Nanoclays for Biomedical Applications

Laura Peña-Parás, José Antonio Sánchez-Fernández, and Román Vidaltamayo

Abstract

Clays are naturally occurring layered mineral materials that are low cost and environmentally friendly. Nanoclays are clay minerals with at least one dimension in the order of 1–100 nm. In nature, two forms of nanoclays, anionic and cationic clays, are present depending on the surface layered charge and the types of interlayer ions. Commonly found nanoclays in the literature are montmorillonite, kaolinite, laponite, halloysite, bentonite, hectorite, laponite, sepiolite, saponite, and vermiculite, among others. Nanoclays have been widely used as reinforcements for polymer matrix composites improving mechanical, thermal, and anticorrosion properties, for example. Due to being nontoxic, nanoclays and their composites have been studied for biomedical applications such as bone cement, tissue engineering, drug delivery, wound healing, and enzyme immobilization, among others. This chapter presents the state of the art of biomedical application of nanoclays and nanoclay-polymer matrix composite materials.

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Introduction

Clay minerals are minerals that constitute sedimentary rocks and derived soils made of layered silicates [1]. These aluminosilicates have a general chemical formula of (Ca, Na, H)(Al, Mg, Fe, $Zn)_2(Si, Al)_4O_{10}(OH)_{2-x}H_2O$, where x represents the amount of water [2]. The interaction between water and the solid surfaces affects the properties of both phases [3], and these interactions are of great interest due to their possible applications in important applied fields, such as for biomedical applications [3].

Clay minerals may also be broadly classified into two categories: natural and synthetic clays [4], and their structures consist of alternating tetrahedral SiO_2 and octahedral AlO_6 sheets with varying ratios (Table 1) that can be: (a) 1:1, with one octahedral layer linked to a tetrahedral one; (b) 2:1, with two tetrahedral sheets on either side of an octahedral, and (c) 2:1:1, with a positively charged brucite sheet sandwiched between layers that restrict swelling. Chlorites with a 2:1:1 structure are not always considered clays and are sometimes classified as a separate group within the phyllosilicates [4].

Clay platelets also undergo structural rearrangements in order to form nanofibers, nanotubes, and plate-like structures with thicknesses of 1 nm and lateral dimensions ranging in the order of micrometers [7]. This is largely due to the isomorphic substitution of alumina cations (Al^{3+}) within the silicate layers [7]. For example, in the case of a 2:1 structure, the trivalent Al-cation in the octahedral layer is partially substituted by the divalent Mg-cation to form montmorillonite (MMT) [3].

Saponite, for example, is able to intercalate cationic molecules in its interlayer spaces, enabling the fabrication of organic−inorganic hybrid materials that can accommodate functional molecules [8]. An organo-saponite clay containing intercalated cetyltrimethylammonium cations was synthesized by Bisio et al. [9] without affecting the clay morphology. Moreover, the clay structure stabilized and protected the surfactant molecules.

The sepiolite (another nanoclay) and lipid hybrids include other interaction mechanisms such as hydrogen bonding of the lipid headgroup moieties with the Si-OH groups and the coordinated water molecules located at the external channels of this silicate. These obtained bio-organoclays have been tested for potential applications in a mycotoxin retention study (Wicklein et al. [10]).

Halloysite nanotubes (HNTs), a nanoclay commonly found in the literature for a wide range of biomedical applications, have a hollow tubular structure with

Table 1 Common clay types according to structure [5, 6]

Clay structure	Common examples
1:1	Halloysite, kaolinite, rectorite
2:1	Bentonite, hectorite, laponite, montmorillonite, sepiolite, saponite, vermiculite
2:1:1	Chlorite

diameters of 50–80 nm, lumen of 10–15 nm, and lengths of ~1 μm [11]. Halloysite is similar to kaolinite; however, in halloysite the neighboring alumina and silica layers, and their water of hydration, create a packing disorder causing them to curve and roll up, forming multilayer tubes [12].

MMT is a widely employed filler for composite materials [2, 13, 14] and for developing other functional nanomaterials, due to its high specific area and the ability to be exfoliated into layers with thicknesses in the order of nanometers [15]. This particular characteristic makes MMT a good candidate for the preparation of polymer nanocomposites with tunable physical and mechanical properties [15], as reviewed in section "Polymer–Nanoclay Composites."

Biocompatibility of Nanoclays

Clay materials are considered to be safe or environmentally friendly [16–18], thus making them attractive for a range of biomedical applications [16]. The toxicity of MMT has been evaluated by Li et al. [16], finding that these nanoparticles failed to affect the mortality rate of Sprague-Dawley (SD) rats by oral feeding at a dose level of 5,700 nm/kg. No mutagenic effect was observed, and although MMT could accumulate and adhere onto cell surfaces it showed no apparent changes in cell morphology. The in vitro toxicity testing of two nanoclays, clinoptilolite and sepiolite, demonstrated to be well tolerated in highly phagocytic cultures [19], with results comparable to talc powder. In this study, clinoptilolite had lower toxic effects. HNTs, with a fiber-like morphology, have also shown no cytotoxic effect after a 24 h exposure in C6 glioma cell cultures with concentrations of 500 μg/mL [17]. Furthermore, toxicity measurements with neoplastic cell line models as a function of concentration and incubation time showed that HNTs are safe for cells at concentrations of up to 75 μg/mL [18]. As a reference, asbestos, another fiber-like material, is highly toxic at concentrations 1,000 times lower [18]. As reported by Vergaro et al. [18] this is due to the larger length of asbestos of 5–20 μm, compared to the length of HNTs of ~1 μm that can be more easily removed by macrophages.

Polymer–Nanoclay Composites

Nanoclays have been widely employed for preparing polymer matrix–nanoclay biomedical composites due to their effect enhancing matrix properties [20–24]. One of the first works in this field was performed by Blumstein [25] in

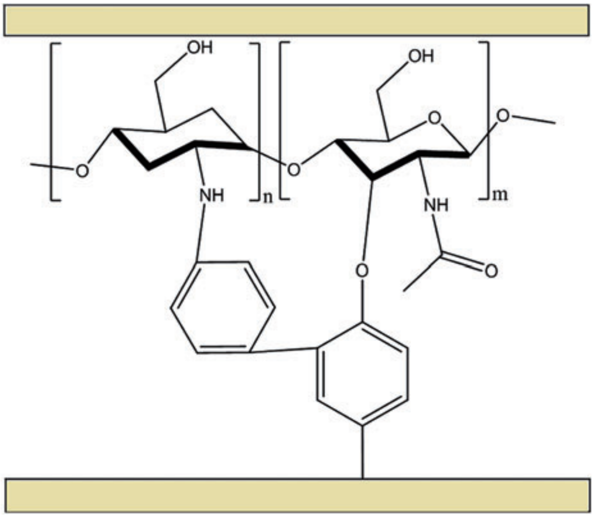

Fig. 1 Schematic representation of a nanocomposite obtained by direct melt intercalation and possible Van der Waals interaction

Table 2 Mechanical properties of clay materials

Nanoclay	Geometry	Dimensions	Young's modulus
HNTs	Hollow tubular	Diameter: 50–80 nm, lumen: 10–15 nm, length: ~1 μm [11]	130–140 GPa [29, 30]
MMT	Flake-like	Thickness: ~1 nm, length: 10 μm [31]	4–14 GPa [32]

the 1960s, where he carried out the polymerization of methyl methacrylate that was adsorbed onto MMT clay and found an oriented growth of the polymer.

Polymer–clay nanocomposites may be prepared by: (a) melt blending, with partially exfoliated clays, (b) in situ polymerization, and (c) melt intercalation (Fig. 1) by conventional polymer extrusion process [26], microwave and ultrasound irradiation [27], among others [7]. Attempts to enhance the biocompatibility of clay minerals have recently been undertaken, and different types of clays have been functionalized by assembly with different biopolymers [28].

As mentioned, the properties of polymer matrices (namely, the mechanical properties) may be enhanced by the addition of nanoclay. Table 2 shows the Young's modulus of nanoclays commonly found in the literature for reinforcing polymer nanocomposite materials, in this case HNTs and MMT. In particular, HNTs with their tubular shape are very attractive for this purpose due to their superior mechanical properties.

Tables 3–5 show the improvement in the mechanical properties of tensile/flexural strength and Young's modulus of polymer–nanoclay composites reported in the literature. For HNTs (Table 3) loadings ranged from 0.5 to 7.5 wt.% and overall improvements from 24% to 457% and 17% to 337% in tensile/compressive strength and modulus, respectively. Very slight decreases were also found for some cases,

Table 3 Mechanical properties of HNTs–polymer composites for biomedical applications

Nanoclay content (wt.%)	Polymer matrix	Improvement in tensile/ flexural strength (%)	Improvement in modulus (tension/ compression) (%)	References
0.5	Gellan gum–glycerol	44	150	1. Bonifacio et al. [33]
5.0	Chitosan	34	21	De Silva et al. [34]
7.5	Chitosan	134	65	Liu et al. [35]
5.0	Poly(L-lactide) (PLLA) matrix	24	32	Luo et al. [36]
5.0	Poly (lactic acid)	−15	27	Bugatti et al. [37]
3.0	Poly(lactic-co-glycolic acid)	24	61	Qi et al. [38]
5.0	Poly(vinyl alcohol)	67	–	Zhou et al. [39]
5.0	Poly(hydroxybutyrate-co-hydroxyvalerate)	37	63	Carli et al. [40]
3.0	Poly methyl methacrylate	72	17	Pal et al. [41]
5.0	Poly methyl methacrylate	−10	−4	Wei et al. [42]
3.0	Polypropylene	95	152	Naffakh et al. [23]
2.0	Oligo(trimethylene carbonate)–poly(ethylene glycol)–oligo(trimethylene carbonate) diacrylate (TPT)	457	337	Tu et al. [43]
2.0	Oligo(trimethylene carbonate)–poly(ethylene glycol)–oligo(trimethylene carbonate) diacrylate (TPT), and alginate sodium (AG)	80	−2.2	Tu et al. [43]

usually due to the increase in stiffness of the matrix by the harder nanoclay that reduced the strain at break and tensile strength.

Nanocomposites of polymer matrices filled with concentrations of 1–10 wt.% MMT achieved increases of 22% to even 400% in Young's modulus, as shown in Table 4. Tensile (or flexural) strength has also been greatly improved. Other less common nanoclay–polymer composites with rectorite, hectorite, laponite, and their enhancements in mechanical properties can be found in Table 5.

Table 4 Mechanical properties of MMT–polymer composites for biomedical applications

Nanoclay content (wt.%)	Polymer matrix	Improvement in tensile/flexural strength (%)	Improvement in modulus (tension/compression) (%)	References
10.0	Chitosan	–	22	Katti et al. [44]
10.0	Chitosan–gelatin/nanohydroxyapatite	24	20	Olad et al. [45]
10.0	Chitosan/hydroxyapatite	–	36	Katti et al. [44]
10.0	Chitosan/polygalacturonic acid	–	400	Ambre et al. [46]
3.0	Chitosan/poly (vinyl alcohol)	33	35	Noori et al. [47]
4.5	Poly (ε-caprolactone)	−4	74	López-Arraiza et al. [48]
5.0	Poly (ester amide)/polyaniline	99	–	Pramanik et al. [49]
5.0	Poly (hydroxybutyrate-co-hydroxyvalerate)	−19	103	Carli et al. [40]
10.0	Poly (lactic acid)	−14	30	Fukushima et al. [50]
15.0	Poly (lactic acid)	0	35	Guo et al. [51]
15.0	Poly (lactic acid)	−46	56	Guo et al. [51]
1.0	Poly methyl methacrylate	–	76	Kapusetti et al. [52]
2.0	Polypropylene	22	32	Naffakh et al. [23]

Table 5 Mechanical properties of other clay–polymer composites for biomedical applications

Nanoclay	Nanoclay content (wt.%)	Polymer matrix	Improvement in tensile/flexural strength (%)	Improvement in modulus (tension/compression) (%)	References
Organic rectorite	2	Chitosan	7	–	Wang et al. [53]
Hectorite	10	Poly (lactic acid)	−2.85	75	Fukushima et al. [50]
Laponite	15	P (MEO2MA-co-OEGMA)	1,346	1,406	Xiang et al. [54]

Apart from these properties, some major applications of nanoclay–polymer composites are for enhancing the barrier properties of matrices that are the result of reduced permeability by the addition of nanoclays [55].

Biomedical Applications of Nanoclays

Nanoclays are been extensively studied for various biomedical applications, such as wound healing, drug delivery, tissue engineering, preparation of scaffolds and bone cement, cancer therapy, and enzyme immobilization, among others [56–58]. This section presents the recent advancements in said applications (4.1–4.5) (Fig. 2).

Bone Cement

Bones are complex materials composed of inorganic calcium phosphates that provide strength, and organic collagen which provides flexibility, thus they can be considered to be composite materials [59–61]. Bones can be classified as cancellous or cortical, where cortical bones represent approximately 80% of the total skeleton [59–61]. The mechanical properties of strength and flexibility differ for these two types of bones: for cortical bones the strength and modulus of elasticity ranges between 70 MPa and 200 MPa and 3 GPa and 30 GPa, respectively, whereas for cancellous bone much lower values are observed: tensile strength is about 0.1–30 MPa, and elastic modulus is 0.02–0.5 GPa [59–61]. Polymethyl methacrylate

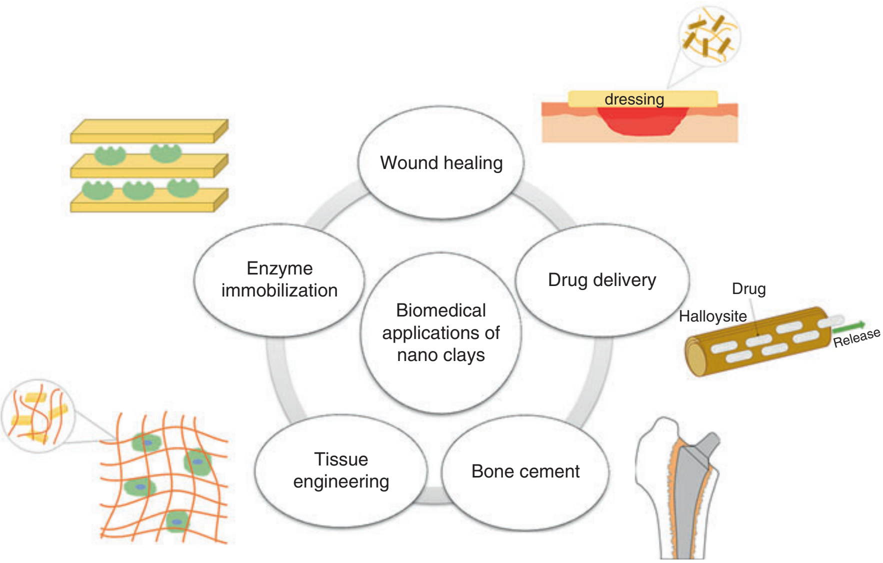

Fig. 2 Biomedical applications of nanoclays

(PMMA) is widely used as a bone cement with the purpose of fixing hip and knee replacement implants into adjacent bones [62, 63]; however, these materials have shown poor fatigue strength and overall inadequate mechanical properties for load-bearing applications [52, 59]. Another disadvantage is that PMMA also possess a high exothermic temperature during polymerization, which may cause necrosis and loosening of implants in the body [52, 64].

Nanoclay materials have been studied as reinforcements for PMMA composites for bone cement applications [41, 42, 62, 63, 65, 66] or bone implants [59] with improved bioactivity and mechanical properties. For example, Kapusetti et al. [52] prepared PMMA bone cement/layered silicate nanohybrids with nanoclays based on MMT in concentrations of 0.5, 1.0, 1.5, and 2.0 wt.% and performed mechanical testing, cell culture studies, and in vivo studies. Findings demonstrated a decrease of 12 °C (from 84 °C to 72 °C) on the exothermic polymerization temperature, which could potentially reduce cell necrosis. Young's modulus and toughness were also enhanced by the nanoclay filler due to their suppression of crack growth, and biocompatibility was also enhanced.

HNTs haven been also used as reinforcements due to their excellent mechanical properties (Table 2), with a reported Young's modulus of 130–140 GPa [29, 30] and a tensile strength of 10.8 MPa [66]. Pal et al. [41] analyzed the thermomechanical performance of PMMA reinforced with HNTs, carbon nanotubes (CNTs), and carbon nanofibers (CNFs). While HNTs did not improve the thermal decomposition temperature of PMMA, mechanical properties of tensile strength and tensile modulus approached those obtained with CNTs at the same concentration, with the advantage of having higher dispersibility and biocompatibility by HNTs. In some cases, however, slight decreases in mechanical properties were found [42]. Since HNTs are hollow nanostructures with a lumen of 10–15 nm, they can also be used as nanocontainers for antibiotics [66–68], improving the antimicrobial activity of PMMA bone cement [62]. Lvov et al. [67] prepared HNTs nanocarriers loaded with the antibiotic gentamicin, which showed sustained drug release in PMMA bone cement. Release time was 250–300 h, thus providing extended antibacterial protection that complies with orthopedic surgery needs.

Tissue Engineering

The purpose of tissue engineering is to improve, maintain, and restore tissue functions [46]. Nanoclays have been incorporated to hydrogels such as polysaccharides (i.e., chitosan, gellan gum) due to the polymer's ability to support adhesion and proliferation of cells [33, 69]. The addition of nanoclay fillers allows for tunable physical and mechanical properties according to the desired application [44–46, 70–72]. Bonifacio et al. [33] proposed a hydrogel composed of gellan gum (GG), glycerol, and HNTs for soft tissue engineering applications like pancreas, liver, and skin regeneration. The addition of glycerol to GG improved the material viscosity, while HNTs decreased water uptake by 30–35%. Membranes of chitosan/HNTs prepared by solution casting by De Silva et al. [34] showed improved mechanical properties by the addition of 5% HNTs, as well as enhancement of thermal stability. Nitya et al. performed in vitro evaluation of a fibrous polycaprolactone/HNT [72] composite scaffold for bone tissue engineering prepared by electrospinning. These scaffolds allowed for greater protein adsorption, enhanced mineralization, and faster proliferation of human mesenchymal stem cells (hMSCs) seeded on these scaffolds. Moreover, a study by Zhou et al. [39] showed that adding HNTs to poly(vinyl alcohol) (PVA) bionanocomposite films resulted in changes in nanotopography and surface chemistry of PVA. These modifications allowed for a significantly higher level of cell adhesion. Additionally, mechanical properties of the films were significantly improved.

A biopolymer consisting on chitosan mixed with HAP and MMT was synthesized by Katti et al. [44] showed an intercalated structure improving thermal stability and nanomechanical properties. Scaffolds based on chitosan/polygalacturonic acid (ChiPgA) complex containing a modified MMT nanoparticles were prepared by Ambre et al. [46] for bone tissue engineering applications. Results demonstrated growth and proliferation of human osteoblasts. Here, the results with the modified MMT were comparable to those commonly shown by the osteoconductive hydroxyapatite (HAP). Porosity of these composites also increased by 90%, facilitating nutrient transport throughout the scaffold. Other scaffolds with MMT in a chitosan–gelatin/nanohydroxyapatite matrix [45] were found to be highly porous. A synergistic effect between MMT and HAP was also determined for swelling ratio, density, biodegradation and mechanical behavior, as well as a decreased degradation rate and increased biomineralization. Particularly, the incorporation on MMT was found to be largely responsible for the moderation of these properties. Furthermore, biodegradable hybrid 3D scaffold with high porosity prepared by Mkhabela and Ray [73] with poly(ϵ-caprolactone) (PCL) and chitosan-modified MMT were degraded and resorbed at a faster rate with increasing nanoclay concentration.

Aliabadi et al. [70] synthesized a biocompatible chitosan ammonium salt *N*-(2-hydroxy) propyl-3-trimethylammonium chitosan chloride (HTCC)-modified MMT with antibacterial properties. The samples were efficient with both Gram negative and Gram positive bacteria. The antibacterial efficiency provided by MMT was due to the entrapment of bacteria between the intercalated structures of HTCC in MMT. Due their outstanding results, these composites were proposed for tissue engineering applications.

Other innovative applications of clay nanomaterials for tissue engineering have been explored. For example, sodium-MMT (Na-MMT) was modified by Payne and coworkers [71] with an amino acid in order to mineralize synthetic HAP, resembling biogenic HAP in human bone. Another study performed by Ambre et al. [74] incorporated these HAP-clay materials into chitosan/polygalacturonic acid (Chi/PgA) scaffolds and films for bone tissue engineering.

Wound Healing

Wound healing applications of nanoclays have also been largely explored to prevent infection, scarring, and minimizing pain [47, 75–78]. In this sense, properties such as flexibility and swelling ability are highly important. A biodegradable poly vinyl alcohol (PVA) composite with carboxymethyl chitosan (CMCh) and MMT prepared by Sabaa et al. [79] demonstrated increased swelling behavior and good antimicrobial potency compared to standard drugs such as penicillin G. Nistor et al. [80] incorporated MMT nanoparticles into collagen/*N*-isopropylamide hydrogels with the purpose of adjusting their stimuli response as scaffold with enhanced healing and regenerative properties. Here, MMT nanoparticles allowed for the formation of new bonds and formed a 3D network of interconnected pores. Another PVA composite with Iranian gum tragacanth (IGT) was prepared by electrospinning was enhanced with a kaolinite-based nanoclay [77]. The addition of nanoclay improved mechanical properties and chemical stability, making it suitable for wound healing applications.

Cross-linked nanoclays, such as semi-IPN sericin/poly(NIPAm/LMSH) (HSP) nanocomposite hydrogels, were also explored as a wound dressing by Yang et al. [78]. The wound healing area treated with the nanocomposites increased threefold over the area covered by gauze after 6 days and showed almost complete recovery by the 13th day. A wound dressing material of gellan gum methacrylate (GG-MA) was combined with laponite to provide delivery of therapeutic agents at the injury site by Pacelli et al. [81]. Here, laponite modulated the swelling behavior of the hydrogel network and was able to lower to the amount of antibiotic released during the first 8 h, compared to unfilled hydrogels.

HNTs/chitosan oligosaccharide nanocomposites were developed by Sandri et al. [75] for wound healing applications. Nanocomposites of these materials demonstrated to be biocompatible with normal human fibroblasts and showed an enhancement of cell proliferation in an in vitro wound healing test. In vivo wound healing demonstrated an advanced degree of revascularization and regeneration of hair follicles. Thus, this treatment could be used for treating difficult skin lesions and burns. Nanoclays based in HNTs were also employed by Demirci et al. [82] in hyaluronic acid (HA) cryogels (hydrogels with enhanced porosity and mechanical strength) since this biodegradable natural polysaccharide is one of the most important components of extracellular matrices. In this study, HNT increased porosity, drug loading, and long-term water retention. Finally, hybrid hydrogels based on cross-linked collagen and thermo-responsive poly(*N*-isopropylacrylamide) with embedded MMT used for wound healing [80] showed good cytotoxicity and biocompatibility.

Enzyme Immobilization

Nanoclays have also been studied for their capability to immobilize enzymes [83–85]. In a study by Tzialla et al. [83] the immobilization of lipase B from *Candida artactita* on laponite and two types of MMTs was characterized. Results indicated enhanced activity and stability in low-water media. MMT was also employed for immobilization of microbial phytases from *Aspergillus niger* and *Escherichia coli.* Here, HNTs were functionalized with γ-aminopropyltriethoxysilane for enzyme immobilization and controlled release.

A biosensor based on atemoya peroxidase immobilized on modified nanoclay for glyphosate biomonitoring was developed by Oliveira et al. [86]. The antimicrobial protein lysozyme was also successfully encapsulated into HNTs and incorporated into PLA nanocomposite by Bugatti et al. [37]. The addition of HNTs improved barrier properties due to a tortuous path effect and improved the mechanical properties.

Drug Delivery

A field where nanoclays have attracted increasing interest is in drug delivery applications [11, 38, 43, 53, 66, 68, 87–102] ranging from antibiotics, antihistamines, anti-inflammatories, antimicrobial, antifungal, antialgal, and anticancer treatments.

Laponite nanoplatelets (LAP) were investigated by Roozbahani et al. [89] as a possible platform for efficient sustained release of anionic dexamethasone (DEX) by encapsulating the drug into the interlayer spacing of LAP nanodisks with a very high efficiency. The release was found to be pH dependent, with faster rates in acidic environments. Organic rectorite, a modified rectoride modified by cetyltrimethyl ammonium bromide to increase its affinity with polymers, have been added to chitosan to obtain nanocomposite films [53]. Films were loaded with bovine serum albumin (BSA), as a model for a drug, to study drug delivery behavior that was dependent on the amount and interlayer spacing of organic rectorite. With the same nanoclay, an encapsulation efficiency of more than 90% was found by Zeynabad et al. [103] for a pH-dependent dual drug delivery system for cancer therapy. In this case, the anticancer drug methotrexate and an antibacterial agent ciprofloxacin was encased in an organo-modified laponite–polymer composite.

Sepiolite, attapulgite, and bentonite were used to prepare “drug – in cyclodextrin – in nanoclays” hybrid single delivery systems with improved dissolution of oxaprozin (an anti-inflammatory drug), with sepiolite demonstrating the best properties (Mura at al. [104]). The use of nanoclays for the entrapment of these drugs proved to be a good tool for enhancing the therapeutic effectiveness of poorly soluble drugs, such as oxaprozin, and for reducing the amount of cyclodextrin needed for obtaining the required drug solubility.

Hydrogels of chitosan and MMT were studied for drug release behavior by electrostimulation [105]. The exfoliated MMT sheets were able to increase cross-linking density, enhance the fatigue behavior of chitosan, and improve long-term drug release performance. Similarly, nanocomposites of poly(ε-caprolactone) filled with montmorillonite were loaded with paracetamol without affecting the mechanical properties of the polymer matrix (Campbell et al. [102]). In another study by

Campbell et al. [106], composites of paracetamol-loaded poly-ethylene glycol and nanoclay were prepared without affecting the structure of paracetamol during the hot-melt process. Nanoclays successfully encased the paracetamol molecules, hence retarding diffusion. A hydrogel consisting of poly(2-hydroxyethyl methacrylate)/ matrix and MMT was developed as a as drug delivery system of paracetamol [107], where nanoclays acted as polymer cross-linkers and extended the release time of paracetamol, delaying also drug clearance which also reduces the need for multiple doses. Also, it was demonstrated that the drug release rate can be adjusted by varying the MMT content in the nanocomposite.

Perhaps, the more widely studied nanoclay for drug delivery are HNTs, due to their microtubule shape [11, 66]. It has been found that at a pH above two HNTs bind cationic drugs to their outer and inner layers for delayed drug release and that optimum binding occurs in solutions above a pH of 4 [68]. Research have demonstrated that HNTs are indeed potential carriers for cationic drugs (antibiotics and antihistamines), with pharmaceutical compound loadings of up to 84 mmol/kg [92]. Porous microspheres of HNTs and chitosan were loaded with up to 42.4 wt.% of aspirin, higher that the 2.1 wt.% shown by pristine HNTs. This was due to the interconnected porous structure of HNTs/chitosan composites, with large pore volume and high specific surface area. Also, these nanocomposites had lower release in the simulated gastric fluid and more release in the simulated intestinal fluid, reducing the side effects on the stomach.

Cytocompatible composite nanofibers of HNTs in poly(lactic-co-glycolic acid) (PLGA) were prepared by Qi et al. [38]. HNTs were loaded with the antibiotic drug tetracycline hydrochloride (TCH). The composite nanofibers were able to release the drug in a sustained manner for 42 days. A HNT nanocomposite biodegradable hydrogel with a matrix consisting of oligo(trimethylene carbonate)–poly(ethylene glycol)–oligo(trimethylene carbonate) diacrylate (TPT) and alginate sodium (AG) with enhanced mechanical properties and drug release behavior was prepared by Tu et al. [43]. Demirci et al. [82] prepared a hydrogel of hyaluronic acid (HA) cryogels with HNTs with sodium diclofenac as a model drug. The pore volume and porosity increased 6.2% and 5%, respectively, and the drug release was 31%. In order to reduce postsurgical infection that results in an early failure of orthopedic and orthodontic implants, a calcium alginate and calcium phosphate cement with HNTs loaded with gentamicin were prepared by Karnik et al. [101]. These nanoclay/hydrogel composites showed a sustained and extended drug release with an enhanced antimicrobial effect.

Control release of anticancer compounds with HNTs has been achieved by capping their tube ends [66]. Stimuli-triggered drug delivery vehicles of HNTS for targeted intracellular drug delivery in cancer therapy were developed by Dzamukova et al. [97]. Brilliant green HNTs, loaded with an anticancer drug coated with cleavable dextrin stoppers for controlled release, served as transmembrane carriers. The accumulation and enzymatically induced release of drug only occurred for malignant cells; hence, noncancerous cells were not affected. In another study, polymer grafted-magnetic HNTs loaded with a cationic drug (norfloxacin) for controlled release demonstrated higher drug loading compared to pristine HNTs [93].

The combination of magnetic properties, high adsorption capacity, and sustained drug release makes it a potential candidate for targeted drug delivery in different forms of cancer. Massaro et al. [91] synthesized a stimuli-responsive prodrug based on HNTs and a covalently linked curcumin, an antioxidant and anticancer compound. Functionalization of HNTs was verified by thermogravimetry studies. Exposure of this prodrug in glutathione-rich or acidic conditions similar to those found in the microenvironment of hepatocancer cells showed an enhanced release of curcumin. Hydrogels for colon cancer drug delivery were synthesized by Rao et al. [108], consisting of sodium hyaluronate in a poly(hydroxyethyl methacrylate) matrix, and an anticancer drug encapsulated in HNTs. In vitro experiments with simulated gastric fluid and intestinal gastric fluid showed that these composite hydrogels had a pH-dependent controlled release, with less than 10% release in the gastric region and higher release in a controlled manner in the intestinal fluid, making them more efficient for colon cancer drug delivery. Pramanik et al. [49] prepared a polymer nanofiber consisting of a poly(ester amide)/polyaniline matrix and MMT reinforcement with partially exfoliated nanoplatelets. These nanocomposites exhibited efficacy against gram positive and gram negative bacteria, as well as antifungal and antialgal activity.

Conclusions and Future Outlook

This chapter presents recent advances in biomedical applications of nanoclay materials. These natural aluminosilicate structures have been shown to be nontoxic and biocompatible and thus have been widely studied for tissue engineering, drug delivery, wound healing, fillers for bone cement, and enzyme immobilization, among others. In drug delivery systems, nanoclays' excellent biocompatibility, high anion exchange capacity, and pH-sensitive solubility related to the drug load content make them great potential candidates for this purpose. It is demonstrated that inorganic materials such as clays and their intercalated nanocomposite hybrids may pave the way for the development of new polymer composite materials with tunable mechanical properties that could be taken advantage for biomedical purposes where high strength and modulus is required.

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