Received: 12 February 2022 | Revised: 26 April 2022 | Accepted: 16 May 2022

DOI: 10.1002/jbm.b.35105

REVIEW ARTICLE

Recent advancement in polymer/halloysite nanotube nanocomposites for biomedical applications

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Abstract

Halloysite nanotubes (HNTs) have recently been the subject of extensive research as a reinforcing filler. HNT is a natural nanoclay, non-toxic and biocompatible, hence, applicable in biomedical fields. This review focuses on the mechanical, thermal, and functional properties of polymer nanocomposites with HNT as a reinforcing agent from an experimental and theoretical perspective. In addition, this review also highlights the recent applications of polymer/HNT nanocomposites in the biomedical fields.

KEYWORDS
biomedical applications, halloysite nanotube, mechanical properties, nanocomposites, thermal properties

1 | INTRODUCTION

Nanotechnology is a thriving field with numerous applications in science and technology such as food science and textile engineering,[1,2] industry such as energy storage product,[3,4] the environment, and energy conversion.[5,6] Nanotechnology is also essential in medical applications, including tissue engineering, cancer treatment, and therapeutic modalities.[7–9] According to the US National Nanotechnology Initiative and European Commission, materials with a dimension less than 100 nm are considered nanomaterials,[10] and one of them is nanotubes. Nanotubes are one of the most successful nanomaterials in nanotechnology research that consist of organic or inorganic atoms that formed single or multi-walled structure tubes with sizable internal volumes.[11] De Heer et al. reviewed many technologies of the nanotubes over the last decades such as hydrogen storage, transistor, electronic applications and more.[12] Nanotubes' advantages include a large inner volume, high aspect ratio, and tubular nanostructure. These advantages enable them to store chemicals or proteins, provide multiple attachment sites for various functionalization along the nanotube axis, and make the inner volume and surface accessible.[13]

Nanotubes include carbon, inorganic titanium (NiTi), silica, zirconia, and halloysite.[14] Many scholars reviewed the different types of nanotubes in polymer nanocomposites.[15–19] Meanwhile, one of the most popular nanotubes applied in biomedical application is carbon nanotubes (CNTs). Tadayyon et al. highlighted the CNT in poly(glycerol sebacate urethane) nanocomposites as a biodegradable strain sensor that successfully improves the mechanical properties of the nanocomposites.[20] Research on CNT can be found in tissue engineering,[21–27] suture,[28,29] drug delivery,[30] implant,[31,32] and other medical devices.[20,33–38]

Despite its wide application in biomedical fields, there is a concern about the higher amount of CNTs applied in the human body, leading to higher cytotoxicity.[39] Kobayashi et al., reviewed various toxicity test of CNTs which have been conducted mainly on mice.[40] From their review, they concluded that CNTs are carcinogenic that can trigger inflammation, fibrosis, and, lung cancer. Therefore, there are efforts to utilize other nanomaterials with lower risk in biomedical application, such as halloysite nanotubes (HNTs). HNTs are applicable in the biomedical field as cost-effective biocompatible nanotubes,[41,42] with excellent dispersion properties and reinforcing ability.[43] HNTs have sparked interest as a potential new additive for improving the properties of polymers, such as mechanical, thermal, and fire-retardant performance.[42,44,45] They are also environmentally safe as no profound toxic were reported in an in-vivo test conducted by

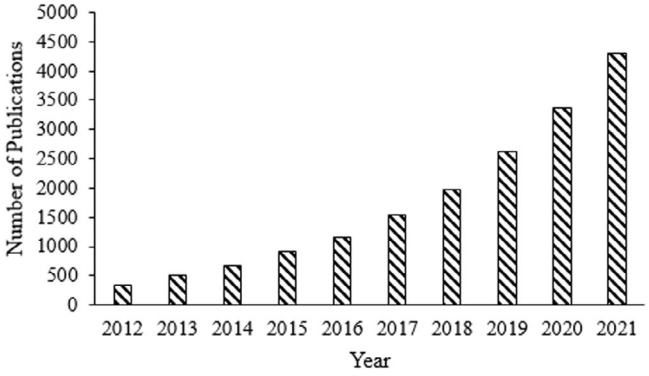

FIGURE 1 Number of publications for the term "halloysite nanotubes" from the year 2012 to the year 2021 (Data were obtained from the Google Scholar search engine, as of January 28, 2022).

Fakhrullina et al.[46] HNTs can also be used for tissue scaffolds and self-healing composites and strengthen microvascular networks and bone fixation plates.[44]

Figure 1 presents the number of HNT-related publications based on a Google Scholar search over the past 10 years. Figure 1 clearly shows that there has been active research interest in HNT for the past 10 years, and that interest is expected to grow in the future.

Figure 2 shows an infographic of polymers/HNT nanocomposites, their properties and applications for the current review. To date, many industrial and academic research aimed at producing optimum polymer properties by incorporating only a small amount of nanofiller using a diverse range of fabrication techniques.[47–50] Also, the investigation of nanocomposites composed of HNTs and biodegradable polymers, specifically for biomedical applications, appears to be an area of intense research.[51–53] Based on the author's knowledge, different techniques and types of polymer/HNTs and their properties applied in the biomedical application have been recently reviewed. However, those reviews are limited to the HNTs' toxicity for drug delivery approaches.[5,42,54,55] Meanwhile, the authors believed that it is also essential to review the mechanical properties of polymer/HNTs nanocomposites in biomedical applications, as different applications such as human scaffolds, sutures, and implant plates require a different level of mechanical strength.

Hence, the authors decided to review the mechanical properties of polymer with HNTs nanocomposites that focus on biomedical applications. The authors also included the thermal and intermolecular interaction of the polymer/HNTs nanocomposites in their review to support further the effect of HNTs on the mechanical properties of polymer nanocomposites. This paper aims to see how HNTs affects polymer-based nanocomposites' mechanical and thermal properties and intermolecular interaction. The conclusion should be how polymers incorporated with HNT with improved mechanical, thermal, and functional properties can be introduced into polymer nanocomposites for biomedical application.

2 | BIODEGRADABLE POLYMERS AND HALLOYSITE NANOTUBES (HNTS) FOR BIOMEDICAL APPLICATION

The biodegradable polymers market in industries has kept expanding from time to time due to their excellent properties such as being biodegradable, biocompatible, processability, and environmentally friendly. In this section, the authors explained the application of biodegradable polymers and included their advantages and disadvantages in biomedical applications. There are many ways of improving the properties of biodegradable polymers, which were also introduced in this section.

2.1 | Biodegradable polymers

The term "biodegradable" has led to a significant interest for researchers in medical purposes such as drug delivery,[56–58] tissue engineering,[59] fixation plates,[60] theranostic system,[61] and sutures.[62] The biodegradable implant can remove the need for a second surgery, reducing the cost of removing the material after the bone is healed. Some of the alternative products that are commercialized in medicinal industries include biodegradable polymers like polylactic acid (PLA),[63–65] and polylactic-co-glycolic acid (PLGA),[66–68] polycaprolactone (PCL),[62] and polypropylene carbonate (PPC).[69] These biodegradable polymers are highly advantageous compared with conventional medical devices such as titanium or other metallic materials, given that they do not result in stress shielding on the bone when placed in the human body.[70]

Among all these, PLGA and PLA are the most predominant biodegradable thermoplastic polymers commercialized for biomedical applications such as surgical instruments.[71–74] For instance, PLA can be effortlessly formed into screws, pins, plates for regenerative bone surgery, and scaffolds for tissue engineering and drug delivery devices.[75–77] Despite their success in the medical field, polymers such as PLA have inherent brittleness, limiting their application in medical areas.[78,79] Thus, blending two or more polymers will produce a new material with improved physical properties.[80] This method has gained much attention as an effortless and profitable method of developing polymeric materials with versatility for commercial applications.

Advantages are those which preserve biodegradability—for example, the blending of PLA with PPC,[81,82] PCL,[83] and PBS.[84] However, since most polymer blends are immiscible, blends of polymers such as PLA with higher toughness and ductile polymers will produce a weaker mechanical property than neat PLA. These limitations have restricted its applicability in medical applications, such as implant plates and screws. As a result, many alternatives have been reported[85,86] for improving the miscibility of polymer blends.

One alternative to enhancing the polymers' properties in biomedical applications is by incorporating nanofiller such as HNTs. As reinforcement for biodegradable polymers used in medical applications, the tubes have advantages over other nanoparticles, such as hydrophilicity, good dispersion ability, biocompatibility, entrapment of

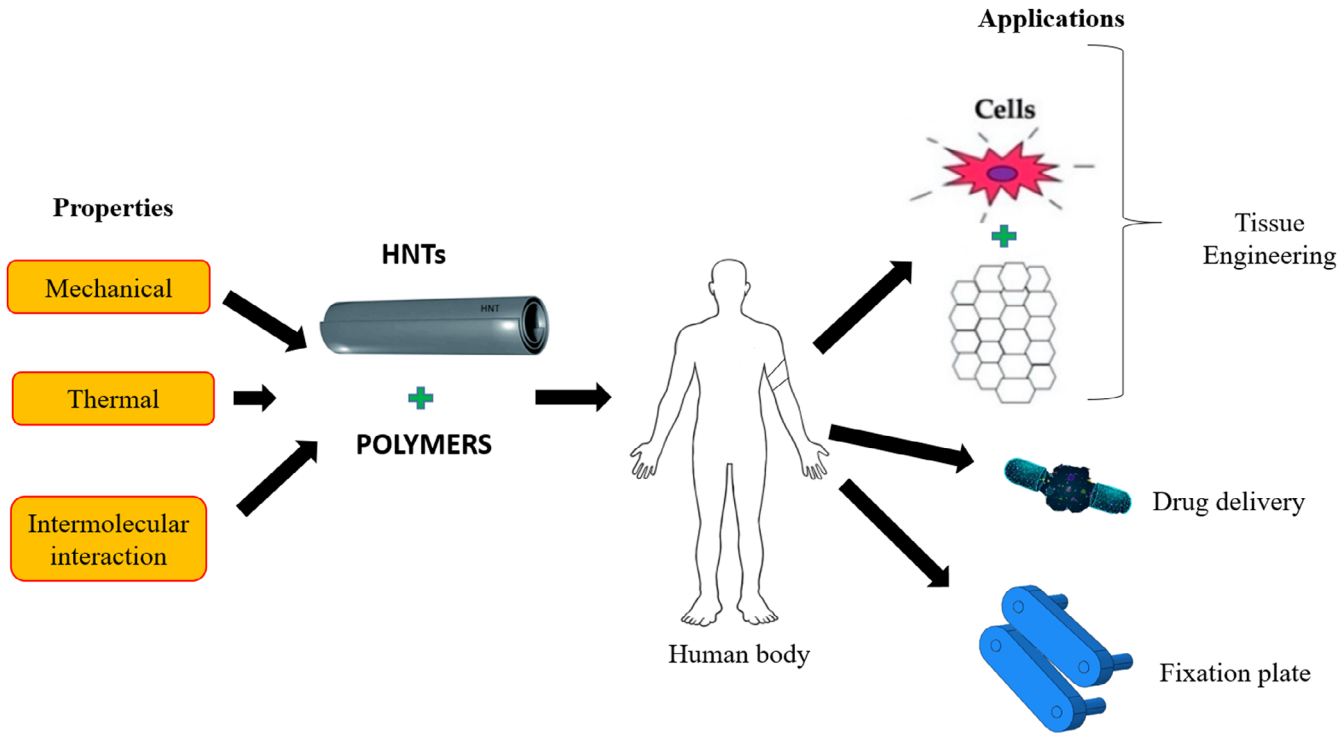

FIGURE 2 Properties and applications of polymer/HNT nanocomposites.

TABLE 1 Physical properties of HNTs

Properties	Values
Tube lengths	40 ~ 30,000 nm
Diameters	20 ~ 600 nm
Mean length	170 ~ 950 nm
Mean diameters	50 ~ 160 nm

Note: Refs. 91,161,162.

drugs, and low cost. In recent years, various studies of biodegradable polymers/HNTs have been explored and exploited by researchers to be applied to medical tools.[87–89] They proved that a small amount of incorporation of HNTs in polymer blends could improve not only the mechanical of the neat polymers but also improve the thermal and molecular properties of the polymers in polymer nanocomposites, which will be further explained in Section 3 in this review.

2.2 | Halloysite nanotubes

Incorporating a nanofiller such as HNTs is one alternative method for improving the properties of the polymer blends. HNTs have been an earth-forming natural clay nanotube for millions of years, available in the United States, China, and New Zealand.[45] They are new, multi-functional nanomaterials consisting of two layers of aluminium, silicone, hydrogen, and oxygen. It consists of an ultra-tiny hollow tube with a diameter smaller than 100 nm.[90] Table 1 shows the physical properties of HNTs reported by Hillier et al.[91] HNTs have good reinforcing ability and are easily dispersed in polymers[92] due to their nanosized and high aspect ratios.[93]

The schematic diagram and HNTs structure are shown in Figure 3.[94] HNTs have molecular formula of $Al_2Si_2O_5(OH)_4.nH_2O$ and consist of "halloysite-(10 Å)" and "halloysite-(7 Å)". Different between these two categories of HNT depends on the value of n in its molecular formula. The n equal to 2 refers to halloysite-(10 Å), a hydrated form of HNT, while n equal to 0 refers to halloysite-(7 Å), and a diverse form of halloysite-(10 Å).[95,96] HNTs' main constituents are aluminium (20.90%), silicon (21.76%), and hydrogen (1.56%).[97] HNTs have molecular formula similar to kaolinite and montmorillonite[98,99] and nanotube geometry similar to CNTs. The only difference is that it has a hydroxyl group.[100,101] HNTs provide a better alternative in medical fields with a lower production cost than CNTs and montmorillonite.

Several studies of cytocompatibility and blood compatibility of HNTs with the human body provided numerous positive feedback in biomedical applications.[102–104] Despite that, information on their degradability still requires further exploration. Though HNTs are expected to improve the polymer blends' properties, the concern is whether the HNTs will eliminate the polymers' biodegradability, a superior feature for regenerative bone surgery. De Silva et al.,[105] in their study, reported that blends of PLA with HNTs would not undermine the biodegradability of PLA composite due to the following reasons:

1. The structure of HNTs are similar to montmorillonite and kaolinite. Since both montmorillonite and kaolinite are degradable, it is expected that HNTs behave similarly.

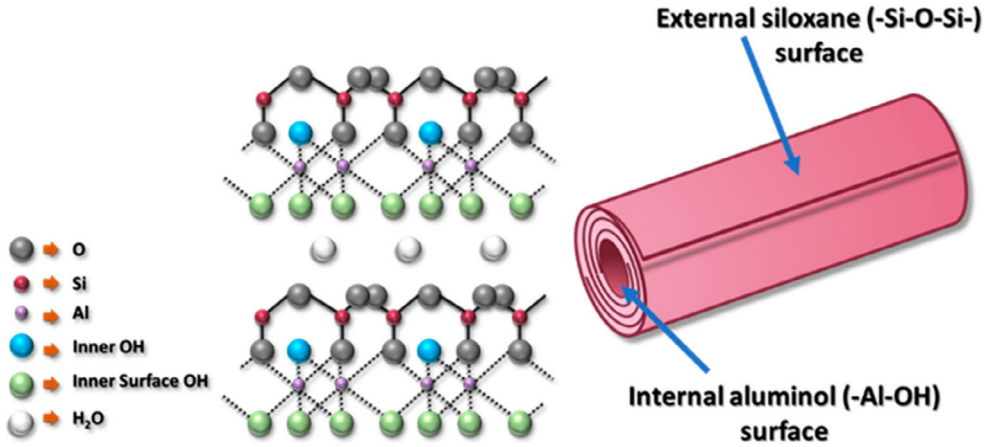

FIGURE 3 Schematic diagram of Hal-10.[94] (Adapted from Ref. 94)

2. The inclusion of hydroxyl groups in layered silicate improves the biodegradability of PLA/layered silicate composites.
3. Further research has shown that these composite degradation rates have not been affected or noticeably changed when kaolinites and synthetic kaolinites (similar to the HNTs structure) have been incorporated into the PLA matrix.

However, some papers have reported that HNTs are non-degradable.[105–107] Furthermore, according to Massaro et al.,[96] the human body cannot provide the aluminosilicate's biological mechanisms to degrade. Hence, treatment such as injectable drug delivery for HNTs is unsuitable, resulting in thrombosis. For this reason, the potential application of HNTs is only ideal for creams and implants.

Despite uncertainty regarding the degradability of HNTs, Lvov et al. showed that the HNTs were efficiently removed from an organism by macrophages.[108] HNTs are also generally regarded as safe (GRAS) by the FDA; hence, they are considered a healthy and biocompatible material.[109] A few research on HNTs incorporated with biodegradable polymers proved that HNTs would not affect polymers' degradability. For example, Chen et al.[110] have conducted a test on the degradation of PGS/HNTs composites in a tissue culture medium and reported that the addition of 3%–5% of HNTs results in a low percentage of weight loss. However, as the amount of HNTs increased, the weight loss of the blends increased.

Another study of biodegradable polymer/HNTs blend was conducted by Hasan et al.[111] They revealed that the biodegradation of poly (3-hydroxybutyrate-co-3-hydroxy valerate) films was faster with the addition of HNTs. Another study conducted by Liu et al.[112] reported that HNTs were commonly used as catalyst for polymer biodegradation. Pasbakhsh et al.[106] stated that future studies should focus on the possible and safe amount of HNT sustained or degraded in the body.

3 | THE PROPERTIES OF POLYMER/HNT NANOCOMPOSITES

As shown in Table 2, many studies on HNTs reinforced polymer-based nanocomposites have been published. The polymer/HNT nanocomposites' efforts include various compositions, fabrication processes, characterization, and clinical evaluation. Among all, one can see that a significant body of research has been done on PLA/HNT nanocomposites.

3.1 | Mechanical properties of polymer/HNT nanocomposites

HNT's achievement as a filler reinforcement to polymers has been documented in numerous research papers, as it improved tensile strength, elongation, and Young's neat polymers module.[110,113–115] According to Alakrach et al.,[116] the tensile strength increases to more than 25 MPa when only 2 wt% HNT is added to neat PLA. This result is consistent with the findings of Tham et al.[117] and Dong et al.[118] Therias et al.,[119] on the other hand, reported that adding HNT to PLA does not affect its tensile strength. However, the rigidity of PLA/HNT shows some improvement as there is a gradual increase in Young's modulus as HNT increases.

According to some researchers, the tensile strength of polymer/HNT nanocomposites decreases as the HNT content increases. This result is supported by Ismail et al.,[120] where the tensile strength of the matrix was first increased from 9.17 to 11.19 MPa for the first 2 wt% of HNTs, later decreasing as the amount of HNT increases. Also, there is a small, gradual increment of Young's modulus with no significant change in the PP/rNRg nanocomposites' elongation. A work on PLA/polyamide 11 reinforced with HNT demonstrated by Rashmi et al.[121] revealed that the blends' elongation decreases at 4 wt % of HNT added to the blends. This research can be supported by Alakrach et al.,[116] where the tensile strength and elongation of PLA/HNT started to decrease when HNT increased to more than 4 wt%.

Moreover, incorporating HNTs in polymer nanocomposites also improves their compressive strength.[122–124] Recently, Liu et al. have successfully developed halloysite nanotube/polyvinyl alcohol (HNT/PVOH) aerogel composites where the compressive strength of HNT/PVOH aerogel was tested by using the electronic universal testing machine. The result shows that the compressive strength of

TABLE 2 List of recent works made by the different researchers on the HNT reinforced polymeric composite from 2010 to 2020

Reinforcement	Matrix	References
Halloysite nanotubes (HNTs)	Polyglycerol sebacate (PGS)	110
	Poly(3-hydroxybutyrate-co-3-hydroxy valerate)	111
	Polypropylene/recycled natural rubber gloves (PP/rNRg)	120
	Polypropylene/polylactic acid (PP/PLA)	132
	Polylactide	113,129
	Polylactic acid/polyamide 11 (PLA/PA11)	121
	Polylactic acid/ethylene-co-vinyl-acetate (PLA/EVA)	131
	Polyetherimide/Silicone	163
	Polylactic acid	51,52,116–119,127,130,133,144,146,164
	Natural fiber/polylactic acid	143
	Polycaprolactone (PCL)/PLA	165
	Polylactic acid/zirconium hydroxide (PLA/ZrO2)	166
	Polylactic acid/polyethylene glycol (PLA/PGA)	135
	Polyethylene	167
	Unsaturated polyester	168
	Polypropylene (PP)	169
	Polyvinyl alcohol	122
	Cellulose	123
	Polyurethane	124

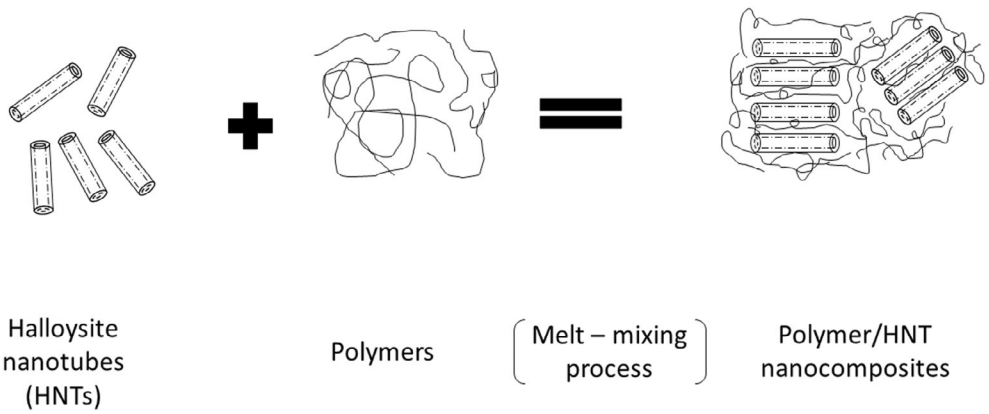

FIGURE 4 Structure relationship between polymer and HNT in polymer/HNT nanocomposites.

HNT/PVOH aerogel was significantly increased from only 0.4–2.9 MPa with 7 wt% of HNT.[122] Besides that, Huang et al. have incorporated HNTs into cellulose to form hydrogel for curcumin delivery. They reported a significantly increased compressive strength from 29.8 kPa of pure cellulose hydrogel to 128 kPa of the composite hydrogels with 66.7% HNTs.[123] The significant enhancement of both materials with the addition of HNTs indicates that HNTs have strong cellulose-reinforcing ability.

As shown in the above discussion, it is concluded that the role of HNT in polymer blends is intricate and is influenced by many factors. One of the crucial factors is the geometrical structure of HNT. Figure 4 represents a schematic diagram to understand this factor. HNT is a tubular nanostructure with a large aspect ratio, consisting of an aluminol network at the inner surface and a siloxane network on the outer surface. It is believed that during melt-mixing, the polymer chain will diffuse from the bulk polymers melt into the interlayer of these nanotubes, resulting in a well-ordered multilayer with alternating polymer, siloxane, and aluminol network layer of HNT.[125] HNT will then enhance the tensile strength and modulus of the polymers due to its high modulus and strength.

Besides, the large aspect ratio HNT has enabled it to bind with other components, the polymer blends.[5]

Furthermore, in their research, Lecouvet et al.[126] stated that HNT has a peculiar chemical property that consists of a multilayer structure and a few hydroxyl groups located on the surface of the nanotubes. These hydroxyl groups exhibit a low secondary interaction among HNTs by hydrogen bond and van der Waal's force. Due to this reason, HNTs are easily spread in non-polar polymers matrices such as polypropylene and polylactic acid, which improves polymers' mechanical properties.

However, some researchers reported a reduction in polymers' mechanical properties by incorporating HNT.[110,116,121,127] The decrease in mechanical properties maybe because the matrix and the filler are not well entangled, as Narimissa et al.[128] reported. One reason behind this problem was the agglomeration of the fillers.[129] Excessive HNTs do not constantly improve the blends' mechanical properties; instead, the opposite result will appear.[130]

Singla et al. conducted a scanning electron microscopy on PLA/EVA with 9.1% of HNT and reported that the increased amount of HNTs leads to an agglomeration problem that causes a weak phase adhesion between the matrix and HNT. Due to the weak phase adhesion, the mechanical performances of the nanocomposite decreased.[131] Rajan[132] studied polypropylene/polylactic acid (PP/PLA) incorporated with HNTs ranging between 0% and 10%. However, his experiment discovered that 6 wt% of HNTs are still sufficient to reinforce the mechanical properties of PP/PLA. Hence, it is essential to highlight the optimum range of HNTs added in the blends to affect the interfacial adhesion and the filler's dispersion.[133,134]

3.2 | Thermal properties of polymer/HNT nanocomposites

Differential scanning calorimetry (DSC) can be used to investigate the thermal properties of polymer/HNT nanocomposites, obtaining information such as crystallinity (χ_c) and glass transition temperature (T_g), crystallization temperature (T_c), and melting temperature (T_m). Several studies on polymer/HNT nanocomposites' thermal properties have been well reported in the literature.[107,130,135,136]

Incorporating HNT has a slight effect on the T_g of polymer/HNT nanocomposites, as the values of T_g only differ by 1–3°C from the T_g of the neat polymer.[130] Cobos et al. demonstrated a thermal test on PLA/HNT nanocomposites fabricated using a direct melt mixing method and reported a slight increment of T_g between 0.5 and 1.44°C.[51] The increase of T_g shows that incorporating HNT has hindered the migration and diffusion of PLA molecular chains, which leads to a decrease in neat PLA flexibility.[51,135,136] Sharma also reported a shift of T_g of PLA/PEG from 51.10 to 52.7 when 10 wt% of HNT was added to the blend.[135]

Meanwhile, some researchers reported a slight shift of T_g of polymer/HNT nanocomposites to a lower temperature.[116,118,137] As discovered by Risyon et al., the T_g of PLA gradually reduced from 58.49 to 57.42°C with an increasing amount of HNT from 0 to 6 wt%.[138] A reduction of the T_g value shows that the addition of HNT has disrupted the polymer molecular chain's entanglement and interaction, enabling the polymer/HNT nanocomposites to change from glassy to rubbery at a lower temperature.[116,118,130,138] Moreover, lower T_g improved the polymer's flexibility due to the nanotubes' bridging effect.[136]

The crystallization behavior of polymer nanocomposites is influenced by HNT.[116,118,137,139–142] It typically affects polymer crystallization by acting as a heterogeneous nucleating agent in the polymer matrix. Alakrach et al. conducted thermal analysis on PLA incorporated with different types HNTs and reported a decrease of T_c in PLA/HNT nanocomposite.[116] Dong et al. also reported decreased T_c from 84.3 to 79.4°C when 1 wt% of HNT was added to the PLA matrix.[118] According to Alakrach et al., HNTs, with their tubular structure and large surface area, act as an effective nucleating agent, allowing PLA to crystallize more quickly, lowering T_c.[116]

On the other hand, the T_c of PVA/HNT nanocomposite demonstrated by one research[137] shows an insignificant but gradual increase from 191 to 196°C as HNT increased from 0 to 2.5 wt%. According to research, PVA consists of a semicrystalline structure containing physical and chemical properties such as inter-chain polymer interaction due to the H-bond between the hydroxyl groups. Therefore, as HNTs are added to PVA, it will alter the intermolecular and intramolecular forces between the polymer chains by its –OH groups, leading to changes in the physical structure and crystallization behavior of PVA.[139]

Tham et al. reported that incorporating HNT does not affect the T_m of neat PLA. However, with the addition of 2 wt% of HNT, two T_m values 150.7 and 157.5°C, had changed to only one T_m, 153°C, due to the H-bonding between nanofiller and polymer matrix inhibiting a crystal reorganization process.[117] Meanwhile, Risyon et al. reported a slight increase of T_m of neat PLA from 152.27 to 152.64°C when incorporated with 3 wt% of HNT. This is because HNT as a nucleating agent helps reorganize the crystalline structure of PLA from less perfect to a higher ordered crystal which requires a higher heat to break the crystal structure and melt, resulting in a shift T_m to a higher value.[138]

Few researchers also reported a decrease in T_m value with incorporating HNT.[118,143] For example, Chen reported a slight decrease of T_m of neat PLA from 173.61 to 172.46°C when neat PLA was incorporated with 15 wt% of HNT. Dong et al. explained decrease in T_m value is due to the incomplete crystalline structure formed by the HNT heterogeneous nucleation with thinner or less perfect crystalline lamella. Hence, further investigation on the thermal properties of polymer/HNT nanocomposites to clarify two different findings of T_g, T_c, and T_m of polymer matrix incorporating HNTs.

As aforementioned, the increase of HNT leads to agglomeration in polymers. This problem will also affect the thermal properties of the polymers. Initially, T_m and crystallinity of poly(3-hydroxybutyrate-co-3-hydroxy valerate) (PHBV) increased as the amount of HNT incorporated in PHBV increased from 0 to 10 wt%.[111] Based on different studies[137,138] reported, it is confirmed that the agglomerate of HNT in the PHBV matrix has reduced its nucleating abilities due to smaller

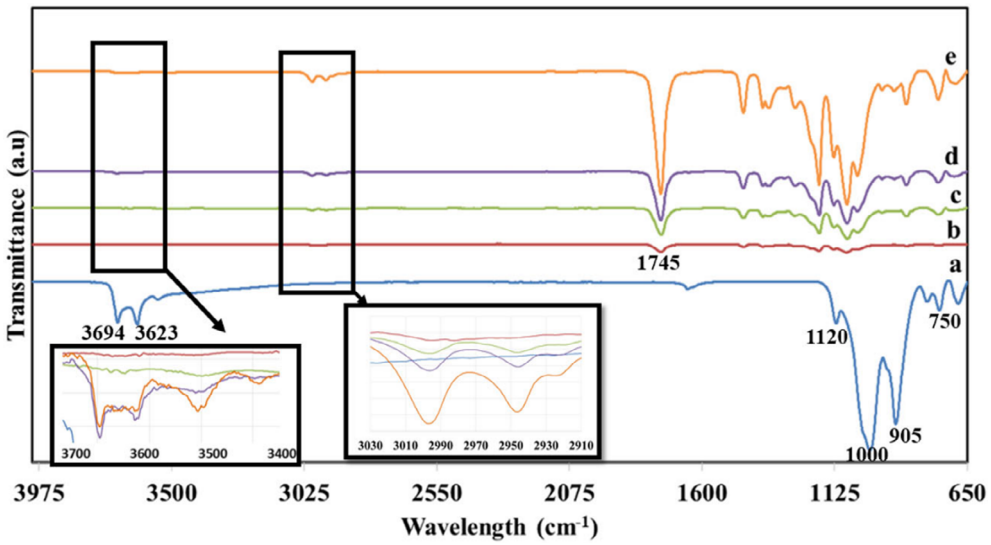

FIGURE 5 FTIR spectra of (A) HNT; (B) neat PLA; (C) PLA/1wt%HNT; (D) PLA/3wt %HNT; (E) PLA/5wt%HNT.[142] (Adapted from Ref. 142)

specific surface areas resulting in a less perfect crystal order. Hence, a low melting temperature is required to break the PHBV chain and melt.

3.3 | Intermolecular interaction in polymer/HNT nanocomposites

HNT reinforces polymer matrixes like polylactic acid, polyamide, polypropylene, epoxy resin, ethylene-propylene-diene monomer rubber, and styrene rubber by acting as a filler.[107] HNTs physically contain hollow tubes with a very high surface area with a high aspect. This one-of-a-kind physical property encourages a good filler-matrix interaction. When HNTs are added, tensile, fracture, impact strength, and other mechanical and thermal properties are believed to be significantly improved.[144] Hence, this section will explain the mechanism of HNT as a reinforced filler that improves the mechanical properties of polymer nanocomposites.

Many researchers have conducted an FTIR-spectroscopy on polymers-HNTs.[80,92,108,145] For example, Liu et al.[112] showed an FTIR on HNT with PLA. They reported some interaction between them, such as PLA hydroxyl or carbonyl groups with the hydroxyl of HNT (at the inner and octahedral surface), Si-O-Si groups of HNTs via hydrogen bonds, which likely contributed to the optimization of PLA's mechanical properties. Furthermore, Kruglikov et al.[146] performed a theoretical study called a density functional theory (DFT) for more in-depth knowledge of the mechanisms of HNT with PLA and reported that the bonding mechanism in halloysite nanotubes-PLA nanocomposite is formed by Van der Waals attraction between the LA and HNTs, and also hydrogen bonds.

The study of intermolecular interaction between PLA and HNT was recently reported by Eryildiz and Altan, as illustrated in Figures 5 and 6.[142] As displayed in Figure 5, the HNT spectrum shows two bands at 3694 and 3623 cm $^{-1}$ refers to the terminal OH groups. Meanwhile, for neat PLA, no bands were observed between these

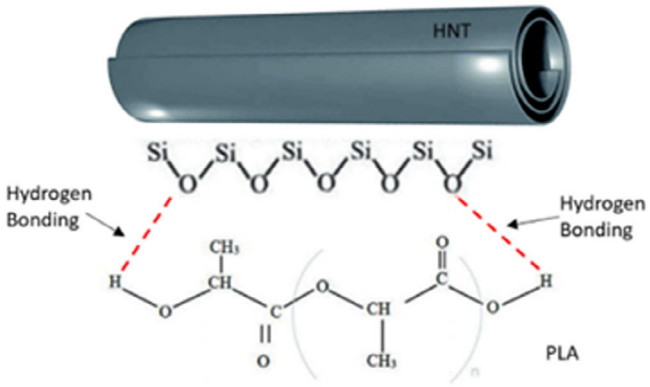

FIGURE 6 Schematic diagram of intermolecular interaction between HNT and PLA.[142] (Adapted from Ref. 142)

ranges. However, the OH terminal's intensity in PLA/HNT increases as HNT increases. This increase in intensity clearly shows the existence of HNT in PLA. Besides, wavenumbers of 905 and 1000 cm^{-1} on the HNT spectrum refer to the Al-OH and SiO groups. These bands exhibited a definite shift to 1042 cm^{-1} as the amount of HNT in PLA composites increased to 5 wt%. Also, two PLA/HNT spectrum bands are observed within 3000–2900 cm $^{-1}$. As the amount of HNT increased, a band was seen. Wavenumber shift within 905 and 1000 cm^{-1} to 1042 cm^{-1} is due to intermolecular interaction between HNT and PLA, SiO, and OH, illustrated in Figure 6.

4 | BIOMEDICAL APPLICATION OF POLYMER NANOCOMPOSITES

4.1 | Tissue engineering scaffolds

Historically, tissue engineering is defined as creating biological substitutes that restore, sustain, or enhance tissue function by integrating different engineering, life sciences, and methods.[147] There are a few

crucial aspects to consider for an ideal tissue scaffold: a porous structure, biocompatible, biodegradable, high stiffness, and toughness. The incorporation of HNT in polymers such as PLA,[142] PVA,[148] PLGA,[149] and PCL[150] for tissue engineering has been well reported.

PLA/HNT nanocomposites scaffolds with 1, 3, and 5 wt% of HNTs were successfully fabricated using foam injection molding.[142] The addition of 3 wt% of HNTs successfully improved the human scaffolds' mechanical properties and cell viability due to improved scaffold morphologies. There was a decrease in glass transition temperature from 63.54 to 61.90°C with 5 wt% HNTs also proved that the HNTs had improved the flexibility of the neat PLA.

The cytotoxicity test also proved that HNT could enhance the cytocompatibility of the nanofiber. Eryildiz and Altan demonstrated a cytotoxicity test on PLA/HNT scaffolds and proved that HNT in PLA scaffolds improved its surface area, increasing cell proliferation. Improved pore density due to incorporating HNT improves the scaffold efficiency in cell adhesion, nutrient, and waste transportation.[142] Qi et al. proved that the HNT-doped PLGA enables optimum cell growth and proliferation nutrition, allowing more protein adsorption.[149]

4.2 | Drug delivery

Drugs are transmitted to the targeted organ or tissues through "burst released." Initially, the availability of drugs transmitted to the organ or tissues cannot be prolonged and predicted over a while. There might also be a risk that the drug will degrade earlier before reaching the targeted site. Hence, the healing process cannot be achieved.[151] For example, although PCL is extensively applied in biomedical and pharmaceutical fields, its hydrophobic features lower the ability of drug loading and releases ability.[152]

Many researchers have reported HNT as a crucial technology for drug deliveries.[52,96,151–154] Massaro et al. stated that HNT could be used as a natural nanocarrier for loaded active substances and nanocomposites thanks to its large surface area, high dispersion, hollow tubular structure, large cavity volumes, and flexible surface structure. Other attractive properties include non-toxic, hydrophilic, and low production costs.[96] Hence, it is believed that reinforcing polymers with HNT could develop a better performance of the drugs delivery system. HNT/polymer nanocomposites for drug delivery consist of powders, suspension,[153] and a fibrous scaffold,[152] with many potentials for clinical treatment, such as curcumin.

Another reason for this HNT to function as a drugs delivery agent can be further understood based on Figure 3. From Figure 3, one can see that HNTs consist of three components: aluminium, silicon, and oxygen, which form a negatively charged siloxane group (Si-O-Si) on the external surface, and the positively charged aluminol groups (-Al-OH) on the internal surface that can carry many synthetic and biological components.[5] Wei et al. have demonstrated a schematic figure of encapsulating the HNT with the benzotriazole-copper film to extend the release rate of the antiseptic.[155] They have shown that the negative charge of the siloxane attracted the benzotriazole and Cu^{+2} ion. Hence, the complexation and release rate can be easily controlled by varying the concentrations of these two components.

Since HNTs easily to carry many synthetic and biological components, Venkatesh et al. have studied the effect of loading the aspirin into the lumen of the HNTs prior to forming an HNT/PLA nanocomposite. They successfully loaded the aspirin into the HNTs before melt-compounding it with the PLA, which resulted in sustained release of the aspirin from the PLA/HNT nanocomposites.[52]

Satish et al. have reported that two types of hydroxyl groups exist inside and outside HNTs that can be used as an active site for functionalization and drug loading through modification. Meanwhile, surface modification of HNTs can be achieved either through physical modification or chemical modification. Therefore, a surface modification of HNT has been studied to improve its application in PCL/PEO electrospun fibrous membrane for drug delivery. In this study, the HNTs were modified by two different types of saline modification which are 3-Aminopropyltriethoxysilane (APTES) and 3-Glycidoxypropyltrimethoxysilane (GPTMS).[138] The silane-modified HNTs (HNT-APTES and HNT-GPTMS) demonstrated a much higher Cur loading capacity, while APTES modified HNT showed the maximum encapsulation efficiency of 97.1 ± 1.9% compared to PCL/PEO- Cur, which calculated as 71.8 ± 3.2% only.

Bediako et al. (2018) developed an intriguing method to improve the properties of HNT for loading and sustain release applications. First, the modification of HNT was conducted through chemical modification, by which 1 g of HNTs were treated using 0.01 M of sulfuric acid. The sample was then stirred on the hot plate at 40°C for about 1 h. Next, the acid-treated halloysite was washed several times with deionized water until the pH of the supernatant was close to neutral. The sample was then dried in an oven at 50°C for 24 h. As a result, the inner lumen size of the HNT was successfully enlarged. This enlargement is due to sulfuric acid reacting with the inner alumina of the halloysite.[151] Besides that, Bediako et al. also reported that polymer/HNT composites' formation had prolonged the release rate of drugs, hence making it able to release drugs to the targeted organ or tissue at a controlled rate.

HNT through modification is also proposed to enhance curcumin's bioavailability, a potential drug for cancer treatment that has been well reported.[152,154] First, HNT was modified by succinic anhydride, resulting in carboxyl groups forming (HNTs-COOH). Later, the HNTs–COOH was blended with chitosan through N-(3-dimethyl aminopropyl)-N0-ethyl carbodiimide (EDC)/N-hydroxysuccinimide (NHS) reaction, forming HNTs-g-CS.[154] Also, a slow-release profile of Curcumin (Cur) was observed for PCL/polyethylene oxide (PEO) blended with HNT modified by 3-Aminopropyltriethoxysilane (APTES).

4.3 | Bone fixation plate

Bone fixation or implant is used in the medical industry to correct any injuries or bone fractures resulting from malformation, tumor resection, or accidents. The standard fixation plate includes dental implants,

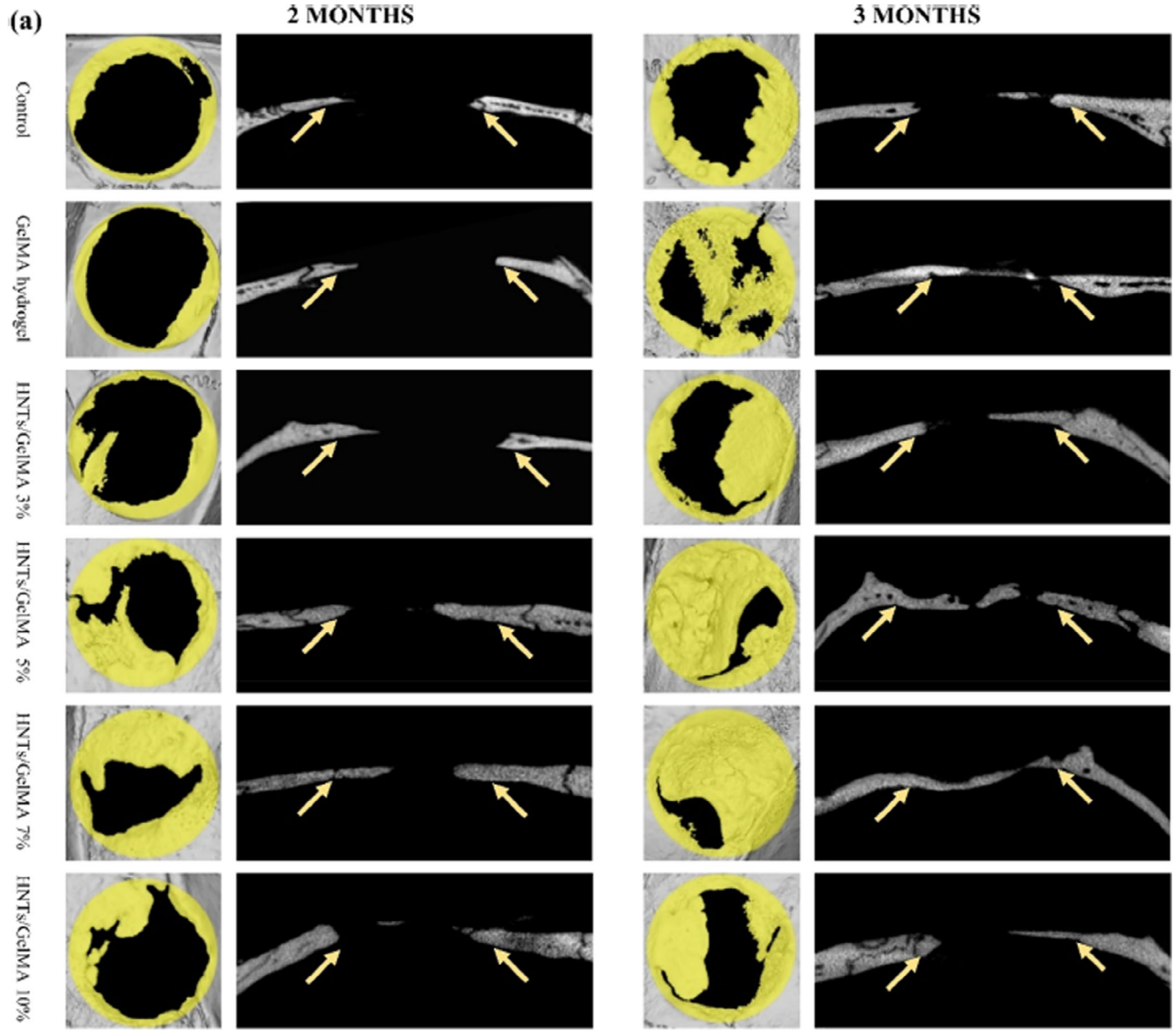

FIGURE 7 Micro-CT image of calvarial bone defect after 2- and 3-month implantation. Reprinted (adapted) with permission from Ref. 156. Copyright (2022) American Chemical Society

mandibular fixation plates, and orthopedic. The commonly used fixation plate are acrylic materials such as poly(methyl methacrylates (PMMA). Many researchers promoted the incorporation of HNTs in bone fixation plates.[156] Its well-known nanotubular structure and unique properties, such as good biocompatibility and functionality, provide advantages in bone regeneration. The osteogenic activities were reported by Huang et al. through an in-vitro and in-vivo study of different HNTs' ratios of HNTs/GelMA hydrogel on the animal's calvarial bone.

For the in-vitro study, the osteogenic behaviors of human dental pulp stem cells (hDPSCs) in HNTs/GelMA hydrogels were evaluated by alkaline phosphate (ALP) assay. On the 7th day, ALP synthesized by hDPSCs in the group with HNTs/GelMA 5% hydrogels was increased, while hDPSCs treated with HNTs/GelMA 7% hydrogels produced more ALP than other groups. Therefore, results demonstrated that 7% HNTs/GelMA hydrogel enhanced hDPSCs proliferation and osteogenesis in vitro. The results may partly account for the Si element on the surface of HNT regulating the osteogenic behavior of hDPSCs. In addition, it has been proven that silicate ions could strengthen the in vivo bioactivity of hydroxyapatite.

To further determine the capability of HNTs/GelMA hydrogels in bone regeneration, the model of calvarial defects was applied with the implantation of HNTs/GelMA hydrogels. As shown from Figure 7, at 2 and 3 months after implantation, an improvement in bone formation could be found in the group treated with the hydrogels containing the HNTs. At 3 months after implantation, the newly formed bone had almost covered the defects in HNTs/GelMA 5% and 7% group, whereas only a thin layer of bone tissue had formed in the control

group, as confirmed by the statistics of bone mineral density, bone volume, and trabecular thickness.

Gawdzinska et al. reported a new invention of PMMA with the addition of gelatin-modified halloysite nanotubes (HNTs-g) and silane-coupled aluminium trihydrate (ATH-sil). The incorporation of the modified nanofiller provides an improvement in the flexural modulus and strength of acrylic material (methyl methacrylate with methyl methacrylate monomer [MM/mMM]).[157] The incorporation of 5 wt% of HNT increased flexural strength from 2.23 to 2.32 GPa. Meanwhile, for modified HNT, the flexural strength of PMMA increased further to around 2.69 GPa.

A three dimensional (3D) printing of polymer/HNTs nanocomposites in various medical application, especially medical implant, have increased in the research area.[46,156,157] For instance, a new 3D printed design of PLA/HNT loaded with zinc nanoparticles was demonstrated by Luo et al.,[158] by which HNTs were used to enhance the properties of PLA and release bioactive agents in a sustained manner.

According to Venkatesh et al.,[53] incorporating nanofillers such as HNTs resulted in a higher viscosity of the polymers. However, it will then affect the printability of the nanocomposite filament. Hence, as an alternative, they have developed the polymer PLA with a nanoclay HNT by hot-melt extrusion (HME) to produce a pellet form of PLA/HNT nanocomposite. Next, through the fused filament fabrication (FFF) method, the filaments were to make standard tensile bars for mechanical characterization.

In recent years, Mrówka et al. have developed a novel thermoplastic polyurethane (TPU) incorporated with HNTs for future personalized intervertebral disc implant applications.159 In this research, the TPU/HNT nanocomposites were prepared by the twin-screw extruder and underwent a few tests such as tensile, and MTT cytotoxicity tests before the TPU/HNT filament was fabricated. The results showed that with only 2% HNT, the nanocomposite could withstand 26% increased stress and 50% increased elongation compared to pure TPU. Meanwhile, A MTT cytotoxicity assay confirmed the cytotoxicity of all tested materials against human epidermal keratinocyte cells (HaCaT) as after 72 h, the survival fraction of all compositions increased, ranging between 95% and 98%, relative to the control, which is 100%.

5 | CONCLUSION

HNT is a novel, multipurpose natural clay nanotubes consisting of an ultra-tiny hollow tube with a diameter of 100 nm. Many works on HNT reinforced polymer-based nanocomposites have been reported, including various compositions, fabrication processes, characterization, and clinical evaluation. In conclusion, HNT plays a significant role as a reinforcing agent in polymer nanocomposites, significantly improving mechanical properties such as stiffness and flexibility in immiscible polymer blends. Theoretically, due to the large aspect ratio of HNT, the polymer chain will diffuse from the bulk polymers, melt into the interlayer of the Aluminol network at the inner surface, and a siloxane network on the outer surface, and hence improve the tensile strength and modulus of polymers. However, there are cases where the tensile strength decreases with the addition of HNT due to the agglomeration problem.

Moreover, HNT affected the thermal properties of the polymers such as PLA nanocomposites. For instance, incorporating HNT in PLA increases T_g of neat PLA, showing that HNT has hindered the migration and diffusion of PLA molecular chains, which leads to a decrease in neat PLA flexibility. Also, HNT plays a critical role in the polymers' crystallization behavior by acting as a heterogeneous nucleating agent in the polymer matrix. As a result, increased crystallinity and crystallization temperature, the minimum activation energy for crystallization, and finer spherulites occur.

Besides, HNT has a peculiar chemical property that consists of a multilayer structure and a few hydroxyl groups located on the nanotubes' surface. These hydroxyl groups exhibit a low secondary interaction among HNTs by hydrogen bond and van der Waal's force which are easily spread in non-polar polymers.

Finally, HNT is highlighted as a valuable and low-cost material used as a reinforcing agent in polymer nanocomposites and a promising candidate in biomedical applications as it is produced from natural resources and the biocompatible human body. Future studies should focus on the unresolved fundamentals and properties, such as the agglomeration problem, to develop a high performance of HNT/polymer nanocomposites in the biomedical field.

DATA AVAILABILITY STATEMENT

The data that support the findings shown in Figure 1 are openly available in Google Scholar search engine, as of January 28, 2022. Figure 2 Graphical illustration of properties and applications of polymer/HNT Nanocomposites. The image of HNT was obtained from Ref. 142. The image of tissue engineering was adapted from Ref. 160 which are openly available in MDPI at https://doi.org/10.3390/jfb13010001. Human body and fixation plate were available from the author. Data that support the findings displayed by Figure 3 is adapted with permission "Membranes" at https://doi.org/10.3390/membranes10010002, Ref. 94. Data displayed by Figure 4 were available from the author. Data that support the findings displayed by Figures 5 and 6 adapted with permission from "Fabrication of polylactic acid/halloysite nanotube scaffolds by foam injection moulding for tissue engineering" at https://doi.org/10.1002/pc.25406, Ref. 142. Data that support the findings displayed by Figure 7 adapted with permission from "Halloysite Nanotube Based Scaffold for Enhanced Bone Regeneration" at https://doi.org/10.1021/acsbiomaterials.9b00277, Ref. 153.

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How to cite this article: Mohamed Haneef INH, Mohd Shaffiar N, Buys YF, Syed Shaharuddin SI, Abdul Hamid AM, Widiyati K. Recent advancement in polymer/halloysite nanotube nanocomposites for biomedical applications. *J Biomed Mater Res*. 2022;1-15. doi:10.1002/jbm.b.35105