delivery system was developed from polylactic acid (PLA) and HNTs using ASP as a model drug. The model drug (ASP) was into HNTs lumen (lumen-loaded), and ASP was directly loaded into the polymer matrix (matrix-loaded). The burst release (21–28%) was observed in 1–8 h from the lumen-loaded drug delivery system. The burst release was due to the quick release of ASP from the outer lumens of HNTs. In the second sample, sustained ASP release was observed from the PLA matrix after an incubation of 8 h due to diffusion phenomena (Venkatesh et al., 2019a).

6.1.5. Others drug delivery system

Several drugs were loaded into HNT-polymer nanocomposites to improve their bioavailability and release profile over time. Drug-loaded HNT was dispersed with biodegradable polyvinyl alcohol to create a drug delivery carrier for diphenhydramine hydrochloride (DPH), a well-known antihistamine drug for the treatment of hypersensitive reactions (PVA) (Ghebaur et al., 2012). The SEM analysis of the system displayed good biocompatibility between DPH-HNT and the PVA matrix. In addition, an *in-vitro* drug delivery study showed that the drug delivery process is pH-dependent. The PVA layer is responsible for the delayed release of DPH from the polymeric nanocomposite. Another study used surface-initiated atom transfer radical polymerization to graft functionalized-HNT with pH-sensitive polymer (i.e., poly (N, N-dimethyl aminoethyl methacrylate)) for long-term DPH delivery. (Hemmatpour et al., 2015).

Compared to the HNT carrier alone, HNT-PDMAEMA had a lower drug release concentration and a lower initial burst of DPH. This finding suggests that polymer chains slow the release of DPH molecules. The polymer chains obstruct the movement of drug molecules, slowing the rate of release. Ceramic pellets made of HNT and microcrystalline cellulose were used to create a highly potent opioid, Fentanyl (Forsgren et al., 2010). Drug release profiles studied the simulated swallowing of Fentanyl pellets without or with chewing. Intact pallets showed a 3–4 h sustained release, whereas crushed pellets showed a 2–3 h sustained release of the opioid. Moreover, the ceramic carrier was found to have a low risk of dose dumping during the investigation. As a result, it could be a potential biomaterial for oral opioid dosage forms.

The controlled and sustained release of sodium salicylate was compared between drug-loaded HNT/polyvinyl and alcohol (PVA)/acid-treated HNT by solution casting method (Mohebali et al., 2020). According to SEM and TEM analysis, acid-treated HNT has a higher loading capacity and a considerable drug amount released, which could be due to the enlarged lumen of HNT during acid treatment. This discovery suggests that acid-treated HNT could be used to deliver a large number of drugs over time. During the synthesis of the HNT/PVA composite, a consistent polymer layer was formed around the HNT. As a result, sodium salicylate drug release was found to be delayed and sustained than acid-treated HNT. The HNT/PVA composite had a longer-lasting drug release than the acid-treated HNT. Acid-treated HNT released more drugs than the HNT/PVA composite. The surface-modified HNT is offered to sustain drug delivery regardless of increased or decreased drug quantity. The drug delivery was controlled manner by following the diffusion mechanism.

A vacuum-assisted procedure was used to load Khellin, an active chemical extract from the Khella plant commonly used to treat psoriasis, vitiligo, and asthma (Qi et al., 2013). The negatively-HNTs were attracted by attracting cationic biopolymer, and then loaded-HNTs were then coated with chitosan. The results show that chitosan-coated loaded HNT reduced -khellin release, whereas uncoated HNT burst khellin release. In other studies, tea polyphenol was loaded into HNT and used to make a chitosan/HNT/tea polyphenol nanocomposite film using the solution casting method (Venkatesh et al., 2019b). The findings revealed that HNT was evenly distributed throughout the chitosan matrix, which improved mechanical properties. Excess HNTs, on the other hand, cause accumulation, which lowers film efficiency. The researchers found that nanocomposite films with a 6:4 chitosan HNT volume ratio and 10% tea polyphenol had the best efficiency of all the samples tested. Table 1 summarises the entire HNT-nanocomposites-loaded drug mentioned above.

6.2. Tissue engineering scaffolds

Scaffolds are used in tissue engineering to provide structural support for new tissue growth, typically seeded with biological cells, growth factors, or bioactive molecules (Aslam Khan et al., 2021; Zamri et al., 2021). HNTs have been combined with synthetic and natural biopolymers to create scaffolds with improved functional properties. PLA, PLLA, PCL, PVA, polydioxanone, and acrylic acid are examples of synthetic polymers (Khan et al., 2021c; Khan et al., 2020c; Khan et al., 2020d). L. Yu et al. developed a PLLA/PGA scaffold that incorporates modified montmorillonite (MMT) to improve the compatibility of PLLA and PGA for bone tissue regeneration in load-bearing applications. They reported an increase in tensile strength (110%) and tensile modulus (70%). These composite materials were also found to be cytocompatible when it came to the adhesion and proliferation of human osteoblast-like MG-63 cells (Yu et al., 2020). Y. Yang et al. have fabricated reduced graphene oxide reinforced Zn scaffold and studied their microstructure evolution and texture tailoring. The cell culture assays confirmed that these materials support cell growth and differentiation. They also reported that the synthesized materials possess enhanced mechanical performance with cytocompatibility for bone repair (Yang et al., 2021). Venkatesh et al. prepared 3D printed PLA/HNT nanocomposite scaffolds and discovered that the addition of HNT enhances mechanical characteristics. (Lisuzzo et al., 2020; Venkatesh et al., 2019b). The PLA/HNT nanocomposite scaffold has been fabricated by foam injection molding in other studies (Eryildiz and Altan, 2020). They discovered that HNT improved not only the mechanical features but also the viability of fibroblast cells. Electrospinning with PLLA/HNT was used to create scaffolds for skin tissue engineering (Cai et al., 2015). The findings demonstrate that PLLA/HNT nanofiber performs better than PLLA nanofiber regarding

Table 1 HNT-polymer nanocomposite for controlled and sustained drug delivery.

Class of Drugs	Name of Drugs	HNT-Polymer nanocomposite	Ref
Anticancer	Curcumin	HNT-APTES-PMVEMA@MF	(Kerdsakundee et al., 2017)
	Curcumin	HNT- PNIPAAM	(Cavallaro et al., 2015)
	Curcumin	HNT–COOH/Chitosan	(Liu et al., 2016)
	Doxorubicin	HNT-g-Chitosan oligosaccharide	(Yang et al., 2016)
	Doxorubicin	DNA-wrapped HNT	(Lee et al., 2013)
	Doxorubicin	HNT- β Cyclodextrin	(Hu et al., 2017)
	Paclitaxel	HNT-Poly(methacrylicacid-co-methyl methacrylate)	(Yendluri et al., 2017)
	Resveratrol	HNT-Polyelectrolytes	(Aras et al., 2014; Vergaro et al., 2012)
	Methotrexate	HNT-Polyelectrolytes	(Sun et al., 2016)
	5- fluorouracil	HNT-Poly(L-glutamic acid)/chitosan	(Yan et al., 2011)
	5- fluorouracil	HNT-Poly(HEMA)/Sodium Hyaluronate	(Rao et al., 2014)
Anti-hypertensive	Diltiazem hydrochloride	HNT-polydopamine	(Ganguly et al., 2016)
Antibiotic and	Tetracycline hydrochloride	HNT/PVA, PMMA	(Kelly et al., 2004)
antibacterial	Tetracycline hydrochloride	HNT/PLGA	(Qi et al., 2010)
	Amoxicillin	HNT/PLGA/chitosan	(Tohidi et al., 2016)
	Ofloxacin	Chitosan/Fe_3O_4/HNT	(Wang et al., 2014)
	Norfloxacin	Polymethacrylic acid- magnetic HNT	(Viseras et al., 2009)
	Norfloxacin	HNT/chitosan	(Li et al., 2016a)
Anti-inflammatory	Ibuprofen	AHNTs-PECs	(Fan et al., 2013)
&analgesic	Diclofenac sodium	HNT/Sodium alginate	(Ghebaur et al., 2012)
	Aspirin	HNT/PLA	(Venkatesh et al., 2019a)
Antihistamin	Diphenhydramine hydrochloride	HNT/PVA	(Hemmatpour et al., 2015)
	Diphenhydramine hydrochloride	HNT/Poly (N,N-dimethylaminoethyl methacrylate)	(Forsgren et al., 2010)
Miscellaneous	Fentanyl (opioid)	HNT/MCC	(Aras et al., 2014)
	Sodium salicylate (NSAID)	HNT/PVA	(Bediako et al., 2018)
	Khellin	HNT/chitosan	(Qi et al., 2013)
	Tea polyphenol	HNT/chitosan	(Venkatesh et al., 2019b)

mechanical efficiency and protein adsorption from fetal bovine serum. In addition, PLLA has incorporated with HNT to develop polymeric nanocomposite to fabricate scaffold for tissue engineering. Guo et al. introduced HNT grown silica (HNT@silica) to PLLA and used selective laser sintering to create scaffolds (Guo et al., 2020). The PLLA/HNT@silica scaffolds improved human adipose tissue-derived stem cell adherence and osteogenic differentiation. It was also observed that their apatite-forming abilities and hydrophilicity were also enhanced. In other studies, 3D printed scaffolds made of PLLA, magnesium carbonate whisker, and HNT were used to improve cell adherence, migration, and differentiation that promotes osteogenesis (Liu et al., 2020). A comparative study was conducted to observe the performance of PCL/HNT and PCL/hydroxyapatite scaffolds. PCL/HNT scaffold has better mechanical performance than PCL/hydroxyapatite scaffold, according to Jing et al. (Jing et al., 2017). In addition, PCL has been combined with gelatin reinforced with HNT to develop composite electrospun nanofibers with improved mechanical properties (Švachová et al., 2016). The chitosan/PVA/HNT nanofibers have been fabricated for skin tissue engineering (Koosha et al., 2019). Mechanical properties, hydrophilicity, and fibroblast cell attachment are all improved by HNT reinforced nanofibers. Electrospinning was used to create new polydioxanone/HNT scaffolds for regenerative endodontics (Bottino et al., 2015). The polymeric nanocomposite-based scaffolds encourage adhesion and proliferation of Human dental pulp-derived fibroblast cells.

Nanocomposite materials were produced to improve the performance of natural polymer scaffolds (like alginate, arabinoxylan, apple pectin, beta-glucan, xyloglucan, chitosan, gelatin, hyaluronic acid, glycerol, xanthan gum, and gellan gum, etc.) (Al-Arjan et al., 2020; Aslam Khan et al., 2021; Aslam Khan et al.; Khan et al., 2021b). Zineh et al. reported 3D printing to synthesize nanocomposite materials alginate/methylcellulose/HNT/polyvinylidene fluoride scaffolds for cartilage tissue engineering (Zineh et al., 2018). They discovered that adding HNT to the scaffold improved its mechanical properties. Zineh et al. fabricate alginate/hyaluronic acid/HNT/polyvinylidene fluoride 3D printed scaffolds in their other studies (Zineh et al., 2020b). According to the findings, increased HNT content improves mechanical properties but decreases the biological performance of scaffolds. They discovered that HNT at a 40 mg/ml concentration outperformed HNT at a lower concentration in mechanical and biological tests. Hyaluronic acid and HNT were used to make cryogel polymeric composites for tissue engineering scaffolds. (Suner et al., 2019). The mesenchymal stem cells (MSC), cervical carcinoma cells (HeLa), and colon cancer cells viability, proliferation, adhesion, and differentiation were enhanced by increasing HNT contents into the polymeric composite to fabricate scaffolds. Abdollahi Boraei et al. (2020) use freeze-drying to create a gelatin/HNT nanocomposite scaffold for bone tissue engineering applications (Abdollahi Boraei et al., 2020). Adding HNT to gelatin-based scaffolds increases the porous behavior, water absorption, and biomechanical characteristics. A polymeric nanocomposite film was fabricated from aldehyde-modified biopolymers (carrageenan and gelatin)/HNTs using the solution casting method. It was observed that the mechanical tensile strength of the fabricated film was enhanced due to the HNT corporation (Afshar and Ghaee, 2016). The tensile strength of the nanocomposite film was improved by adding HNT. With increasing HNT content, water absorption capacity and degradation rate improved and increased, respectively. Furthermore, the films were hemocompatible and showed no cytotoxicity in an MTT assay for NIH 3T3 fibroblast cells. Table 2 summarises the HNT/polymer nanocomposite as scaffolds for the tissue engineering study mentioned above, as well as another research study.

6.3. Wound healing applications

Wound dressing materials are frequently fabricated with antibiotic or antibacterial properties to speed up the wound healing process. HNT with these properties has been extensively studied when combined with natural and synthetic polymers. Qi et al. has fabricated antibiotic composite nanofibrous mats via electrospinning. The mate was fabricated from tetracycline hydrochloride (TCH)-loaded HNTs with a poly(lactic-co-glycolic acid) matrix (Wu et al., 2020). The inclusion of HNTs polymeric matrix enhanced the mechanical strength and was found to be biocompatible against mouse fibroblasts cell lines. The highly antibacterial composite nanofibers have sustained release of TCH for 42 days for prolonged antimicrobial activities. Another study reported a PLGA/HNT/amoxicillin/chitosan nanofibrous mat using a dual electrospinning process. Improved mechanical properties, high biocompatibility, improved hydrophilic properties, and controlled amoxicillin release behaviour were observed in the nanofibrous mat. These findings suggest that the PLGA/HNT/amoxicillin/-chitosan nanofibrous mat could be used as a wound dressing (Tohidi et al., 2016). Aside from that, a polyvinyl alcohol (PVA)/HNT/minocycline film for burn wound dressing has been developed (Mohebali et al., 2020). Antibacterial effects were observed, as well as acceptable degradability. The film has controlled and sustained drug release and control further bacterial growth by absorbing wound exudate. Wali et al. have reported the fabrication of nanofiber mats from cellulose ether-PVA and HNT/gentamicin sulphate using an electrospinning technique for faster wound healing. The faster wound healing was observed on Wistar rats due to HNTs and gentamicin sulfate (Wali et al., 2019). Antimicrobial drugs such as Brilliant Green, amoxicillin, and potassium clavulanate doped HNT/PCL electrospun nanocomposites sutures and surgical dressings have been proposed in another study (Patel et al., 2016). All bacterial agents were released in a sustained pattern by HNT/PCL nanocomposite mats, which inhibited bacterial growth for up to a month. Pavliáková et al. look into the possibility of a PCL/gelatin mat reinforced with HNT nanofibers being used for wound healing (Pavliňáková et al., 2018). Based on interactions with mouse fibroblasts NIH-3T3 cells, HNT reinforced nanofibers have been shown to be non-cytotoxic, preferable for quick wound healing applications.

The use of HNT in wound healing with gelatin, carrageenan, and chitosan nanocomposite has been investigated. Shi et al. and co-workers have developed nanocomposite membranes from HNTs and gelatin-elastomer for wound-healing applications. To improve the antibacterial effect for quick wound healing, ciprofloxacin and polymyxin-B sulfate-loaded HNTs were incorporated into a polymeric nanocomposite. The polymeric nanocomposite film has improved mechanical strength, and ciprofloxacin and polymyxin-B sulphate release is controlled (Shi et al., 2018). Carrageenan/HNT

Table 2 HNT/polymer composite for tissue engineering scaffolds.

Polymer composites	Methods of fabrication	Results/Findings	Applications	Ref
PLA/HNTs	3D printing	HNT increases the mechanical properties	Implants for tissue engineering	(Venkatesh et al., 2019b)
PLA/HNTs	Foam injection molding	HNT improved mechanical strength and fibroblast cell viability	Tissue engineering	(Eryildiz and Altan, 2020)
PLLA/HNTs	Electrospinning	Improved mechanical strength, protein adsorption, cell adherence	Skin tissue engineering	(Cai et al., 2015)
PLLA with silica grown on HNT	Selective laser sintering	Supported cell adhesion, proliferation, and osteogenic differentiation stem cells and offered improved apatite-formation and hydrophilicity	Bone tissue engineering	(Guo et al., 2020)
PLLA, Magnesium carbonate whisker/HNTs	3D printing	Enhanced mechanical behavior and promote cells adhesion, migration, proliferation, and osteogenic differentiation	Bone tissue engineering	(Guo et al., 2020)
PCL/HNTs	Co-extrusion and gas foaming	Mechanical performance	Bone Tissue engineering	(Jing et al., 2017)
Gelatin, PCL/HNTs	Electrospinning	Improved mechanical properties of strength (2x), elongation (4x), and modulus (2x)	Tissue engineering	(Švachová et al., 2016)
Chitosan, PVA/HNTs	Electrospinning	Improve mechanical, surface morphology and hydrophilic characteristics, and cell adherence	Skin tissue engineering	(Koosha et al., 2019)
Polydioxanone/HNTs	Electrospinning	Support cell adhesion and proliferation of human dental pulp-derived fibroblast cells	Regenerative endodontics	(Bottino et al., 2015)
Alginate/methylcellulose/ polyvinylidene fluoride/ HNTs	3D printing	Enhanced mechanical properties	Cartilage tissue engineering	(Zineh et al., 2020a)
Alginate, hyaluronic acid, polyvinylidene fluoride/ HNTs	3D printing	Enhanced mechanical behavior characteristics but decreases biological performance due to increasing HNTs amount. Without HNTs, much higher mechanical and biological performance	Cartilage tissue engineering	(Zineh et al., 2020b)
Hyaluronic acid/HNTs	Freeze drying	Enhanced thermomechanical stabilities and improved viability, proliferation, adhesion, and the growth of various cell lines	Tissue engineering	(Suner et al., 2019)
Gelatin/HNTs	Freeze drying	Increased pore size, porosity, water absorption, and mechanical properties	Bone tissue engineering	(Abdollahi Boraei et al., 2020)
Aldehyde modified carrageenan, gelatin/HNTs	Solution casting	Increasing HNTs enhances water adsorption and degradation rate, biocompatibility against NIH 3T3 fibroblast cell lines	Tissue Engineering	(Afshar and Ghaee, 2016)
Chitosan, agarose, gelatine/ HNTs	Freeze-drying	HNTs enhanced mechanical stability and wettability with biocompatible effects and cell growth in vitro, uniform cell distribution, and morphology	Tissue engineering	(Naumenko et al., 2016)
Chitosan, alginate/HNTs	Freeze drying and amine treatment on scaffolds	Improves mechanical strength, cell adherence and growth	Tissue engineering	(Afshar and Ghaee, 2016)
Sodium alginate, xanthan gum/HNTs	Freeze drying	Improves thermomechanical behavior, cytocompatibility	Bone tissue engineering	(Kumar et al., 2017)
Gellan gum, glycerol/HNTs	Solution mixing and chemical crosslinking	Support higher metabolic activities and fibroblast cell survival	Soft tissue engineering	(Bonifacio et al., 2017)
Sodium alginate/HNTs	Solution mixing and chemical crosslinking	Improved stiffness and compressive strength, lower cytotoxicity and increased cells adhesion and proliferation	Bone tissue engineering	(Huang et al., 2017a)

nanocomposite film has also been shown to be an effective wound healing material (Wahab and Abd Razak, 2016). The delayed release of the model drug in the methylene blue release experiments indicated possible drug delivery applications, making it a suitable material for wound healing applications. Chitosan reinforced with HNT could be used to help heal wounds. Huang et al. demonstrated that adding HNT to chitosan hydrogel improves mechanical properties and cytotoxicity in MC3T3-E1 cells (Huang et al., 2017b). For doxorubicin, composite hydrogels have a much higher maximum drug entrapment efficiency than pure chitosan hydrogels. In other studies, an enhanced mechanical strength, biocompatibility of

fibroblast and endothelial cell lines was observed against chitosan/HNT composite sponges for chronic wound healing application. The blood clotting and platelet activation were also observed for burn, chronic, and diabetic wound healing (Liu et al., 2014).

M. Liu et al. have reported the synthesis of chitosan/HNTs to improve hemostatic and wound healing by studying in-vivo evaluation on excision wounds Sprague-Dawley rats. They have reported that composite sponges enhanced wound healing compared to pure chitosan (Fig. 6). The addition of HNTs improved faster re-epithelialization and collagen deposition to heal wounds after one week (Liu et al., 2014). In-vivo wound healing testing also confirms the improved ability to heal. Gelatin-sericin nanofibers reinforced HNT loaded with therapeutic zinc or copper ions were fabricated in a comparative study (Massoumi et al., 2019). According to the study, zinc-loaded nanofibers were found to have the best fibroblast cell attachment, viability, and collagen secretion, as well as suitable mechanical properties and antibacterial activity for use as an antibacterial wound dressing. The antibacterial composite film was fabricated via layer-by-layer methodology from HNTs and polymeric (poly (lactic-co-glycolic acid)/chitosan) materials sustained delivery of minocycline. Before preparing the composite film, different acids were used to treat HNT-lumen to enhance drug loading efficiency. Composite films had an antibacterial effect and were compatible with blood. *In-vivo* wound healing assay using rat model exhibit that burn wound healed faster than control sample (PVA film). The HNT as mentioned above/polymer nanocomposite for wound healing applications is summarised in Table 3.

6.4. Dentistry

Dental medicine and oral medicine are two terms used to describe dentistry. Dentistry is the science of studying, diagnosing, preventing, and treating diseases, disorders, and conditions of the oral cavity, particularly dentition (Meurman, 2005; Yang et al., 2020). However, it also includes the oral mucosa and adjacent and related structures and tissues, especially in the maxillofacial (jaw and facial) region. Dentistry, which is not limited to teeth, includes the temporomandibular joint and other supporting such as muscular, lymphatic, nervous, vascular, and anatomical structures (Lombardero et al., 2021; Nelson et al., 2020). HNTs are commonly used in resins, cement, implants, and composites. The non-toxicity, biocompatibility, inherent antibacterial activities, high mechanical strength, and durability of halloysite nanotubules make them a potential target material in dentistry (Cho et al., 2020; Tammaro et al., 2020). Infected and dead pulp tissues are removed during endodontic therapy, which is known as root canal treatment. Primary infections are associated with pathogens that resist the intracanal antimicrobial process, while secondary infections are triggered by microbes incorporated during or after root canal filling. Several studies have been focused on the development of polymeric resins contained HNTs. Kiho Cho et al. have reported the synthesis of dental material from chitosan-HNTs and dispersion of chitosan-HNTs was enhanced in urethane-dimethacrylate/triethylenegly col-dimethacrylate. They have observed improved mechanical behavior (i.e., flexural strength, modulus, and breaking energy)

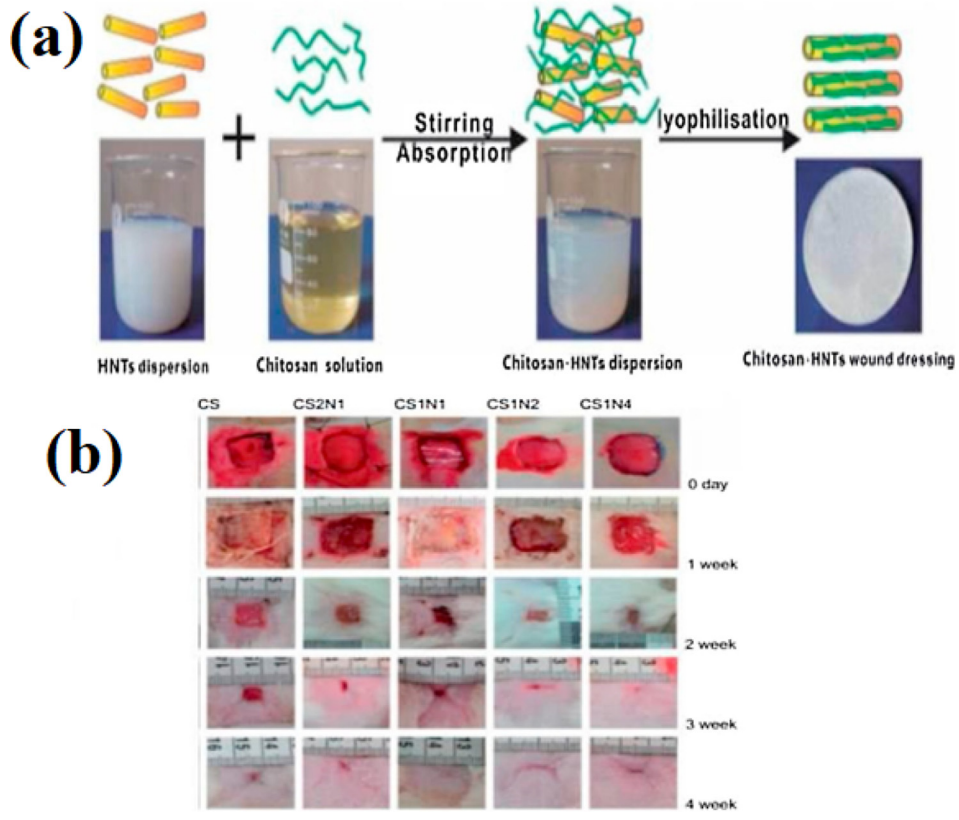

Fig. 6 (a) Schematic diagram of chitosan/HNTs composite and (b) wound healing using pure chitosan and its composites (Liu et al., 2014).

Table 3 HNT/polymer nanocomposite for wound healing applications.

Polymer Composites	Drugs Loading	Type of Wound Dressing/ Healing	Ref
PLGA	Tetracycline Hydrochloride	Electrospun nanofiber mats	(Qi et al., 2013)
PLGA, chitosan	Amoxicillin	Electrospun nanofiber mats	(Tohidi et al., 2016)
PVA	Minocycline	Film	(Mohebali et al., 2020)
Cellulose ether, PVA	Gentamicin Sulfate	Electrospun nanofiber mats	(Wali et al., 2019)
PCL	Brilliant Green, amoxicillin, and potassium clavulanate	Electrospun nanofiber mats	(Gaaz et al., 2015)
PCL, gelatin	NA	Electrospun nanofiber mats	(Pavliňáková et al., 2018)
Gelatin	Ciprofloxacin and polymyxin B sulfate	Film	(Shi et al., 2018)
Carrageenan	NA	Film	(Wahab and Abd Razak, 2016)
Chitosan	Doxorubicin	Hydrogel mould	(Huang et al., 2017b)
Chitosan	NA	Sponges	(Liu et al., 2014)
Gelatin, sericin	Zinc and Copper ions	Electrospun nanofiber mats	(Massoumi et al., 2019)
Poly (lactic-co-glycolic acid), chitosan	Minocycline	Film	(Makita-Chingombe et al., 2016)

with enhanced antibacterial activities (Cho et al., 2020). In a similar kind of study, Tejas Barot et al. and co-workers have reported the Farnesol-loaded HNTs as fillers to investigate their physicochemical and mechanical properties. They have reported that adding mass fraction of Farnesol-HNTs increases the compression strength, flexural strength and conversion degree. They also reported an increase in zone of inhibition for Streptococcus mutans and highly biocompatibility against NIH-3T3 (mouse embryonic fibroblast cells) cell lines (Barot et al., 2020b). Fig. 7 presents the HNTs assisted material for dental treatment.

Tejas Barot et al. and colleagues also designed silver mobilized HNTs to treat dental problems with enhanced physicochemical, mechanical behavior, and biological activities. They further reported that composite material didn't exhibit significant cytotoxicity against NIH-3T3 cell lines (Barot et al., 2020a). In another study, Qi Chen et al., have prepared Bis-GMA/TEGDMA dental resins with and without conventional glass filler. It was observed that increased mechanical properties were observed and but no significant increase in machinal behavior after impregnating a large mass fraction (5%). However, HNTs/Bis-GMA/TEGDMA dental resins/-composites have substantial mechanical properties (Chen et al., 2012).

Halloysite nanotubes can also be used to encase drug molecules and deliver them to periodontal disease-affected areas. This method reduces dosage-related side effects by selectively depositing a controlled amount of drugs. Controlled disintegration of drugs to release them at the right time is also beneficial (Bonifacio et al., 2017). Arestin® (minocycline microspheres), for example, delivers a sustained release of minocycline to the periodontium (Barot et al., 2021). In severe

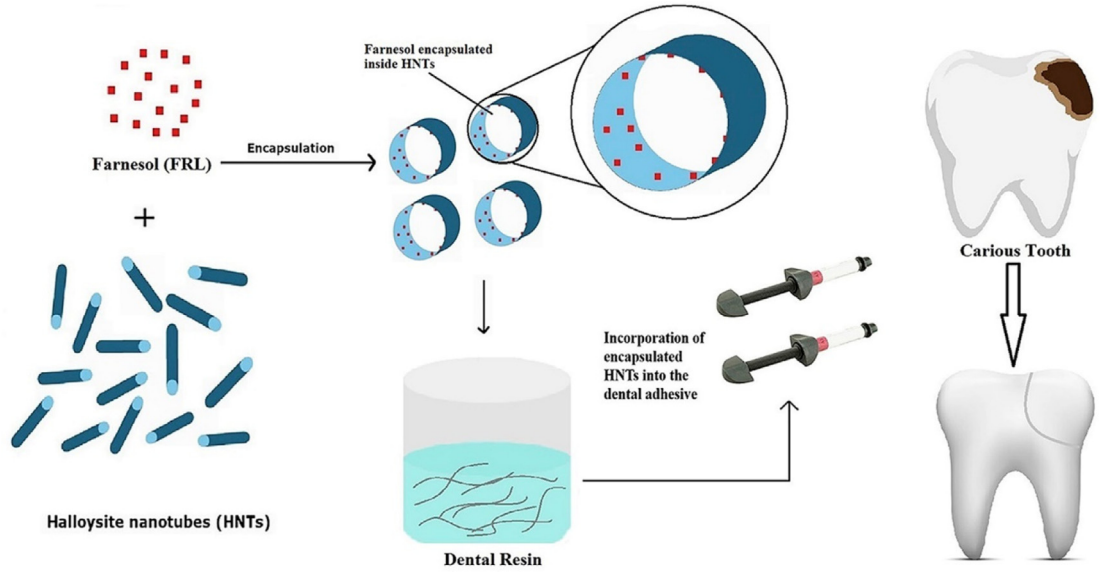

Fig. 7 Illustrate the healing of dental treatment using HNTs-based composite material. "Reprinted with permission from J. Mechanical Behavior of Biomedical Materials. Tejas Barot et al. and co-workers. Physicochemical and biological assessment of flowable resin composites incorporated with farnesol loaded halloysite nanotubes for dental applications, with permission from Elsevier" (Barot et al., 2020b).

periodontitis, however, microspheres may not be able to penetrate deeper lesions. Ceramic crowns and bridges, such as zirconia or alumina, meet aesthetic and functional requirements, but they are brittle with low elasticity. Katarzyna Gawdzinska et al. reported gelatin-modified halloysite nanotubes (HNTs-g) with silane-coupling of aluminium trihydrate as an innovative nanofillers system (ATH-sil). They discovered that methyl methacrylate and methyl methacrylate monomer (MM/mMM) synergistically affect acrylic materials. They investigated various analyses such as hardness, buffer solution absorption, and abrasion resistance. Besides these analyses, they also performed fall tests for dental applications (Gawdzinska et al., 2019).

7. Future perspectives

Nanoparticulate HNT-materials are abundant, environmentally friendly, and affordable nanoparticulate HNT-materials with no toxicity. These HNT-materials can be used in all medical fields, nanotechnology, and purification on a global scale. These can deliver targeted drugs to specific locations while controlling drug release, wound healing, and tissue engineering applications. More research using HNTs-based composites with natural polymers (arabinoxylan, beta-glucan, xyloglucan, chitosan, and others) is needed for tissue engineering and drug delivery for tissue engineering and drug delivery reinforcing mechanism of such additives. The nanofiber/HNTs in PMMA dental base resins is needed. Nanofibers/tubes could provide a new strategy for strengthening PMMA resins in the future and could be considered as encouraging reinforcing agents for denture base resin materials. In the near future, we believe HNT will be used in topical cosmetics formulations, animal therapeutic interventions, skin ointment, traditional oral formulations, and anti-microbial sprays, allowing medical formulation effectiveness to be extended (Kushwaha et al., 2021).

8. Conclusion

Natural sources of halloysite nanotubes are inexpensive and plentiful. Due to specific natural forces involved in their formation, Halloysite nanotubes have a wide range of morphology. Minerals have distinct properties such as pore size and porosity, surface area, and physicochemical and biomechanical properties useful in various biomedical applications. Halloysite nanotubes are a low-cost, biocompatible, nontoxic, and cytocompatible material used in a wide range of biomedical applications. With the perfect proportion of HNTs, the sustained release of therapeutic agents can be significantly increased in an aqueous environment. Due to the unique chemistry of HNTs, high surface area, and superior loading rates, the hybrid materials could provide a sustained-release delivery, tissue engineering, and dentistry system for biomedical applications. As a result, this paper has reviewed previous literature on HNT and HNT-polymer nanocomposites for biomedical applications in-depth, which may facilitate researchers in expanding the potential applications of HNTs-based polymeric composites.

CRediT authorship contribution statement

Muhammad Umar Aslam Khan: Writing - original draft, Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing. **Khalida Fakhruddin:** Visualization, Visualization, Data curation, Formal analysis, Software, Writing - original draft. **Sabrina Naula Allisha:** Visualization, Data curation, Formal analysis, Software. **Rozita Hassan:** Supervision, Funding acquisition, Project administration, Writing - original draft. **Saiful Izwan Abd Razak:** Validation, Supervision, Conceptualization, Funding acquisition, Investigation, Project administration, Resources, Writing - review & editing. **Maen Hussni Zreaqat:** Funding acquisition. **Hadafi Fitri Mohd Latip:** Resources, Methodology. **Mohd Najeb Jamaludin:** Methodology, Resources. **Anwarul Hassan:** Investigation, Resources, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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