Chapter 9

Development of Clay Nanoparticles Toward Bio and Medical Applications

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Abstract

Clay nanoparticles are among the most applicable and cost-affordable materials, all of which have a variety of applications in case of medical science. In this chapter, key characteristics of the clay nanoparticles along with their major groups, structure, morphology, and physicochemical properties were evaluated. Thereafter, the applications of clay nanoparticles in the field of nanocomposite, polymeric matrices, and medicine were investigated, while specimen production procedures were also reviewed. The main focus of this chapter is to investigate the applications of clay nanoparticles in bio- and medical science. In fact, organically modified clay nanoparticles (organoclays) are an attractive class of hybrid organic–inorganic nanomaterials with potential applications in case of polymer nanocomposites, rheological properties modification, and drug delivery carrier.

Keywords: clay nanoparticle, bioapplication, medicine, nanocomposite

1. Introduction

Clay nanoparticles are natural materials in nanoscale that originate from clay. They have attracted much attention in recent years due to their widespread applications. The interest in exploiting clay nanoparticles for various purposes is due to their high surface and unique physical and chemical properties.

In 2013, a group of researchers focused on clay nanoparticles as a drug delivery system. Preparation, physical/chemical properties, and bioaccumulation of clay nanoparticles based

on drug delivery systems, as well as their application in the food system as a nanocarrier for vitamins, antioxidants, linoleic acid, and the other foods, were discussed [1]. In addition, studies have shown that nanotechnology will revolutionize the food industry [2]. Nanoscale food control can lead to the correction of micromolecular properties of foods such as taste, aroma, texture, sensory characteristics, processing ability and stability throughout the process, and storage. Nanotechnology applications grow rapidly in the food and ingredient sector. Advanced nanoelectronics, in combination with good nanomaterials and intelligent biological components, are able to develop very specific and selective measuring devices to identify potentially hazardous agents, including viruses, pathogenic microorganisms, as well as inappropriate physical and chemical substances in foods [3–5]. The micro/nanotechnology accelerates the decreasing size of the sensor to the extent appropriate for application (applied field) [6–8].

In addition to ensuring food safety, nanotechnology improves our lives by monitoring quality and nutrition status [9, 10]. Food packaging is another area that has used nanomaterials to increase the shelf life of the food by improving the preserving properties. Nylon-based nanocomposites are currently used to produce beverage bottles in Korea and the United States [11]. Polymer nanoparticles are made by dispersing nanoparticles into a polymer matrix [12]. For example, nylon/silicate nanocomposite containing 2% non-mineral nanoparticle has two times higher tensile strength and thermal stability (at a temperature above 100°C) than pure nylon [12]. Nylon-based nanocomposites are formed by the dispersion of silicate layers on a continuous polymer matrix. This structure significantly reduces the amount of oxygen or carbon dioxide release (diffusion) in encapsulation, since these gases should be distributed through the space between dispersed nano-silicate layers [13]. Properties such as strength and thermal stability make this nanocomposite ideal for packaging food. Several attempts and experiments have been carried out to provide various types of antioxidants, nutrients, minerals, drugs, and other applicable factors through food [14]. Currently, most efforts to develop delivery systems focus on drugs. While safety and cost concerns are one of the most important factors in choosing food for the customer, high production costs of drug delivery systems are still acceptable in medicine. Clay nanoparticles are minerals in clay that have attracted much attention due to the biological application of their abundance in nature, simplicity of construction, and biocompatibility [15–18]. Clay nanoparticles also have a great potential for nutrition because they have been used to treat and protect as a traditional medicine since the beginning of human civilization [19–21]. Clay minerals have been used as laxatives, antidiarrhea, anti-inflammatory agents, blood purification, reducing infections, and healing of stomach ulcers [22]. In addition, biocompatible clay minerals are currently used as oral antioxidants [23, 24]. Clay nanoparticles have unique layer structures, including the accumulation of nanoparticles with metal ions and intracellular ions for charge balancing [25]. The two-dimensional (2D) structure illustrates interesting strategies for the development of new nano-hybrid systems by enhancing active biochemical molecules into space (**Figure 1**). Intrinsically, unstable agents can be protected against processing conditions and hard-working environment and ultimately released with a controlled pattern in a desirable environment [26–28]. Many studies have shown that nano-layered materials can encapsulate DNA [29, 30], nucleotides [31, 32], drugs [33, 34], proteins [35], and even viruses [36]. These nano-hybrid systems are designed to enhance the efficient delivery to cells and the effectiveness of biochemical molecules [37–39]. However, the application of nanoscale materials to nutrients delivery is very limited.

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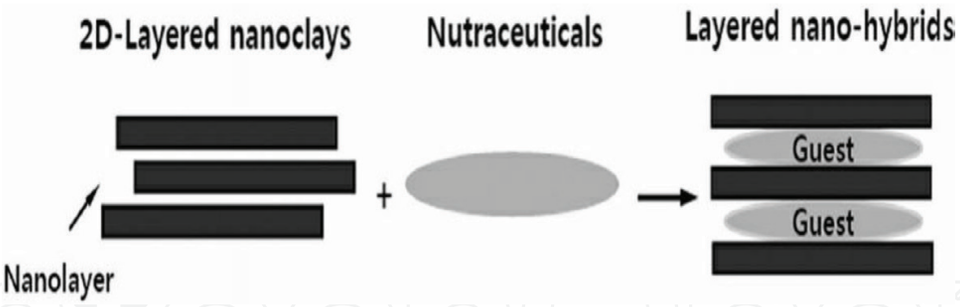

Figure 1. A scheme of clay-layered nanomaterial systems [1].

2. Delivery efficiency and biocompatibility of clay nanoparticles

2.1. Structural and physical properties of nanoclays

Nanoclays are fine-grained crystalline materials. A layer is the basic structural unit of nanoclays, and these layers are prone to arrange themselves over one another like pages of a book. Individual layers are composed of the tetrahedral and/or octahedral sheets, and this arrangement of sheets plays a vital role in defining and distinguishing these clay minerals. In tetrahedral sheet, the silicon-oxygen tetrahedra are linked to neighboring tetrahedra by sharing three corners while the fourth corner of each tetrahedron forms a part to the adjacent octahedral sheet. The octahedral sheet is usually composed of aluminum or magnesium in a sixfold coordination with oxygen from the tetrahedral sheet and with hydroxyl.

2.2. Structural features

Clay layer nanoparticles are divided into two different types of anion and cation depending on the level of layer charge and the types of interlayer ions. Anionic layer nanomaterials typically have been created by double-layered hydroxides (LDHs) with alterable anions in interlayer spaces. LDHs include a wide range of chemical compounds and their layered structure that can be of a great variety to produce poly-types. For example, aluminosilicate cationic nanoparticles like montmorillonite (MMT) have octagonal and quadrilateral plates with high internal surfaces. The main structure of cationic clays is based on a framework, where the unit structure is composed of an octagonal-twisted sheet between two quadrilateral plates. In **Figure 2**, the structure of the double-layer hydroxide and cationic clay (MMT) is presented.

Therefore, cationic and anionic clay nanoparticles can be applied as transfer carriers, which depend on the charge of molecules and essentially on their unique layered structure.

2.3. Biocompatibility

In general, clay nanoparticles are considered as biodegradable materials. In fact, cationic minerals have traditionally been applied in a variety of fields including skin chemotherapy, laxatives, antidiarrhea, and anti-inflammatory agents as well as antimicrobial agents [40–42]. Recently, they are used as lubricants and distributary in pharmaceutical programs to improve chemical, physical, and organoleptic properties [43–45]. MMT can be considered as an

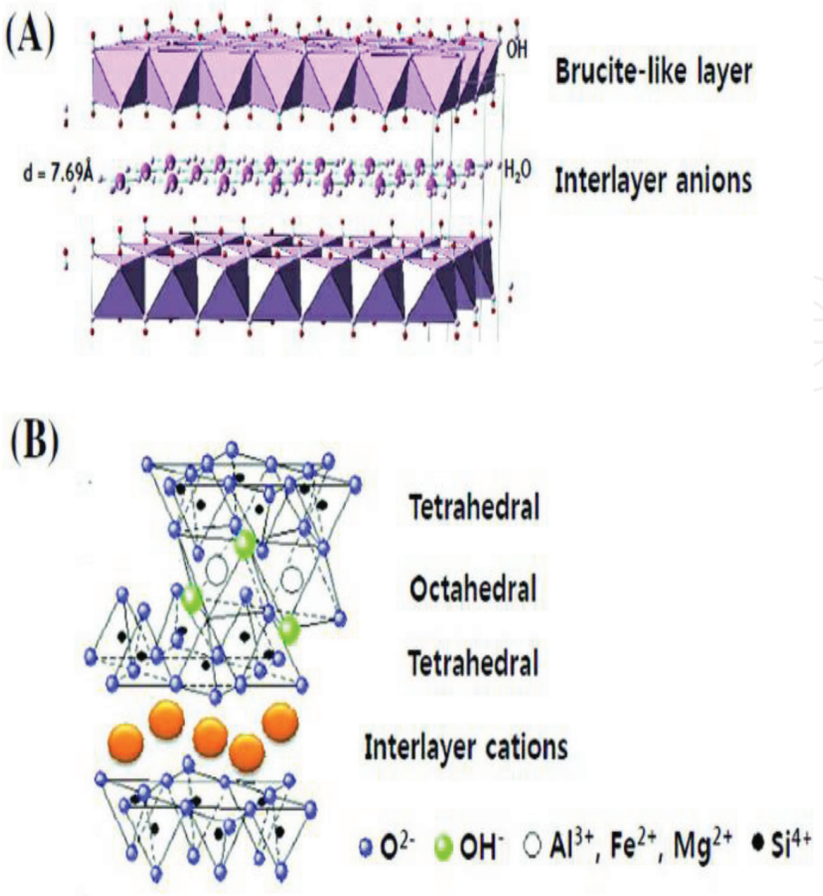

Figure 2. (A) Double-layer hydroxide and (B) cationic clay (MMT) [1].

eco-friendly cationic clay [46], which is commonly used in many pharmaceutical formulations as an active and additive substance [47]. In addition, anionic nanoparticles of LDH in carbonate form are used as an antacid agent (antipepsin) to neutralize gastric acid, which is related to its alkaline properties under physiological pH [48]. The results show that LDH has a lower toxicity compared to single-walled carbon nanotubes and iron oxide and silica nanoparticles.

2.4. Clay nanoparticles for nutrient delivery systems

As previously described, clay nanoparticles are biocompatible materials with a high internal space, a high ion exchange capacity, and a low toxicity that these properties make them ideal for the bioactive compound delivery systems. The nanoclay encapsulation system can be prepared in a relatively simple and inexpensive process compared to other delivery systems. In addition to improving the solubility of the drug or active compounds, the nanoparticle encapsulation system has been considered for oral applications due to its high adhesion properties that are useful for molecules against GI barriers [49]. Choi's research team reports an easy way of encapsulating the strongest antioxidant by MMT with cation exchange reaction (**Figure 3(A)**) [50]. γ-L-glutamyl-L-cysteinylglycine (GSH) is a cellular antioxidant protector (preserver) against reactive oxygen species by neutralizing free radicals. GSH stability can be increased by encapsulating GHS on MMT. The tested GSH-MMT on mice resulted in a significant increase in the bioavailability and high activity of antioxidants in the plasma (**Figure 3(B)**).

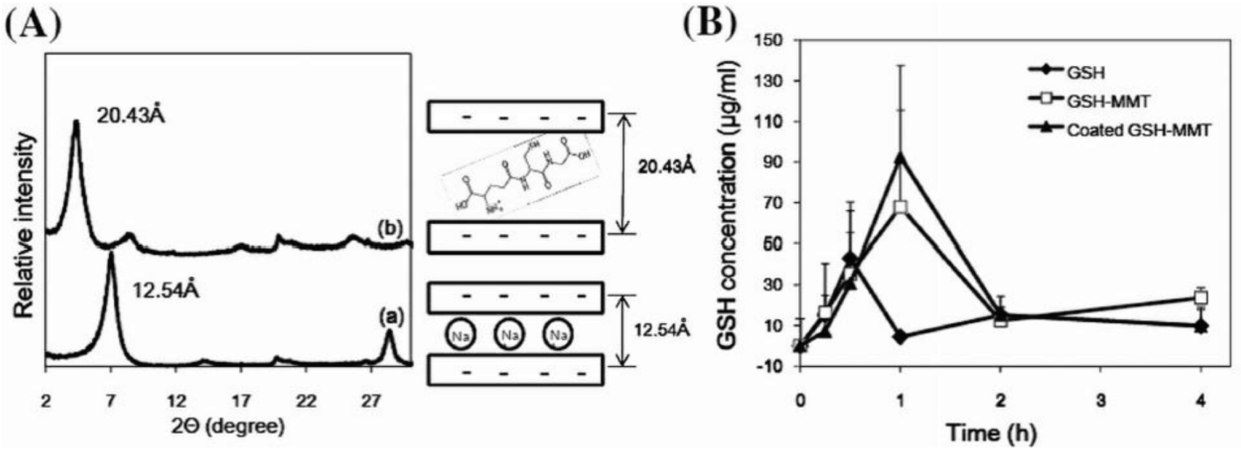

Figure 3. (A) X-ray pattern of (a) MMT and (b) GSH-MMT hybrid; and (B) GSH concentration in mice plasma [1].

Clay nanoparticles have attracted a great deal of attention as a good candidate for packaging of various materials, and it clearly demonstrates the increase in the sustainability and bioavailability of functional molecules.

2.5. The effect of clay mineral nanoparticles on the growth performance of internal organs and blood biochemistry of chickens compared to vaccines and antibiotics

Al-Beitawi et al. [51] investigated the effect of three levels of nanoclay minerals (1, 1.5, and 2%) on the growth performance of internal organs and blood biochemistry of chickens compared to vaccines and antibiotics. The experiment was conducted in nine diets for more than 36 days [51]. Groups 1–3 were fed with diet without clay mineral nanoparticles, and group C1 (positive with vaccines and antibiotics), C2 (positive only with vaccine), and C3 negative and without any of them (as control group). Treating groups with a similar diet to the levels mentioned earlier were done once or twice in a week. Performance of chickens, which fed with 2% clay nanoparticles, significantly improved in terms of body weight and feed conversion rates compared to control groups. With regard to blood biochemistry, high-density lipoprotein that is beneficial to the body was increased. Current results indicate that the mineral clay nanoparticles at certain levels and doses improve the performance of chickens. Nanotechnology is considered as a new potential tool for improving broiler chickens. Researchers believe that the beneficial and positive effects of the use of mineral clay nanoparticles as an additive to the diet of broiler chicks may be due to several factors such as the concentration, dose, and nature of nanoparticles [51]. Desai et al. observed that a nano-supplement form would increase the surface area, which may also increase the absorption and consequently the use of minerals [52]. In addition, Weiss et al. reported that the size of nanoparticles may increase the function or bioavailability of nutrients and compounds [53]. Mushtaq et al. reported that Na^+ is the main cation of extracellular fluids involved in several functions including acid-base balance and amino acid absorption and glucose utilization that is beneficial for body growth, which may have a significant improvement in the growth performance of broiler chickens. On the other hand, the interest in using nanotechnology as a new tool in feeding broiler chicks shows that nanoparticles have very different physical and chemical properties from large particles [54]. In 2013, Sawors et al. suggested that the number of muscle cells returns to genetic, environmental, and nutritional factors [55]. On the other hand, creating more accessible mineral resources,

such as clay nanoparticles, can have positive effects on tissue development. According to the obtained results, it can be concluded that the mineral clay nanoparticles have a favorable effect on total serum protein and its cleft [51]. Nanoparticles have been reported to exhibit several new characteristics of transfer and absorption and also have more effective absorption. The researchers suggested that the superior performance of clay nanoparticles may be due to smaller size and larger surfaces that improve intestinal absorption [56].

2.6. Evaluation of the clay nanoparticles toxicity in epithelial cells

The extending continuous use of products containing nanoparticle for a wide range of applications has raised public health and safety concerns. Although products containing clay nanoparticles cannot be toxic, human contact during its preparation, production, or disposal process can have undesirable effects on health, which makes it necessary to evaluate the biocompatibility of clay nanoparticles. A group of researchers examined the effects of platelet toxicity (Bentone MA, ME-100, Cloisite Na+, Nanomer PGV, and Delite LVF) on human lung [57]. They used automated cells for the first time in real-time impedance imaging compositions and also showed the effect of toxicity on the difference in the dose level and the time-dependent of both types of clay nanoparticles [57]. Clay nanoparticles are used in a wide range of modern products such as electronic, food, clothing, tire, medicine, sunscreen, cosmetics, sports equipment, polymer composites, bone implantation, controlled drug delivery systems, protective coatings (such as anti-corrosion, antibacterial, or antimolding), and for the synthesis of materials [58]. Clay nanoparticles, for example, plastic nanocomposites, are being developed to create unique devices for the next generation of biological applications, including antimicrobial agents, drug delivery, and cancer treatment [59–62].

2.7. Characterization of clay nanoparticles

SEM and TEM images are shown in **Figure 4**. In **Table 1**, a summary of the physiochemical properties of clay nanoparticles such as purity, specific surface area, zeta potential, and so on has been shown, which essentially affects the absorption and toxicity of nanoparticles.

2.8. Application of nanoclay-based composites in bone tissue engineering

The properties of MMT clay, such as its ability to absorb various types of toxins and the ability to cross the digestive tract (stomach and intestines) [60, 63–66], along with the ability to carry and transfer the drug [67–71], encourage human to use it in tissue engineering applications. It is reported that these nanoparticles are removed from the body because they cannot be absorbed by the intestines and they can also be dissolved by the acids in the stomach or intestine [72]. In addition, clay is used as an edible laxative and an antidiabetes [72]. The above suggests that clay is suitable for tissue engineering applications, and decomposed products can be disposed without any effects on the normal body function. The use of MMT clay for bone tissue engineering applications needs further research. In the few studies that have been done in the past, MMT has been used to prepare nano-composites that examine the effect of adding clay on the mechanical and biological properties of polymers [73, 74]. Researchers have used 5-aminovaleric acid-modified MMT clay to prepare polymer composites for bone tissue engineering studies [75].

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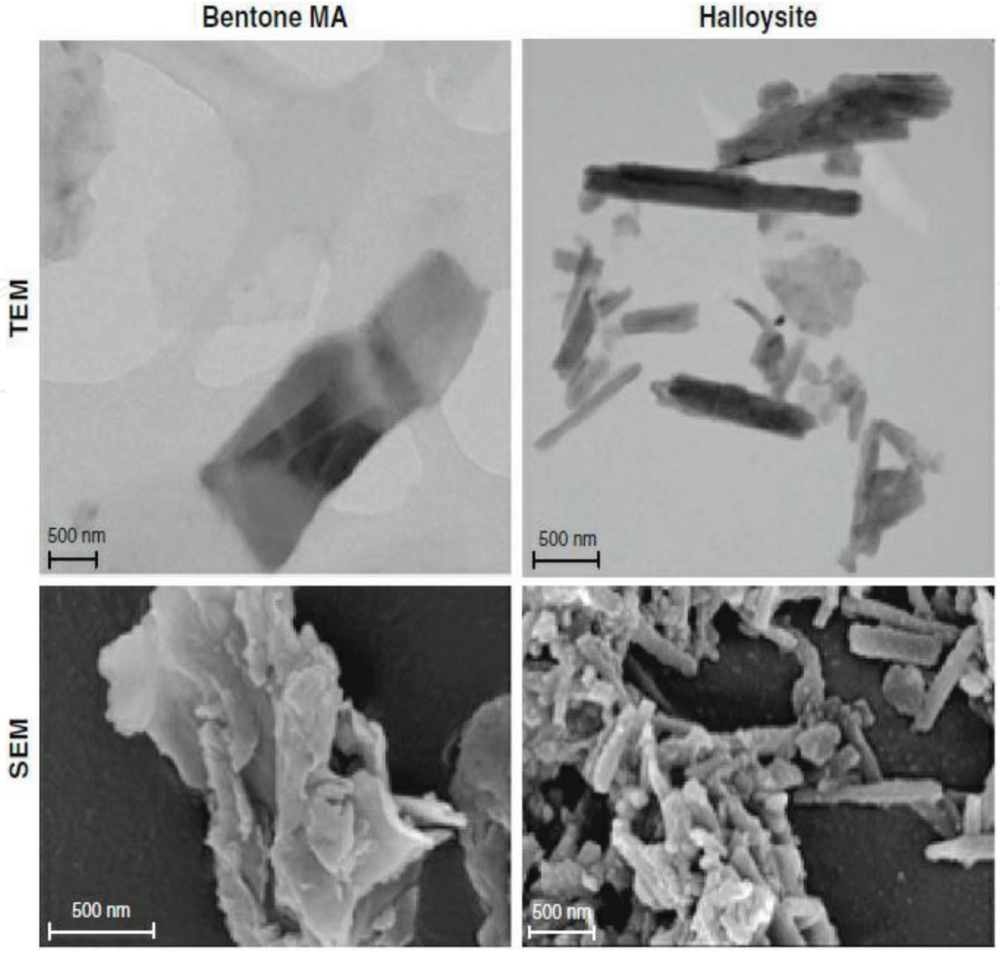

Figure 4. SEM and TEM images [57].

Geometry	Nanoclay	Chemical formula	Purity (%)	Zeta potential (Mv)	Specific surface area (m^2/g)
Tubular	Halloysite MP1	$Al_2Si_2O_5(OH)_4 \times 2H_2O$	90	−41	65
	Halloysite	$Al_2Si_2O_5(OH)_4 \times 2H_2O$	90	−32.1	64
Platelet	Nanomer PGV	$M^+y(Al_{2-y}Mg_y)(Si_4)O_{10}(OH)_2 \times nH_2O$	100	−51.9	ND
	ME-100	$Na_{2x}Mg_{3.0-x}Si_4O_{10}(F_yOH_{1-y})_2$	100	−52.3	9
	Delelite LVF	$(Si,Al)_8(Al,Fe,Mg)_4O_{20}(OH)_4$,Xn,m($H_2O$)	100	−45.1	600
	Bentone MA	$Na_{0.4}Mg_{2.7}Li_{0.3}Si_4O_{10}(OH)_2$	98	−36.6	600
	Cloisite Na^+	$(Na,Ca)_{0.33}(Al,Mg)_2Si_4O_{10}(OH)_2$	98	−48.6	800

ND, not tested.

Table 1. Physiochemical properties of clay nanoparticles [57].

2.9. Montmorillonite (MMT) as a carrier for drug delivery

Clay as a carrier for drug delivery is an amazing interdisciplinary field that brings together biology, materials science, and nanotechnology. Composites based on clay minerals have

effect on a variety of fields, especially in pharmaceutical science. The tremendous variety of these natural materials has made the widespread collection of clays and polymers available to researchers [76–84]. The controlled drug delivery system is a method for the development of nanostructures and materials that can encapsulate high concentrations of materials, pass through a cell membrane, and release the drug in the target region for a given period. Clay minerals have exceptional (unique) characteristics such as low toxicity, better biocompatibility, and are guaranteed for a controlled drug release, and thus they are used in biological applications in pharmaceuticals, cosmetics, and even medical purposes [85, 86]. MMT is a natural mineral clay with a layered structure and prominent features such as a high internal surface area and cation exchange capacity (CEC), a high absorption capacity, and low toxicity [64, 87]. MMT with a net charge of the network can well be swollen in the presence of water and hydrophilic solvents, because positive-charged bioactive compounds can be inserted in interlayer (inside layer) spaces by electrostatic interaction. Many attempts have been made to develop MMT as a carrier for drug delivery, for example, to improve the water solubility of insoluble drugs and control the release of bioactive molecules [61, 83, 84, 88–93]. Biochemical properties, which make clay valuable for pharmaceutical applications, include high absorption capacity, high internal surface, high exchange ability, interlayer spatial reactions with drug molecules, chemical moisture, and low toxicity [61, 72, 83, 84, 94–96]. Clay is widely used as an active agent and an additive in pharmaceutical formulations [97–99]. In pharmaceuticals, MMT has found extensive applications as a suspension and a stabilizer, as well as an absorbent and clear factor. Also, MMT has been used as a drug carrier or an additive in pharmaceutical formulations [71, 72, 99–104]. The MMT's ion exchange capacity provides the possibility of replacing Na + with other organic and inorganic cations to increase performance. It also causes the use of MMT and other clay species as a tissue regeneration agent [71, 76–84, 96, 105] (**Table 2**).

The authors have shown that increasing the concentration of silicate nanoparticles increases the mechanical strength of polymer nanoparticles [107]. Wang et al. prepared 2008 complex

Drug	
5-Flurouracil (anticancer)	Ibuprofen (nonsteroidal anti-inflammatory)
Amino acids	BSA (model protein)
Plasmid DNA (gene delivery)	Donepezil (Alzheimer)
Paclitaxel (anticancer drug)	Docetaxel (anticancer drug)
Lidocaine (local anesthetic drug)	5-Fluorouracil (anticancer drug)
Glutathione (antioxidant)	Doxorubicin (anticancer drug)
Ibuprofen (anti-inflammatory)	Buspirone hydrochloride (antianxiety)
Captopril (hypertension)	Timolol maleate (β-adrenergic blocking agent)
Vitamin B1	Ranitidine hydrochloride (antacid)
Quinine (antimalarial drug)	Procainamide hydrochloride (antiarrhythmia drug)
Tamoxifen (anticancer drug)	Epidermal growth factor (tissue engineering)

Table 2. List of drugs used in clay as carrier [106].

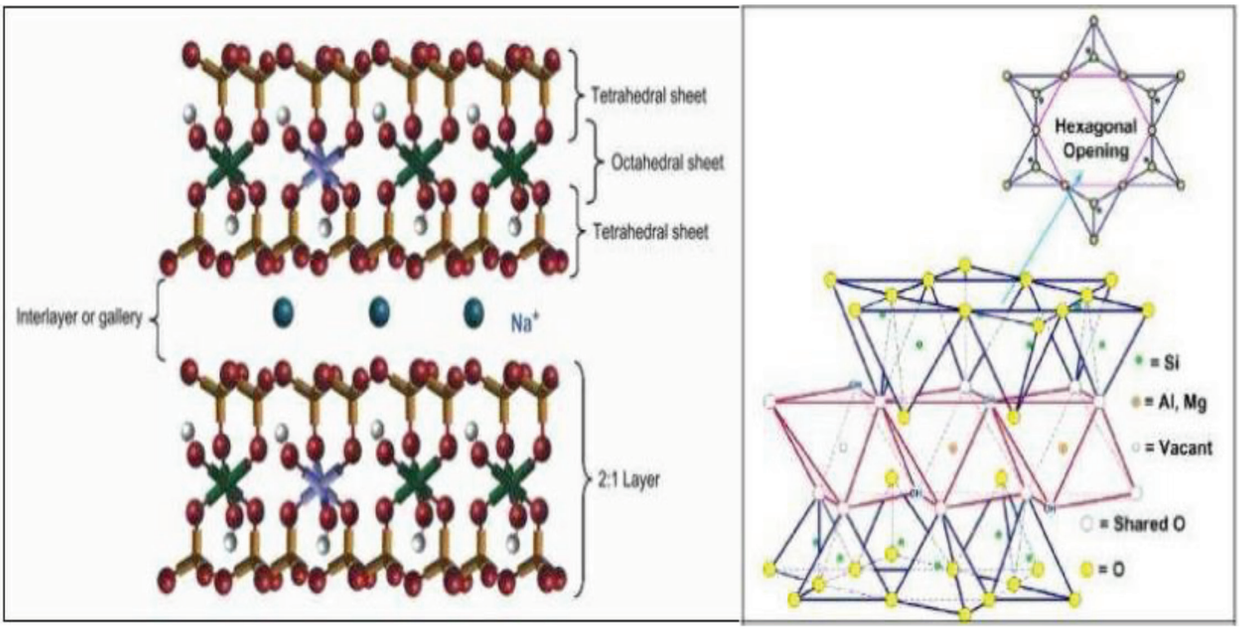

Figure 5. MMT network structure [106].

chitosan-montmorillonite (HTCC/MMT) nanocomposites for the application as protein carriers [103]. In 2010, Shhameli et al. showed a new green color combination for MMT/chitosan nanoparticles (CS) and its antibacterial actions [108]. Lee and Fu found that the properties of the released drug can be controlled by the charge of N-isopropylacrylamide/MMT nanocomposites [109]. In general, the ability to exchange ions, interoperability, and biocompatibility of MMT has made it an ideal candidate for drug delivery. In addition to pharmaceutical use, MMT and its nanocomposites are bioactive agents that have a wide range of applications. MMT can play an important and powerful role in intestinal detoxification, since it can absorb food, microbial, and metabolic toxins and, surprisingly, can increase the hydrogen ions in acidosis. Also, MMT can be used for edible purpose for digestive system detoxification, constipation reduction, internal parasite eradication, strengthening of the immune system, liver detoxification, reduction of stomach pain, and poisoning by bacteria. Revitalizing drugs and tissue engineering programs include bone remodeling as growth agents and wound dressing. The network structure of this is shown in **Figure 5** [106].

MMT is widely used in the treatment of bone pain and damaged muscle, chronic headache, open wounds, special skin conditions (acne, eczema, red seeds on the skin, etc.), diarrhea, hemorrhoids, stomach ulcers, intestinal problems, anemia, rapid recovery of injuries (bruises, stretching, burns, etc.), severe bacterial infections, skin rejuvenation, and various health issues. Therefore, it can be beneficial to health because all its activities are physical and there is no chemical reaction on the body. After taking, no or small amount of MMT is absorbed in the digestive system and the rest is excreted (repulsed) by feces. According to the ISI database, interest in drug delivery by clay shows a significant increase in scientific publications (**Figure 6**) [106].

2.10. Mechanisms of drug-clay interactions

According to the tests conducted, the basis of controlled drug delivery is the use of laminar (layer) interference. Interference may occur by mixing sub-solids (ion converters) with ionic

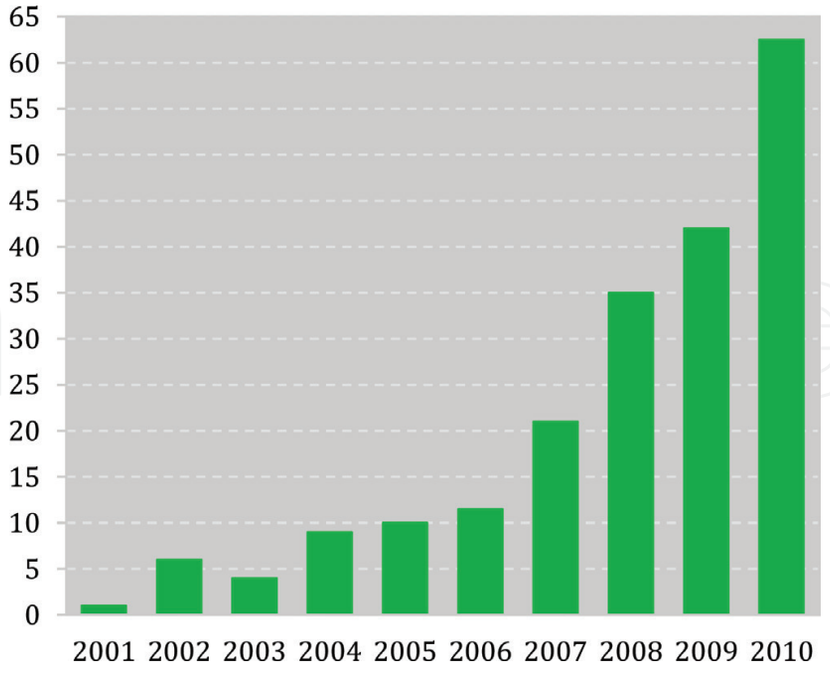

Figure 6. The number of studies on the use of clay nanoparticles as carrier for drug delivery [106].

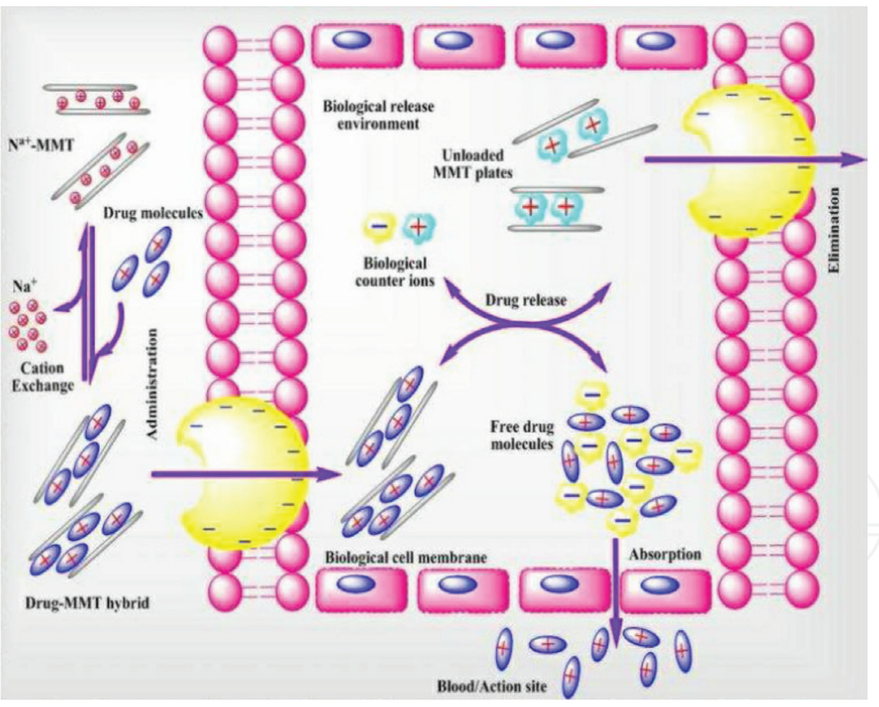

Figure 7. Mechanism of release of MMT and absorption in the body [106].

material in solution. In biological fluids, "anti-ions" can move the drug into the substrate and transfer it to the body, so the converter can be removed or decomposed at the end (**Figure 7**) [106]. Smectites, especially MMT and saponite, have been further studied due to their ionic exchange capacity compared to other silicates (talc, kaolin, and fibrous mineral clay). A specific mechanism depends on factors such as functional groups and chemical physical properties

of organic compounds [109–111]. Silicate-based composites exhibit a good inhibitory (barrier) effect due to complicated intrusive pathways that small molecules need to undergo (pass) in order to clarify the material (**Figure 8**) [112].

2.11. The latest MMT pattern used in drug delivery systems

Lin et al. showed the 5-FU interference on the MMT inner layers [61]. 5-FU-MMT was determined and the successful interference of the drug in MMT was confirmed by opening the inner layer and changing the XRD pattern to the lower 2θ angle, and the results are presented in **Figure 9**. Finally, it can be concluded that the total amount of 5-FU absorbed in MMT is approximately 87.5 mg/g MMT.

Park et al. reported the placement of donepezil molecules on clay (Laponite, LA, saponite, SA and MMT) and provided descriptive information, which confirmed the well-located donepezil molecules in the inner layers of clay (**Figure 10**) [91]. The absorption amount and the donepezil molecular structure depend on the cationic exchange ability of clay, which has designed drug release patterns. The rate of release can be increased easily by using a large cationic polymer. The Eudragit® E-100 hybrid, coated with such a polymer, shows the release of drug at higher speeds over a short period. Therefore, nanoclay materials are proposed as an advanced carrier for drug delivery with a controllable release feature.

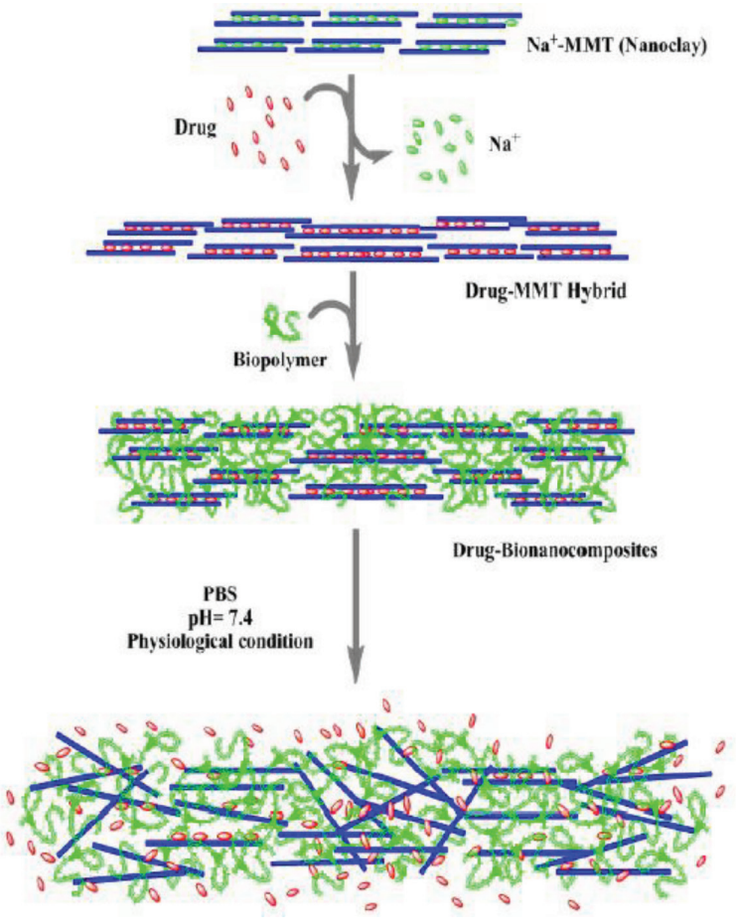

Figure 8. Mechanism of drug release from nanocomposites [106].

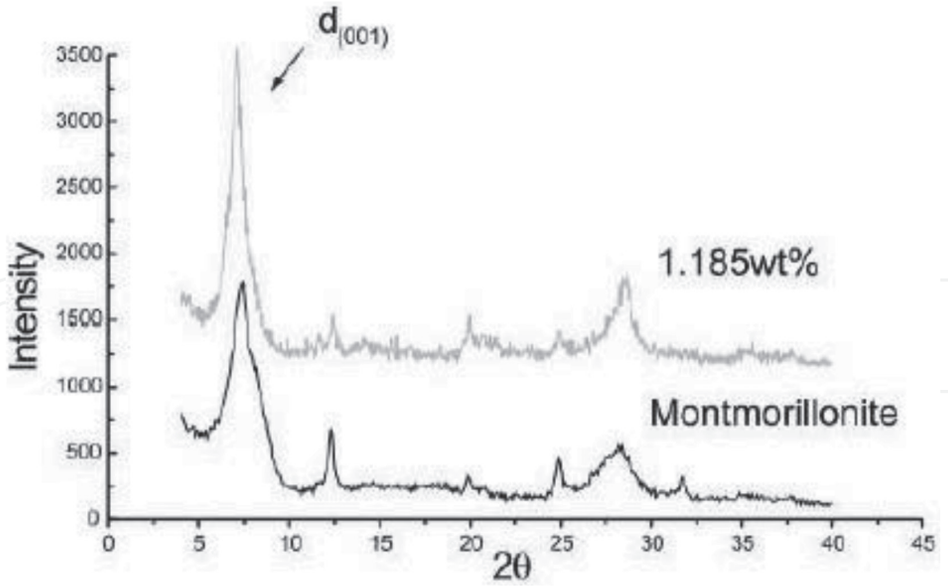

Figure 9. XRD patterns of MMT and 5-FU-MMT [106].

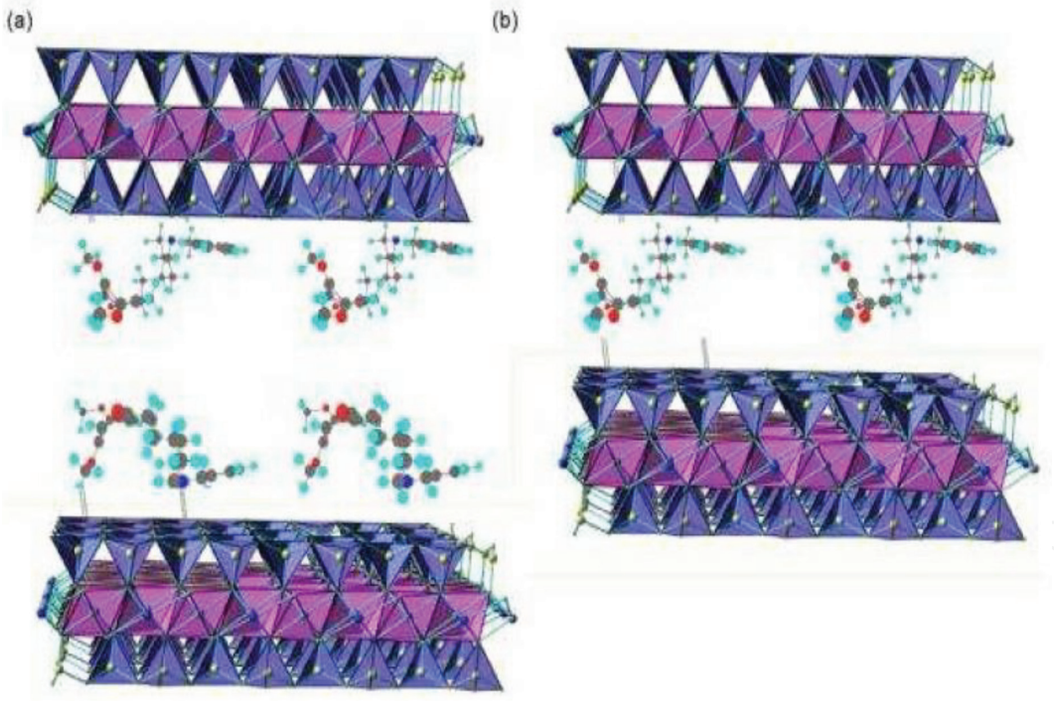

Figure 10. The schematics of donepezil interference in clay nanomaterials: (a) the dual-layer composition and (b) the single-layer composition [106].

2.12. 2D clay nanoparticles for drug delivery in cancer treatment

Two-dimensional kaolinite clay nanoparticles are used in the drug delivery system. The increasing of spacing of the kaolinite nanoparticles from 0.72 to 4.16 nm is due to the interference of guest species with different chain lengths of organic materials that can increase the drug delivery efficiency and reduce the toxicity of doxorubicin (DOX). The kaolinite (Kaolin) and kaolin compounds show a high level of biocompatibility and low toxicity against

pancreatic cancer cells, gastric cancer, prostate cancer, breast cancer, esophageal cancer, and thyroid cancer diagnosis. However, lung cancer and leukemia require structural harder compounds for drug delivery. DOX-Kaolin and its internal contents exhibit more drug release rates in acidic environment than in the neutral environment. The use of two-dimensional clay nanoparticles for a drug delivery system can pave the way for high-performance nanotherapies with superior antitumor efficacy and significant reduction of side effects. As shown in **Figure 11**, it is used for the treatment of tumors [113].

2.13. An overview of clay chemistry

Broadly, clay minerals are structured of two principal units: tetrahedral (T) and octahedral (O) sheets [114, 115]. Each tetrahedron consists of a central cation (mostly Si^{4+}) coordinated to four O^{2-} anions and linked to adjacent tetrahedra through three shared oxygens on the corners (basal oxygens Ob) forming an infinite 2D hexagonal mesh (**Figure 12**). The fourth O^{2-} (apical oxygen Oa) remains unshared, lying perpendicular to the tetrahedral sheet, and is the main site of interaction with the octahedral sheet. Each octahedron consists of a metal cation (M^{n+}) coordinated to six O^{2-} and/or OH^- anions. Adjacent octahedra are linked to each other by sharing edges (two O^{2-} or OH^-), forming an octahedral sheet. If Mn is divalent (Mg^{2+}), a trioctahedral or a brucite-like sheet is produced, if it is trivalent (Al^{3+}), then two out of every three octahedral sites are occupied, leaving a vacant site and the generation of a dioctahedral or a gibbsite-like sheet. Clays can be classified into 1:1 and 2:1 types according to the layering

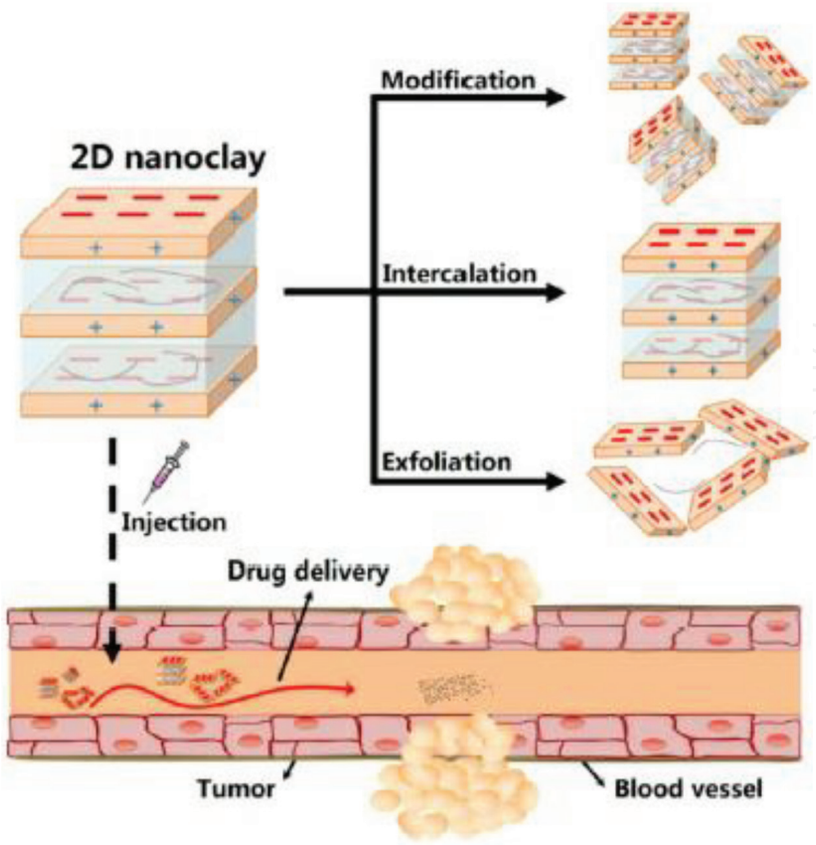

Figure 11. Schematic design and kaolin and kaolin compounds for the treatment of tumors [113].

of T and O sheets. 1:1 (or T-O) clay minerals consist of a single T sheet linked to a single O sheet, and 2:1 (or T-O-T) clay minerals consist of a single O sheet sandwiched between two T sheets (**Figure 12**, **Table 3**).

In the case of smectites, an octahedral sheet of metal oxides (usually Mg^{2+} or Al^{3+}) is sandwiched between two tetrahedral silica sheets. Two types of charges originate on the smectite clay particle: (1) permanent negative charges on the surface due to isomorphous cation substitution in the tetrahedral and/or octahedral sheets (e.g., Li^{+} for Mg^{2+} in Laponite) balanced by exchangeable cations such as Na or Ca^{2+} in the interlayer gallery. (2) Positive (amphoteric) charges on the edges due to broken Si-O, Al-OH, and Mg-OH groups. At pH < Zero Point of Charge (ZPC), these edge charges become positive with anion exchange capacity, while at pH > ZPC, they become negative with a cation exchange capacity. Adapted with permission [116]. Copyright 2014, John Wiley and Sons.

Clay structure and reactivity. The reactivity of clays is largely a function of their swelling capacity. Kaolinite (of the 1:1 clay family) and talc and pyrophyllite (of the 2:1 clay family) possess no structural charges and consequently are non-swelling and of low adsorption capacity. The high-layer charge on vermiculite and illite restricts their swelling and gelling tendency although their surface area and CEC are relatively high. Smectites are characterized by their relatively low-layer charge which allow their particles to undergo complete dissociation in water and give them interesting rheological/gel-forming properties and surface reactivity. Halloysite is formed of hydrated 1:1 layers which role up into nanotubes (alumina sheet on the inside and silica sheet on the outside surface) and sepiolites (and palygorskite) are characterized by their inverted 2:1 ribbon structures. Such arrangements confer large SSA, porosity, and sorptive capacity. Adapted with permission [117].

2.14. Morphology

We focused on the investigation of the potential toxic effects caused by nanoclay particles currently used in tons in several industrial applications. Bentonite, montmorillonite, and

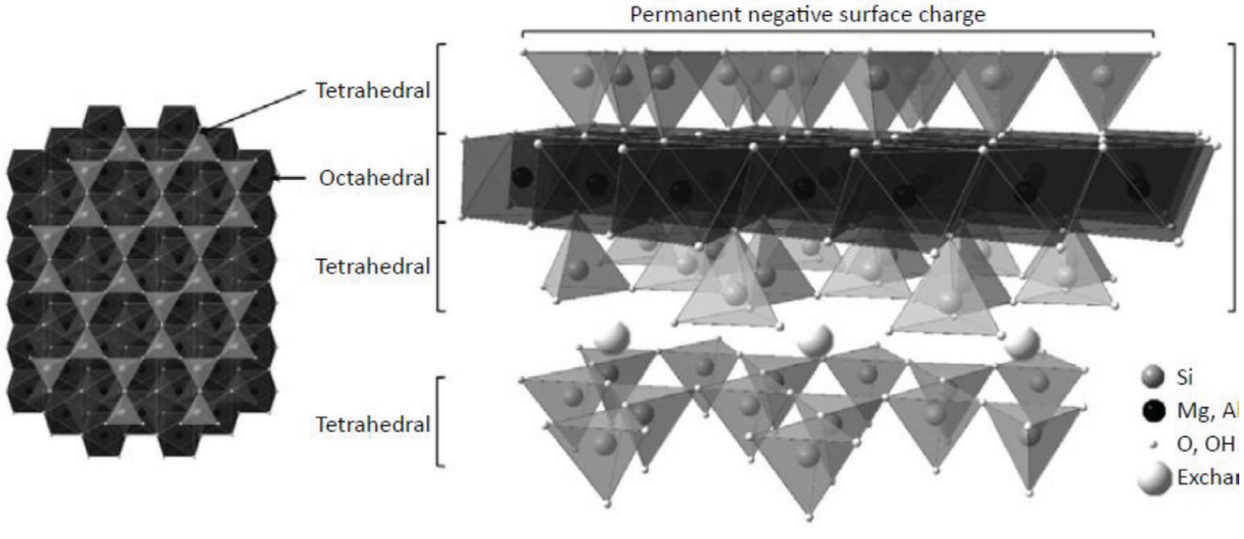

Figure 12. The structure of smectites. Clays are formed of layered tetrahedral (T) and octahedral (O) sheets.

Family group		Species	Chemical formula	Charge/formula unit	CEC	Particle size (nm)
1:1	Serpentine-kaolin	Halloysite	$Al_2Si_2O_5(OH)_4.nH_2O$	~0 [114]	~10 meq/100 g [121, 122]	Nanotube diameter of ~50 nm, lumen of ~15 nm, and length of ~1 mm [119, 126]
2:1	Smectites	Montmorillonite	$Na_m(Al_{2-m}Mg_m)Si_4O_{10}(OH)_2.nH_2O$	~0.2–0.6 [114]	~80–150 meq/100 g [121, 122]	~80–300 nm diameter and ~ 1 nm thickness [127, 129]
		Laponite (synthetic hectorite)	$Na_h(Mg_{3-h}Li_h)Si_4O_{10}(OH)_2.nH_2O$			~25–30 nm diameter and ~ 1 nm thickness [120, 123]
	Sepiolite-palygorskite	Sepiolite	$X^*(Mg, Al, Fe^{3þ})_4(Si,Al)_6O_{15}(OH)_2.nH_2O$	—	~4–40 meq/100 g [124, 125]	Nanofiber diameter of ~15 nm and length of ~200–400 nm [124, 128]

Table 3. Key clay mineral species explored for tissue engineering and regenerative medicine applications with their relevant structural/compositional properties.

kaolin are platy clay particles ranging from nanometers to micrometers, whereas halloysite nanotubes are hollow rod-like particles having a lumen diameter of ~20 nm and a tube length ranging from 300 nm to 2 μm. Spherical silica nanoparticles were also used as a material mimicking the outer silica layer of the clays. Graphene oxide nanosheets having the shape and size close to smectite clays were selected as a material with a relatively high reported toxicity, 30, which was also confirmed in our study. The typical AFM images demonstrating the geometry and sizes of nanoparticles used in this study are given in **Figure 13**.

The nanoparticles used were suspended in water and added to protozoan media at a range of concentrations. Prior to toxicity investigation, the hydrodynamic diameters and surface potential of nanoparticles were determined using dynamic light scattering (DLS) and electrophoretic mobility measurements in water (**Table 4**) [118].

2.15. Ecotoxicological profile

No ecotoxicological studies of nanoclay have been identified as of November 30, 2010. Since clay is a naturally occurring material for which environmental organisms have adapted throughout evolution, the inherent toxicity is expected to be low; however, issues related to small particle sizes may occur [78].

2.16. Toxicological profile

Today, few studies are available, and there is limited knowledge about the toxicity of nanoclays and the chemical derivatives that may be generated during the production and processing of polymer nanoclay composites. However, in general, nanoclay is not considered to pose a major health risk although a possible content of crystalline quartz may constitute a risk.

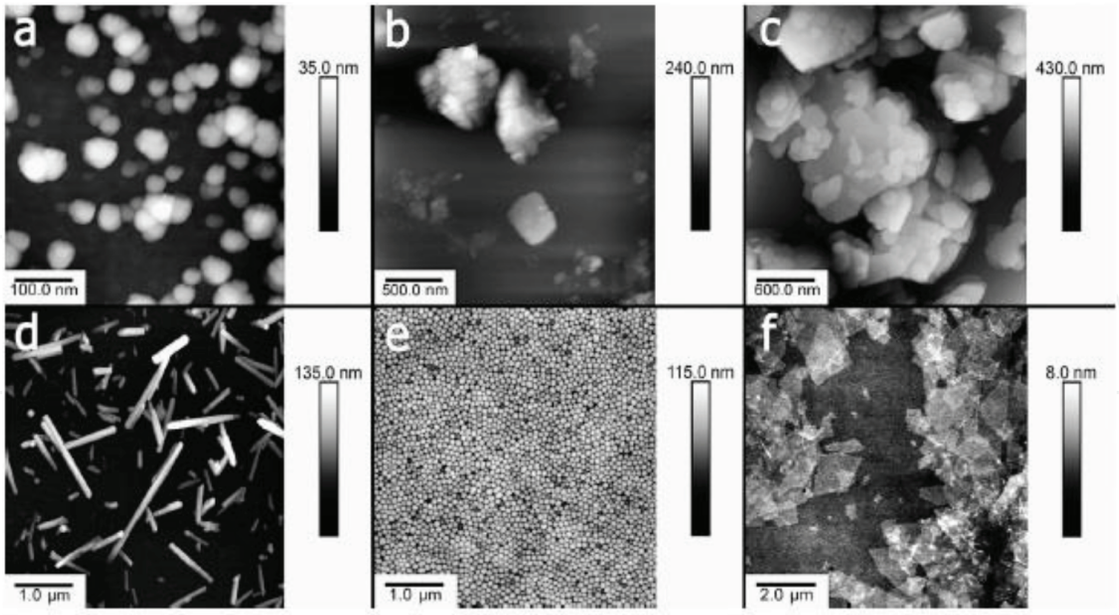

Figure 13. Typical AFM images of (a) bentonite, (b) montmorillonite, (c) kaolin, (d) halloysite, (e) silica, and (f) graphene oxide nanoparticles.

Particles	Hydrodynamic diameter, nm	Zeta-potential, mV	AFM measured dimensions
Halloysite	510 ± 12	−25 ± 3	50 nm diameter, 400–1500 nm length
Kaolin	930 ± 22	−36 ± 1	300–700 nm width, 30–100 nm thick
Montmorillonite	1600 ± 60	−29 ± 1	300–600 nm width, 10–50 nm thick
Bentonite	3040 ± 660	44 ± 2	~4 μm width, ~100 nm thick
Silica	122 ± 3	−39 ± 6	120 nm diameter
Graphene oxide	1940 ± 90	−47 ± 2	2000 nm width, 2–10 nm thick

Table 4. Hydrodynamic diameters, zeta-potential values, and AFM measured sizes of nanoclay particles, silica nanospheres, and graphene oxide nanoflakes.

Furthermore, functionalized nanoclays containing quaternary ammonium or phosphonium functional groups on the surface are described as potentially problematic, as ammonium and phosphonium ions in their pure form can cause asthma symptoms (NFA, 2010) [78].

3. Conclusions

Clay nanoparticles have traditionally been used in many applications such as treatment, skin chemotherapy, and medicine to improve the human health and life. In addition, they have recently been developed as additives, lubricants, and active materials in pharmaceutical formulation. Although their application in food science is relatively limited, they have the potential to

deliver nutrients. Their unique structure is able to place bioactive molecules in the interior space. Nanoparticles that contain nutrients have the ability to protect GI against the environment and control the release features. They can enter the cell and with their adhesion properties facilitate the transfer of GI molecules against barriers. Also, they exhibit low toxicity. Research on the development of clay nanoparticles based on oral delivery systems for nutrients or functional compounds indicates that they are effective in protecting and controlling deliveries and also contributing to the increased bioavailability. The promising potential of the clay nanoparticles makes a new perspectives for the development of nano-based oral delivery systems. The toxicity of nanomaterials is a very important issue. In general, the results show that higher doses of clay nanoparticles result in the death of cells, which is a concern for medical applications. As an important point in the application of clay nanoparticles in delivery systems, to achieve clay-based controlled delivery systems, one of the best ways is to place organic molecules on the underlying layers of mineral clay. Besides, its composites can be used to improve properties.

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