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Properties and use of chitosan/clay nanocomposites for drug delivery: A review

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Abstract

Clay minerals serve as both excipients and active ingredients in pharmaceutical formulations. Due to their swelling capacity and colloidal properties, they are also promising candidates for use in controlled drug release. Besides clay materials, chitosan also plays a crucial role in biomedical applications due to their biocompatibility and biodegradability. By using montmorillonite and halloysite as case examples, this review provides valuable insights into the distinctive characteristics of clay materials, exploring the potential use of their nanocomposites formed with chitosan in drug delivery. It first outlines the fundamental properties of clay materials, followed by a discussion of key fabrication methods for chitosan/clay nanocomposites. Finally, recent advances in the development of carriers based on chitosan/clay nanocomposites and their pharmaceutical performance are discussed. Directions for future research are also highlighted. It is hoped that this article could provide a snapshot of the current understanding of the properties and use of chitosan/clay nanocomposites as drug carriers and offer insights into the future potential of clay mineral hybrids in pharmaceutical applications.

Keywords: Clay; chitosan; nanocomposites; drug delivery; loading; intercalation

1. Introduction

Clays are naturally occurring hydrated aluminosilicates containing exchangeable cations, either in their natural form or in modified form. Due to their abundance and environmentally sustainable properties, clays are often referred to as the "Materials of the 21st Century"[1]. They are used across a wide range of fields, including biomedical, agricultural, engineering, and environmental applications [2-4]. Over the past few decades, clays have been incorporated into various pharmaceutical formulations as lubricants, diluents, pigments, and binders. They have also been used to treat food poisoning, infections, and mineral deficiencies[5]. One example of clays is montmorillonite (MMT), which is a naturally occurring aluminosilicate with a 2:1 layered structure (**Figure 1**). Its structure enables various substances to be intercalated between its layers. MTT shows high cation exchange capacity (CEC), large internal specific surface area (SSA), excellent adsorption properties, and high biocompatibility. It has been approved by the U.S. Food Drug Administration (FDA) for use in food and medical applications. Besides MMT, halloysite is also a naturally occurring clay mineral which has a hollow tubular structure and 1:1 aluminosilicate composition [6, 7]. These nanoscale properties making halloysite suitable for loading, storing, and controlling the release of bioactive agents [8]. The CEC and SSA values of clay minerals are shown in **Table 1** [9-12].

In addition to clay materials, chitosan (CS) and its derivatives have also received extensive attention for drug delivery applications [13-15]. CS can form hydrogels through covalent or non-covalent crosslinking [16-18], with the nanoparticles prepared via ionic gelation or emulsification exhibiting excellent biocompatibility, biodegradability, and mucoadhesive properties [19, 20]. However, clay-only carriers often lack flexibility and the undesirably strong interactions between drug and clay could impede proper drug release and absorption, resulting in poor drug bioavailability [21]. This phenomenon is particularly undesirable for drugs such as antihistamines, whose immediate therapeutic concentration in the blood right after administration is expected [21]. On the other hand, CS-based systems show solubility only in acidic aqueous media [22], limiting the application potential as drug carriers. Formation of nanocomposites between CS and clay, however, integrates the advantages of both components, yielding hybrid materials with enhanced structural stability, controlled drug release characteristics, and improved interactions with biological systems. Notably, the problem of poor drug release and absorption in drug–clay hybrids

is also ameliorated upon coating with CS [21]. These synergistic benefits brought about by CS and clay make CS/clay nanocomposites particularly attractive as drug carriers. Importantly, combining CS with clay minerals has been found to enhance the antimicrobial activity due to the CS and clay inherently showing antimicrobial activity [23]. Additionally, clay enhances the mechanical property of CS [24-26], making this composite ideal for wound dressing applications. Furthermore, the presence of clay in the polymer matrix controls the release rate of bioactive agents [27]. This review provides an overview of the properties of clay minerals and the mechanism of CS-clay interactions. By using MMT and halloysite as case examples, it also offers a snapshot of latest advances in the development of CS/clay-based drug carriers and the reported pharmaceutical performance.

2. Properties of clay minerals

One important property determining the efficiency of polymer/clay nanocomposites, including those generated from clay and CS, for drug delivery is the rate of exchange, which partly depends on the type of clay and the concentration of the solutions. For instance, due to the presence of exchange sites between the unit layers, the process may take several hours in clay materials such as illite and smectite; but in clays such as kaolinite, exchange reactions typically occur almost instantaneously[28]. As far as the process of exchange is concerned, CEC and SSA play a pivotal role as they describe the extent to which the clay minerals can exchange their interlayer cations with cationic-based bioactive agents[29]. The adsorption capacity of ranitidine for MMT is 1.174 mmol/g [30]. One earlier study has found that the loading capacity of chlorhexidine diacetate is higher in MMT (CEC-92.6 meq/100 g) compared to palygorskite (CEC-26.2 meq/100 g)[31], indicating that higher CEC values increase the loading capacity of the agents. Furthermore, they observed that the release rate of chlorhexidine diacetate is 2-fold higher in the MMT system compared to palygorskite during the first 5 hours and even showed a 3-fold increase at 24 hours. Bioactive agent loading or capacity mainly depends on the SSA, as a high SSA increases the drug adherence and also influences the release rate[32]. High encapsulation efficiency of drug molecules is essential for effective use in drug delivery, and MMT generally exhibits high encapsulation efficiency due to high CEC and SSA [32].

Apart from the rate of exchange, the activity of clay minerals determines resulting drug delivery performance. Activity refers to the specific clay mineral present in a soil composition. Clay is considered low-active or inactive when its activity is below 0.75. If the activity ranges between 0.75 and 1.25, the clay is classified as normal. Clays with activity above 1.25 are considered active, indicating the likely presence of swelling clay minerals[33, 34]. Activity is a key criterion for determining the swelling potential of soils[33]. A higher activity level significantly influences the clay fraction's impact on various properties, making them more sensitive to changes in factors such as the type of exchangeable cations and pore fluid composition[28].

Clay swelling occurs when the interlayer space between clay particles expands[35]. Swelling clay have larger interlayer spaces, while non-swelling clays have small interlayer spaces [36-41]. Clay swelling involves osmotic water uptake between two adjacent clay mineral surfaces, leading to the widening the interlayer space[42]. This osmotic water inflow is driven by differences in the concentration levels at the interfaces of the clay and pore water. Additionally, hydration of clay minerals can contribute to swelling, as water is incorporated into the crystal lattice between the silicate layers of the clay[42]. MMT has a three-layered structure, exhibiting high anion (100–500 mEq/100 g) and cation (80–150 mEq/100 g) exchange capacities[43]. It readily adsorbs sodium ions, leading to significant swelling and dispersion. The substantial interlayer spacing and weak interlayer forces in MMT make it more prone to swelling.

3. Interactions between CS and clay

Dispersed stability is a crucial factor to consider in drug carrier design, as it significantly affects absorption and bioavailability[44]. Under physiological conditions, clay dispersions tend to exhibit instability due to high salt concentrations and the presence of polyelectrolytes, such as proteins, which increase the likelihood of colloidal particles flocculating and precipitating[45, 46]. The incorporation of biopolymers (such as CS) enhances the stability of clay dispersions. When clay fillers are combined with polymers, three potential morphologies can emerge: conventional, intercalated, and exfoliated nanocomposites **(Figure 2)**[47]. In a conventional nanocomposite, the clay's structure remains intact, as polymer chains cannot to infiltrate the interlayer spaces of the clay. This leads to the formation of clay aggregates with limited interaction with the polymer[48]. Intercalated nanocomposites, on the other hand, exhibit polymer chains that infiltrate between the

clay layers, resulting in an expansion of the interlayer space [49]. In exfoliated nanocomposite, the clay platelets are completely delaminated from their original arrangement, and randomly oriented within a continuous polymer matrix[49].

The mode of interactions between CS and clay has been shown by Xu and coworkers[50], who investigated the nanostructure and functional properties of CS/clay composites. The incorporation of 1-3 wt% of Na^+-MMT into CS resulted in the disappearance of the characteristic peak of Na^+-MMT at $2\Theta = 7.22°$[50], indicating the formation of a disordered exfoliated structure. Upon increasing the concentration of Na^+-MMT to 5 wt%, a broad peak appeared at $2\Theta = 5.34°$, which was lower than that of pristine Na^+-MMT, suggesting the occurrence of some intercalation alongside exfoliation. Furthermore, when Cloisite 30B was added to the CS solution, a characteristic peak similar to that of pure Cloisite 30B ($2\Theta = 4.8°$)was observed[50]. This indicated that no intercalation has occurred between Cloisite 30B and CS, suggesting that CS molecules were intercalated with Na^+-MMT but not with hydrophobic clay material (Cloisite 30B). In addition, the incorporation of 3 wt% of Na^+-MMT into CS resulted in the good dispersion of clay particles, while increasing the concentration to 5 wt% resulted in the aggregation of particles in the CS solution[50]. Based on these observations, different concentrations of clays in clay/CS nanocomposites would result in different composites. In fact, CS is known to be able to alter the ion exchange properties of natural clays. Clay minerals are generally ineffective at adsorbing negatively charged or neutral bioactive agents, which requires the exchange of interlayer cations for specific organic molecules to synthesize organoclays capable of encapsulating anionic and/or neutral bioactive agents[51, 52]. However, polyelectrolytes such as CS have been suggested for use in these contexts. The feasibility of this has been demonstrated by the fact that polymer-clay nanocomposites containing both CS and MMT, as well as laminar phyllosilicate, exhibit higher anion exchange capacities compared to MMT alone[53].

Apart from the aforementioned, incorporation of clay materials into CS matrices can be a means of manipulating thermal and mechanical properties of the system [54, 55]. This has been demonstrated by Shou et al., who developed a CS/MMT composite and investigated its mechanical performance under various pH conditions and MMT concentrations [56]. Composites prepared at neutral and acidic pH (pH 4) containing 40% MMT exhibited the highest elastic modulus. However,

a higher MMT content led to decreased fracture strength and strain, attributed to structural defects. More recently, Lewandowska also fabricated a composite film by incorporating MMT into a CS and poly(N-vinylpyrrolidone) matrix and examined its thermal and mechanical properties [57]. The addition of poly(N-vinylpyrrolidone) and MMT enhanced the thermal stability and mechanical strength of the CS matrix, primarily due to crosslinking reactions between polymer chains and strong interactions among CS, poly(N-vinylpyrrolidone), and MMT.

It is worth noting that while polymers such as CS are commonly used to modify the properties of clay in nanocomposite formation, the reverse is also true—clay materials can also be incorporated into polymer matrices to enhance the properties of the polymers themselves. This is exemplified by the case of HNTs, which have been used to improve the mechanical and thermal properties of polymeric materials [58]. In an earlier study, Kouser and coworkers prepared a bionanocomposite film by incorporating CS-modified HNTs into a poly(vinyl alcohol) (PVA)/polyvinylpyrrolidone (PVP) matrix and studied its thermo-mechanical behaviour [59]. The thermal stability of the generated film was found to be enhanced with an increase in the content of the incorporated HNTs. Moreover, the inclusion of the HNTs improved both the tensile strength and Young's modulus of the film compared to the PVA/PVP matrix. Elongation at break was also enhanced, due to strong inter- and intramolecular interactions between the modified halloysite nanotubes and the polymer matrix. Similarly, Roy et al. fabricated a composite film by incorporating CS-functionalized halloysite nanotubes (CHT) and rutin into a pullulan/CS matrix and investigated its mechanical and thermal properties [60]. The thermal stability of the pullulan/CS film increased upon the addition of CHT/rutin. The tensile strength of the film improved by approximately 20% with the inclusion of CHT, while the addition of rutin alone led to a 10% increase. The overall improvements in tensile strength and elongation at break were attributed to strong interfacial interactions and hydrogen bonding between the CHT/rutin components and the polymer matrix.

4. Fabrication of CS/clay nanocomposites

As far as generation of CS/clay nanocomposites is concerned, solution intercalation is the major method. It is generally conducted by using an appropriate solvent system in which CS is soluble while the clay remains dispersible, allowing the synthesis of CS-clay nanocomposites. Initially the organoclay is swollen in suitable solvent to facilitate the expansion of the silicate layer space. Next,

the layered silicate solution is combined with the polymer solution, enabling the polymer chains to interact with the solvent molecules and intercalate into the clay layers. The solvent is then evaporated, resulting in the formation of the nanocomposite[61]. By using this method, previously triphenyl-(chloro acetylated CS) phosphonium salt-MMT intercalates were generated for sustained release of 5-amino salicylic acid [62]. During nanocomposite fabrication, sodium MMT was first swelled in water, followed by the addition of a solution of triphenyl-chloroacetylated CS phosphonium salt dissolved in dimethylformamide, with the resulting nanocomposites being finally dried in a vacuum oven. More recently, CS/halloysite nanocomposites have also been generated via solution intercalation [63], in which halloysite nanotubes (HNTs) were dispersed in an aqueous solution of CS oligosaccharide aqueous solution. After that, the nanocomposites formed were recovered by centrifugation and lyophilized. The structure of the nanocomposites generated by solution intercalation is often highly ordered and layered, consisting of inorganic and organic elements arranged in a sandwich-like fashion (**Figure 3**) [64]. The thermodynamic driving force for the intercalation of macromolecular chains in this method is the increased entropy associated with the desorption of solvent molecules [65, 66].

Apart from solution intercalation, melt intercalation has been adopted for the fabrication of clay-based nanocomposites. This process involves mixing molten polymer with clay using external forces such as an internal mixer or extruder. The blended material is then heated above the glass transition temperature of the polymer to soften the matrix material and form nanocomposites [61, 64, 66]. Melt intercalation is eco-friendly as no solvent is used, and can be adapted to processes such as injection molding and extrusion when the nanocomposites are generated, though the properties of the generated nanocomposites are highly sensitive to melt processing parameters, such as extrusion speed, temperature, and mixing time, to optimize exfoliation[67]. In fact, variations in the shear force during melt processing have been found to significantly affect the degree of dispersion and intercalation of clays in the polymer matrix [68]. The interaction between the matrix polymer and the nanofiller, influenced by the molecular weight and polarity of the polymer, can also influence the dispersion of the fillers in the nanocomposites [69]. during melt intercalation, the polymer must be in a molten state, meaning that only thermoplastic polymers can be used. Since CS is not a thermoplastic polymer, CS/clay nanocomposites are rarely fabricated using melt intercalation.

In addition to the methods mentioned above, clay-based nanocomposites can be generated by *in situ* polymerization. This method involves swelling organo-modified clay layers in a monomer solution. The monomers can then move and intercalate into the interlayer space where they polymerize into long organic polymer chains. To enhance the effectiveness of polymerization, catalysts or initiators are sometimes added [64, 70, 71]. This method has the ability to produce exfoliated nanocomposite materials and is compatible with different types of reactive monomers. During *in situ* polymerization, increasing the surface energy of the layered silicate can facilitate the infiltration of monomers into the interlayer space [64], resulting in the formation of elongated macromolecular chains that gradually peel off the clay layers into a disordered configuration, ultimately yielding an exfoliated structure[64]. Although *in situ* polymerization has been adopted to generate multiple clay-based nanocomposites in the literature [72-74], it is not commonly used to generate CS/clay nanocomposites. This is because CS is a naturally occurring polymer that exists in its polymeric form rather than being synthesized from monomers. As a result, *in situ* polymerization is not a suitable method for forming CS/clay nanocomposites.

5. Mechanisms of drug loading into CS/clay nanocomposites

Drug loading is generally conducted after the generation of CS/clay nanocomposites. This process could be achieved via intercalation, which is a process involving the insertion of drug molecules into the interlayer space of clay minerals. Over the years, different intercalation methods have been proposed, ranging from cation exchange [75] and ion-dipole interaction [75, 76] to grafting [77] (**Figure 4**). Apart from intercalation, drug molecules could be loaded into CS/clay nanocomposites via adsorption, which is typically initiated by several physicochemical forces present at the interface between the adsorbent and the adsorbate. The adsorption process between clay and drug materials can be mediated by electrostatic interactions, hydrogen bonding, and the ion exchange process[78, 79]. A schematic representation of the adsorption mechanisms of clay minerals is shown in **Figure 5**. Clay minerals possess a significant surface area and expandable interlayer space that can accommodate drug molecules, making layered silicates potential carriers for various substances. Additionally, electrostatic interactions between the negatively charged layered silicates and the positively charged drug molecules enable adsorption onto the clay surface[80]. Nonionic and anionic drug molecules can also integrate with clay minerals, and interactions between the

drug substances and the clay are often proposed as hydrogen bonding interactions. In some cases, drug molecules are quantitatively associated with the clay material via the cation exchange process[81].

Upon successful drug loading, the CS/clay nanocomposites could release the loaded drug in a sustained manner. In fact, the intercalation of a drug into hydrophilic clay component of the CS/clay nanocomposites can potentially improve the aqueous solubility of the drug[82]. The homogeneous dispersion of the drug in the clay component of the nanocomposites in aqueous media can also prevent the formation of drug crystals [82]. To investigate the release kinetics and mechanism of drug molecules from clays and their nanocomposites with CS, kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models have been widely adopted. The release of drugs from the nanocomposites is primarily initiated when the drug-loaded nanocomposites come into contact with the release medium. The release profile initially shows burst release due to the concentration gradient of the drug present in the nanocomposites [83]. Subsequently, the interlayer structure of clay minerals could potentially retain the drug molecules via intercalation. Intermolecular forces, such as hydrogen bonds, ionic bonds, covalent bonds, and Van der Waals forces, between the drug and the clay substance could also hinder the release of drug molecules [83]. All these leads to sustained drug release, even though the actual drug release rate is the result of multiple factors (including clay concentration, interlayer spacing, and the distribution of clay within the matrix)[84].

6. Development of CS/clay nanocomposites as drug carriers

Over the years, various CS/clay nanocomposites have been developed, many of which have shown promise in enhancing drug delivery performance (**Table 2**) [85-97]. In the following parts of this section, some of the latest advances in the development of nanocomposites formed with CS using MMT and halloysite are presented.

6.1. Chitosan/MMT nanocomposites

MMT is known for its high internal surface area, adsorption capacity, and swelling properties[5, 98, 99]. It shows ability to adsorb the drug molecules onto its alumino-silicate layers and to release the drug in aqueous media[100]. Cardoso and coworkers developed CS/MMT nanocomposite film

for sustained release of 5-fuloruracil[101]. The 5-fuloruracil-loaded nanocomposite film showed a lower rate of drug release than the conventional CS film, indicating that the presence of MMT controls the release behavior of drug molecules. Furthermore, the 5-fuloruracil-loaded nanocomposite film exhibited a significant antibacterial activity on *Escherichia coli* and *Staphylococcus aureus*, while it shows negligible toxicity towards L929 fibroblast cells. By combining κ-carrageenan with CS and MMT, Jafari and coworkers also developed pH- and magnetic-responsive hydrogels, whose drug release rate was found to change upon different pH[102]. More recently, curcumin-encapsulated CS-agarose-MMT nanocomposite hydrogels and curcumin/ciprofloxacin-loaded CS/hyaluronic acid/MMT hydrogels have been reported for cancer treatment[103] and wound treatment[104], respectively. The former exhibited sustained release behavior and released 89% of curcumin at 96 hours[103]; whereas the latter showed a release rate of drugs in the presence of a magnetic field[104], with the drug release sustainability decreasing as the concentration of MMT in the hydrogels increasing. This suggested that the inclusion of MMT plays a crucial role in controlling the drug release behavior[104].

As far as the use of MMT in drug delivery is concerned, one challenge to be tackled is that MMT tends to exhibit flocculation and precipitation because of its high salt concentrations and partial release of bioactive agents[105]. To address this issue, PEGylated CS (PEG-CS) was integrated into MMT to improve the dispersion. As the PEG-CS to MMT ratio increased, the multilayered structure transitioned into a hierarchical lamellar state and eventually into an exfoliated state (**Figure 6**)[105]. Moreover, multilayered nanosheets demonstrated high doxorubicin (DOX) loading capability compared to exfoliated structures, with sustained DOX release being noted in acidic environments[105]. Incorporation of PEF-CS, therefore, proves to be a feasible approach for preventing flocculation and improving MMT dispersion stability.

6.2. Chitosan/halloysite nanocomposites

Halloysite has the potential to be developed as effective carriers for bioactive agent delivery due to their high biocompatibility and relatively low cost [106, 107]. In an earlier study[63], folic acid-conjugated CS oligosaccharide-assembled magnetic HNTs (FA-COS/MHNTs) were synthesized for sustained release of camptothecin. The generated nanotubes exhibited sustained release behavior up to 60 hours and showed cytotoxicity against human epithelial colorectal

adenocarcinoma cells (Caco-2). CS-coated HNTs hybrid nanoparticles incorporated with curcumin and Au nanoparticles were also reported to show pH- and near-infrared responsiveness for cancer drug delivery.[108] The drug release rate of the nanoparticles was higher under acidic conditions and exhibited significant cytotoxicity on MCF-7 cells, highlighting the promising potential of the nanoparticles for pH-responsive drug delivery.

In fact, one of the key roles of incorporating clay materials such as halloysite into polymeric matrices is to enhance the sustainability of drug release from polymeric systems—and the reverse is also true, as polymers can be used to modify the properties of clay materials. This has partly been revealed by Calija et al. [109], who fabricated ionically cross-linked CS–halloysite composite microparticles as drug carriers. Drug release studies showed that at pH 6.8, CS microparticles without halloysite exhibited poorer drug release sustainability than the composites. A similar observation regarding the enhanced drug release sustainability of CS/clay nanocomposites compared to their individual components was also reported by Lisuzzo et al. [110], who developed a layered composite tablet by sandwiching a CS/halloysite composite film between two layers of alginate. *In vitro* release studies demonstrated that sodium diclofenac-loaded halloysite released the drug at a higher rate than sodium diclofenac-loaded CS/halloysite composites. Moreover, the alginate/CS/halloysite layered tablet showed negligible release at pH 3 and significantly higher release at pH 7.8, suggesting its potential suitability for targeted physiological applications. More recently, Nyankson and coworkers have also investigated the release rate of CS-coated HNTs on MCF-7 cells with or without CS coating [111]. The *in vitro* release results showed that CS-coated curcumin-loaded HNTs showed a slower release rate compared to curcumin-loaded HNTs [111]. The MTT results revealed that free curcumin exhibited higher level of inhibitory activity on MCF-7 cells after 24 hours than curcumin-loaded HNTs and CS-coated curcumin-loaded HNTs [111]. This is due to the sustained release of curcumin from HNTs.

Owing to their pH responsiveness and sustained drug release properties, various CS/halloysite nanocomposites have been developed over the years. One example is the pH-responsive CS/halloysite/carbon nanotube nanocomposites reported for sustained release of curcumin [112]. The release profile of curcumin was sustained and achieved 96% release after 96 hours. In addition, curcumin-loaded nanocomposites suppressed the viability of MCF-7 cells compared to free

curcumin after 48 hours. This suggests that the nanocomposites have the ability to control the release behavior of drug molecules, exhibiting significant toxicity on cancer cells as compared to free drug molecules after long exposure. In a recent study, graphitic-carbon nitride (g-C_3H_4) was incorporated into a CS/halloysite matrix to improve the entrapment efficiency of quercetin and enhance its targeted release [113]. The study found that the presence of g-C_3N_4 and halloysite improves the encapsulation, loading efficiency, and prevention of the initial burst release of quercetin. The nanocomposites showed a high release rate at pH 5.4 compared to pH 7.4. Furthermore, the *in vitro* toxicity studies revealed that the nanocomposite exhibited reduced MCF-7 cell viability compared to quercetin alone [113].

Apart from complexing with clay materials, CS could be used directly in surface modification of clay minerals to the physicochemical properties and chemical stability. For example, Liu et al.[114] developed CS-grafted HNTs (HNTs-g-CS) encapsulated with curcumin and investigated the anticancer efficacy of curcumin-loaded HNTs-g-CS. The grafting of CS on HNTs reduced toxicity and improved colloidal stability. *In vitro* release studies showed that curcumin release was higher at cell lysate pH compared to pH 7.4 [114]. They also examined the toxicity of curcumin-loaded HNTs-g-CS against various cancer cell lines and found that the EJ cells were particularly sensitive to the nanocomposites and were subjected to apoptosis. Furthermore, curcumin-loaded HNTs-g-CS generated higher reactive oxygen species (ROS) compared to free curcumin, potentially enhancing anticancer effects [114]. Besides chemical modification of clay materials with CS, clays materials could be modified with other polymers (such as hydrophilic PEG) before complexation with CS. The feasibility of this was partly reported by Arshad et al.[115], who developed microcomposites using PEGylated HNTs and CS for sustained release of ciprofloxacin and hemostatic applications. It was found that the presence of PEGylated HNTs improves the loading and percentage release of the agent. The microcomposites exhibited favorable biocompatibility and enhanced blood clotting properties. Preliminary results of this study suggested that microcomposites have superior efficacy of hemorrhage management for lower gastrointestinal bleeding compared to CS and PEGylated HNTs alone [115].

7. Applications of CS/clay nanocomposites in drug delivery

As far as the routes of drug delivery are concerned, non-invasive routes have gained particular interest due to their convenience, improved patient compliance, and potential for sustained and targeted therapeutic effects. Among these, oral and transdermal delivery stand out as attractive options, offering alternatives to injections and minimizing systemic side effects. The unique properties of CS, such as pH sensitivity and mucoadhesion, combined with the structural reinforcement and drug-loading capacity of clay, make these nanocomposites highly suitable for targeted and sustained delivery via these routes. The following section discusses recent developments in the application of CS/clay nanocomposites for oral and transdermal drug delivery.

7.1 Oral drug administration

Oral delivery is one of the most preferred routes for drug administration due to its high patient compliance, ease of self-administration, and non-invasiveness [116-118]. Anirudhan and Parvathy designed an oral drug delivery system by incorporating MMT into a matrix of thiolated CS and polyethylene glycol (PEG) for insulin delivery [119]. *In vitro* swelling studies showed that the swelling ratio increased with rising pH, while release studies indicated enhanced drug release at pH 7.4. Additionally, Luo and colleagues previously prepared composite microspheres from CS and MMT for the sustained release of tanshinone IIA [120]. *In vitro* results demonstrated that increasing MMT content led to a reduced drug release rate. Pure CS microspheres exhibited faster release compared to the CS/MMT composites. Importantly, cytotoxicity assays indicated that the composites were non-toxic to Caco-2 cells, highlighting their potential for use in oral drug administration.

As a matter of fact, CS/clay nanocomposites are particularly promising for colon-targeted delivery, as CS can protect bioactive agents from the harsh conditions of the gastrointestinal tract and facilitate specific release in the colon [121]. In an earlier study, Farhadnejad et al. developed mucoadhesive bio-nanocomposite hydrogels using CS and MMT to prolong gastric residence time of drug molecules [122]. Their findings showed that the mucoadhesive properties slightly decreased with increasing MMT content, while swelling capacity and drug release rates also declined with higher MMT concentrations. In another study, Sharma et al. fabricated mucoadhesive microbeads from CS and MMT for the controlled release of silymarin [123]. The mucoadhesion of the microbeads improved with increasing CS content, while *in vitro* release

studies revealed that higher CS concentrations reduced the drug release rate. These findings suggest that CS/clay-based composite carriers hold significant potential for gastroretentive drug delivery, enhancing drug absorption and therapeutic efficacy in the stomach.

When oral drug administration is concerned, colon-targeted drug delivery is particularly desirable, as it enables the selective transport of therapeutic agents to specific sites in the gastrointestinal tract, reducing the required drug dose and minimizing side effects [124]. Previously, Li and coworkers developed a colon-targeting delivery platform using Eudragit S100 (EUS100), CS, and halloysite nanotubes for paeoniflorin administration [125]. *In vitro* results showed that halloysite/CS/EUS100 microspheres achieved higher release rates in simulated colon fluid compared to halloysite/CS microspheres, indicating enhanced site-specific delivery to the colon. Sharif and co-workers also fabricated porous mucoadhesive composite films composed of CS and halloysite nanotubes for the controlled release of metoclopramide hydrochloride [126]. The mucoadhesive strength of the films increased with higher CS content, resulting in stronger adherence to intestinal mucosa. Drug release studies at pH 1.2 and 6.8 indicated that the CS/halloysite films achieved a slower and more sustained release profile than pure CS or halloysite films. In a recent study, Jauković et al. synthesized composites using acetic acid-etched halloysite (eHal), low molecular weight chitosan (LChi), and methacrylated low molecular weight chitosan (MeLChi), and evaluated their mucoadhesive properties [127]. Among the formulations, MeLChi exhibited the highest mucoadhesiveness, attributed to stronger electrostatic interactions with mucosal surfaces.

7.2 Transdermal drug administration

In addition to oral drug administration, transdermal delivery is another extensively studied non-invasive route [128, 129]. It allows for the controlled release of therapeutic agents through the skin, and provides several advantages, including improved patient compliance, and bypassing the gastrointestinal tract and liver metabolism [130, 131]. Transdermal drug administration is particularly suitable to be used for drugs that require steady plasma concentrations or for patients with difficulty in taking drugs orally [132]. The potential of CS/clay nanocomposites as carriers for transdermal drug delivery has been demonstrated in part by diclofenac-loaded CS/halloysite nanotube composite patches [133]. Release studies revealed that the composite patches exhibited

a slower release rate than CS alone. Furthermore, cytotoxicity assessments confirmed that the patches caused no significant harm to human endothelial cells.

Such potential has been further corroborated by a recent study, in which a composite carrier for transdermal delivery of tramadol was developed using CS, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), and organically modified MMT [134]. *In vitro* studies demonstrated that the inclusion of nanoclay led to a more controlled and sustained drug release. Permeation studies further showed that composites lacking clay exhibited higher permeation rates than those containing clay, confirming that clay slows the drug release. Apart from this carrier, Thankur and coworkers also developed a transdermal composite film composed of CS and MMT for curcumin delivery [135]. *In vitro* studies revealed that the CS/MMT composite exhibited sustained release behaviour, with higher MMT content resulting in slower and more controlled drug release. Permeation data supported these findings, highlighting the sustained release profile of composites with elevated MMT content.

8. Opportunities and challenges

CS/clay nanocomposites have shown significant potential for drug delivery, as discussed in previous sections. Notably, CS/MMT nanocomposites have even been granted a patent in China as drug carriers [136]. However, their application remains confined to laboratory research and *in vivo* studies, with no advancement to clinical trials to date. One major barrier is the lack of comprehensive short-term and long-term toxicity studies to confirm their safety for human use. Nonetheless, some reports suggest that CS/clay nanocomposites exhibit minimal toxicity. For instance, curcumin/ciprofloxacin-loaded CS/hyaluronic acid/MMT hydrogels were found not to exhibit toxicity on human fibroblastic cells (L929) [104]. In addition, while the curcumin-encapsulated CS-agarose-MMT hydrogel exhibited significant cytotoxicity on MCF-7 cells compared to curcumin alone, the CS-agarose-MMT hydrogel did not exhibit significant cell viability on MCF-7 cells[103]. These findings suggest that chitosan/clay nanocomposites exhibit low toxicity. However, certain safety concerns related to the fundamental properties of clay materials remain valid.

One example is the safety concern regarding HNTs, whose cytotoxic potency was found to be influenced by dosage, cell model, and exposure duration [137]. After 24 hours, the IC_{50} values for HNTs were 152 ± 6.4 μg/mL for A549 cells and above 400 μg/mL for BEAS-2B cells [137]. Similar cytotoxicity was observed in HUVECs and MCF-7 cells, in which a decline in cell viability was noted after treatment with various concentrations of HNTs (2.5–200 μg/mL) for 72 hours [138]. *In vivo* experiments using a Zebrafish model, however, showed no significant acute toxicity or sublethal effects at concentrations of ≤ 25 μg/mL, with no notable effects on survival rate, morphological malformation, or cardiac toxicity throughout zebrafish development [138]. Apart from HNTs, both purified and raw MMT were tested for their toxicity on human fetal osteoblast cells [139]. Although they did not show significant toxicity at low concentrations (up to 250 μg/mL, a decline in cell viability were still observed when the concentrations increased [139]. Further studies using various cell models are needed to assess the toxic effects of MMT and HNTs to offer insights into the toxicity of these materials at different dosage and durations.

To enhance the pharmaceutical performance of CS/clay nanocomposites in future research, one direction that could potentially be promising is chemical modification of clay materials prior to mixing with CS. Over the years, various chemical modifications have been shown to effectively enhance the bioactive agent loading efficiency in HNTs. For instance, sulfuric acid-treated HNTs (tHNTs) were shown to be able to expand the HNT lumens, thereby improving drug loading efficiency [140, 141]. In fact, drug loading efficiency for benzotriazole was found to increase fourfold after 40% dealumination[142], though further dealumination beyond 60% compromised the structural integrity of HNTs and caused a decrease in drug loading efficiency. Apart from treatment with sulfuric acid, after modifying the inner surface of halloysite clay with octadecylphosphonic acid (ODP) and treating the external surface with organosilane, the generated clay was reported to release four times more loaded agents compared to raw HNTs, indicating improved adsorption after functionalization [143]. Modification of clay materials is, therefore, a highly promising future research direction to enhance the performance of CS/clay nanocomposites in drug loading.

Finally, while the focus of this review is on CS/clay nanocomposites, it is worth noting that, in addition to CS, various other polymers have also shown promise in enhancing the pharmaceutical

performance of clay materials. For instance, PVP-stabilized illite microparticles (P-Ilt MPs) have been generated previously by adsorbing polymer on illite surfaces[144]. The PVP coating improved dispersion and free radical activity of illite in biological buffers, enhancing its free radical-scavenging activity and antibacterial properties. In another study, Long and coworkers developed a non-viral gene vector by grafting polyethyleneimine (PEI) onto HNTs for delivery of genetic materials[145]. The transfection efficiency of PEI-g-HNTs was significantly higher than that of PEI alone. Grafting the nanotubes with a hydrophilic polymer moiety reduced toxicity and enhanced colloidal stability during blood circulation [114]. All these demonstrate that CS is not the only polymer that can enhance the stability, biocompatibility, and loading efficiency of clay materials in drug delivery applications.

9. Concluding remarks

The use of CS/clay composites is gaining significant attention in drug delivery research because of their potential to integrate the strengths of both clay and CS in pharmaceutical formulations. While emerging evidence supports the benefits of CS/clay nanocomposites in drug delivery, their toxicity profiles remain inadequately understood. Some *in vitro* studies suggest that the toxicity of clay-based carriers is negligible [103, 104], but contrasting evidence has also been reported [146]. It is challenging to draw definitive conclusions regarding the toxicity of CS/clay nanocomposites and their uses. Further toxicological research is essential to determine the clinical applicability of the composites before they are used in clinical practice. In addition, it is worth noting that the toxicity profiles of clay minerals and their nanocomposites depend on various factors, including exposure conditions (e.g., concentration, temperature, and duration), experimental models, the presence of inorganic or organic modifiers, and the sensitivity of the assays used. As such, innovations in the design and formulation of CS/clay nanocomposites will refine their clinical applications and expand the market for drug delivery.

Here it is also worth noting that, to date, no published clinical studies have specifically focused on CS–clay nanocomposites for drug delivery. However, numerous *in vitro* and *in vivo* studies have demonstrated their promising potential in terms of drug encapsulation efficiency and sustained release, and mucoadhesive properties [147-150]. The individual components—CS and natural clays such as MMT—are already known for their safety profiles and have been used in various

biomedical contexts [151-154]. The absence of clinical data represents a significant gap, and further translational research—including safety assessment, scale-up processes, and regulatory considerations—is necessary to realize the full clinical potential of these hybrid nanomaterials. Given that the inclusion of clay minerals in CS enhances various properties such as the loading capacity of bioactive agents, drug release sustainability, and pH-responsive property. It is anticipated that more extensive research on CS/clay hybrid carriers in the forthcoming decades will help enhance the effectiveness of drug administration in the treatment of various diseases.

Conflict of interest

The authors declare no conflict of interest.

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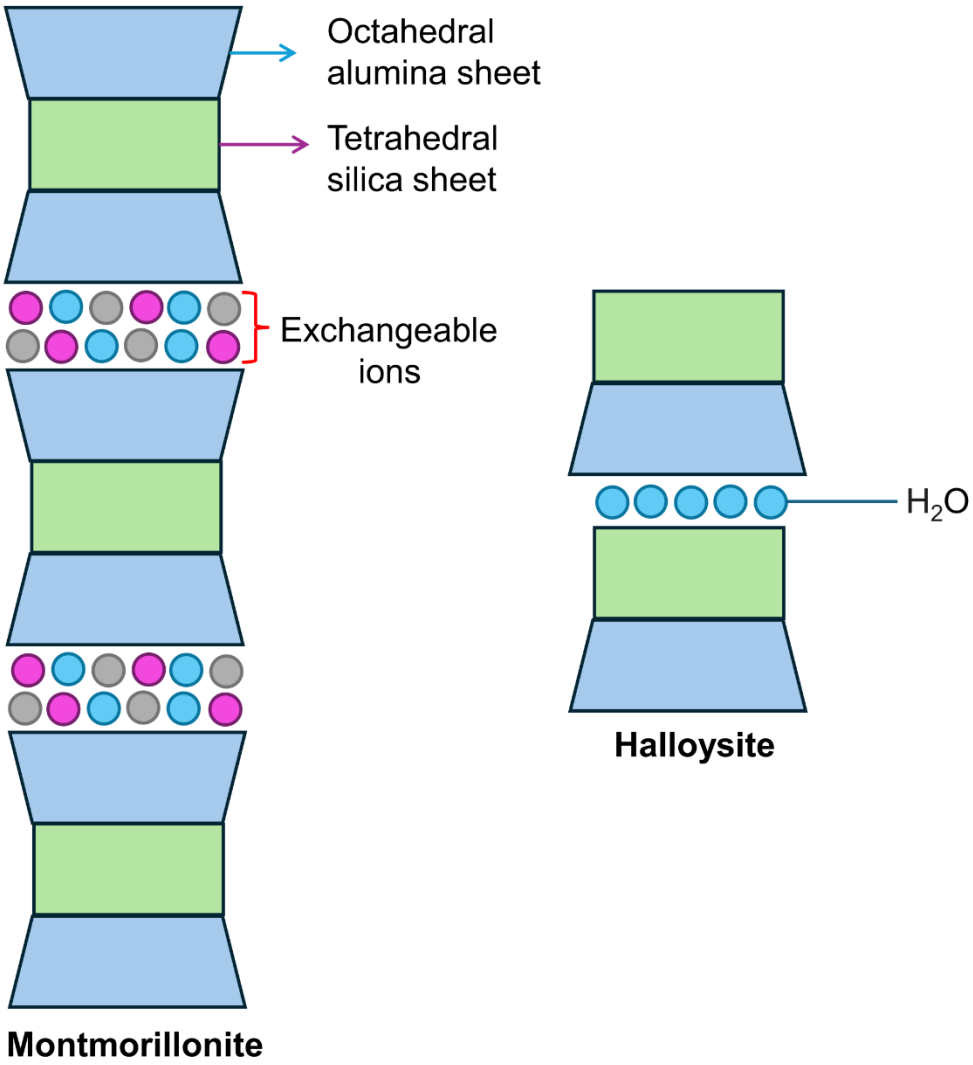

967
968 **Figure 1.** Schematic diagram of MMT and halloysite.

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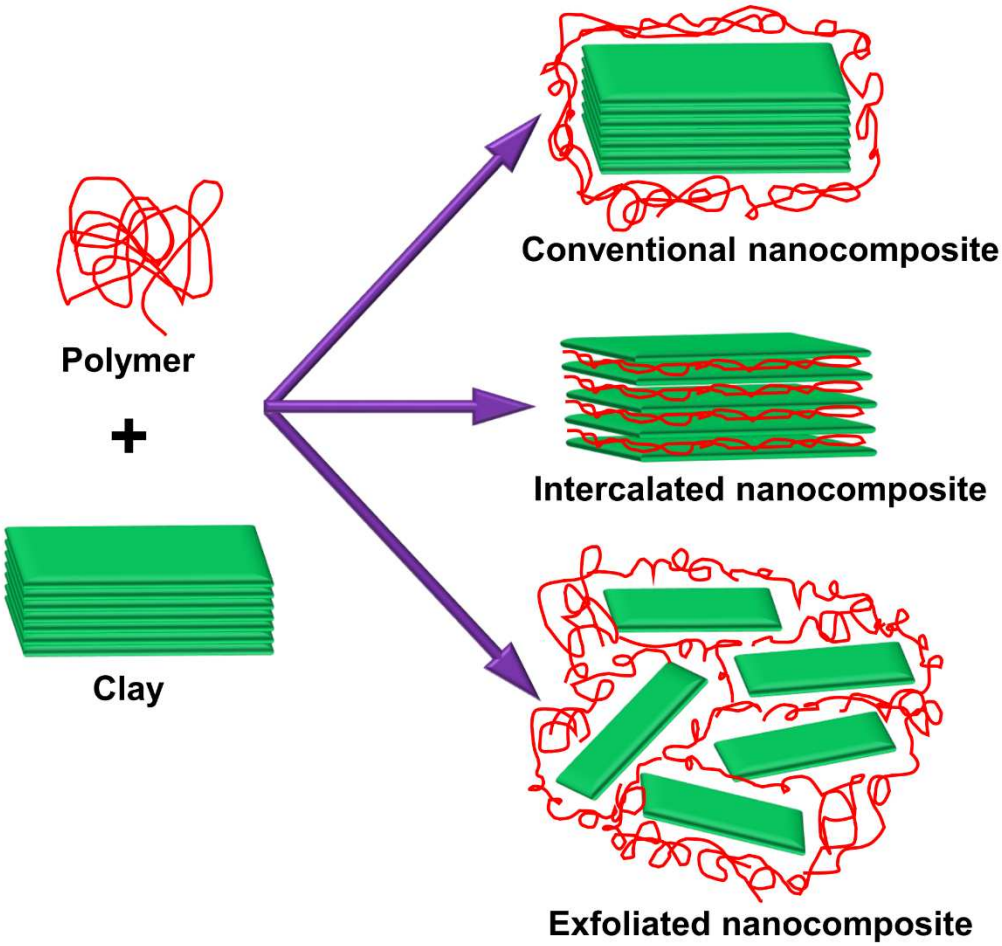

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971 **Figure 2.** Schematic depiction of three polymer-clay nanocomposite structures: Conventional,
972 intercalated, and exfoliated nanocomposites.

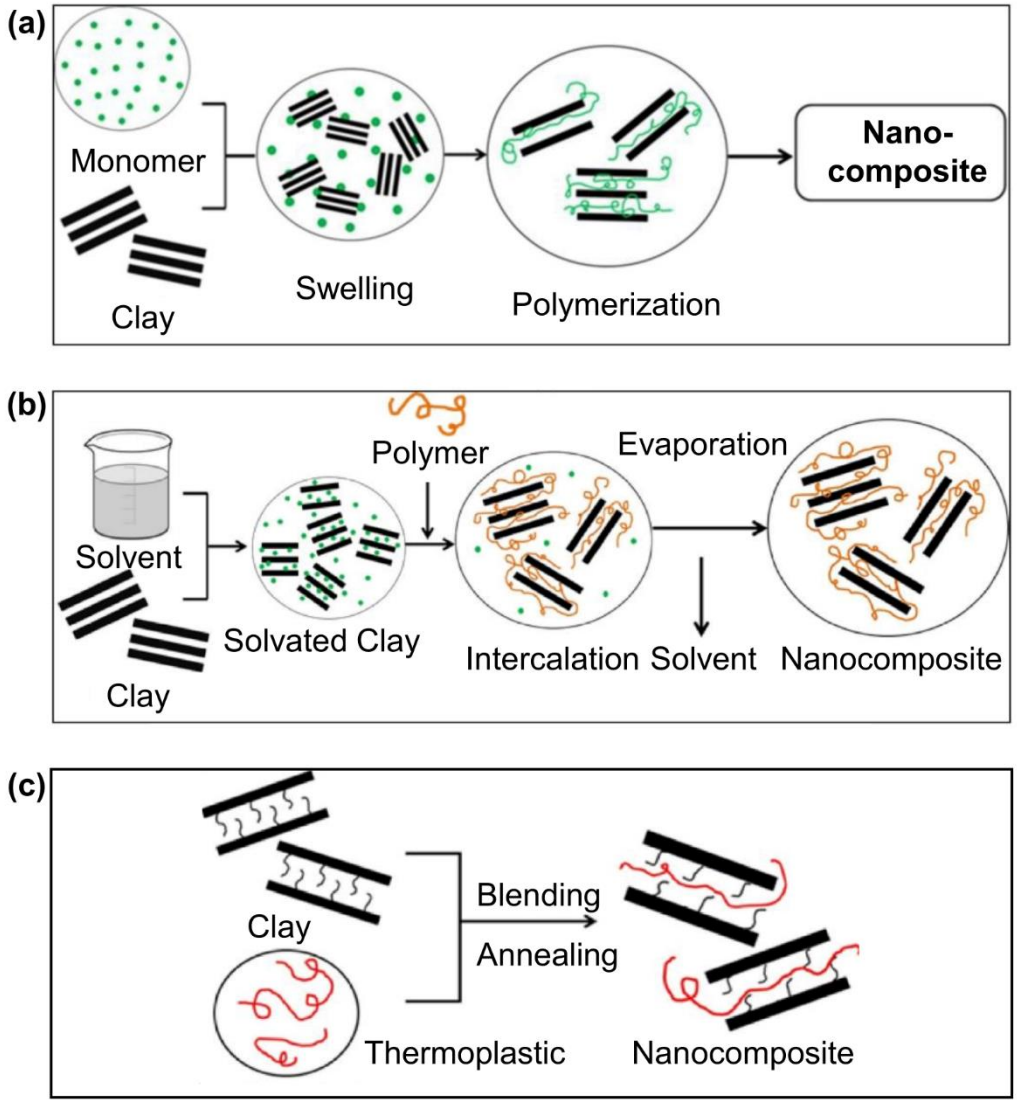
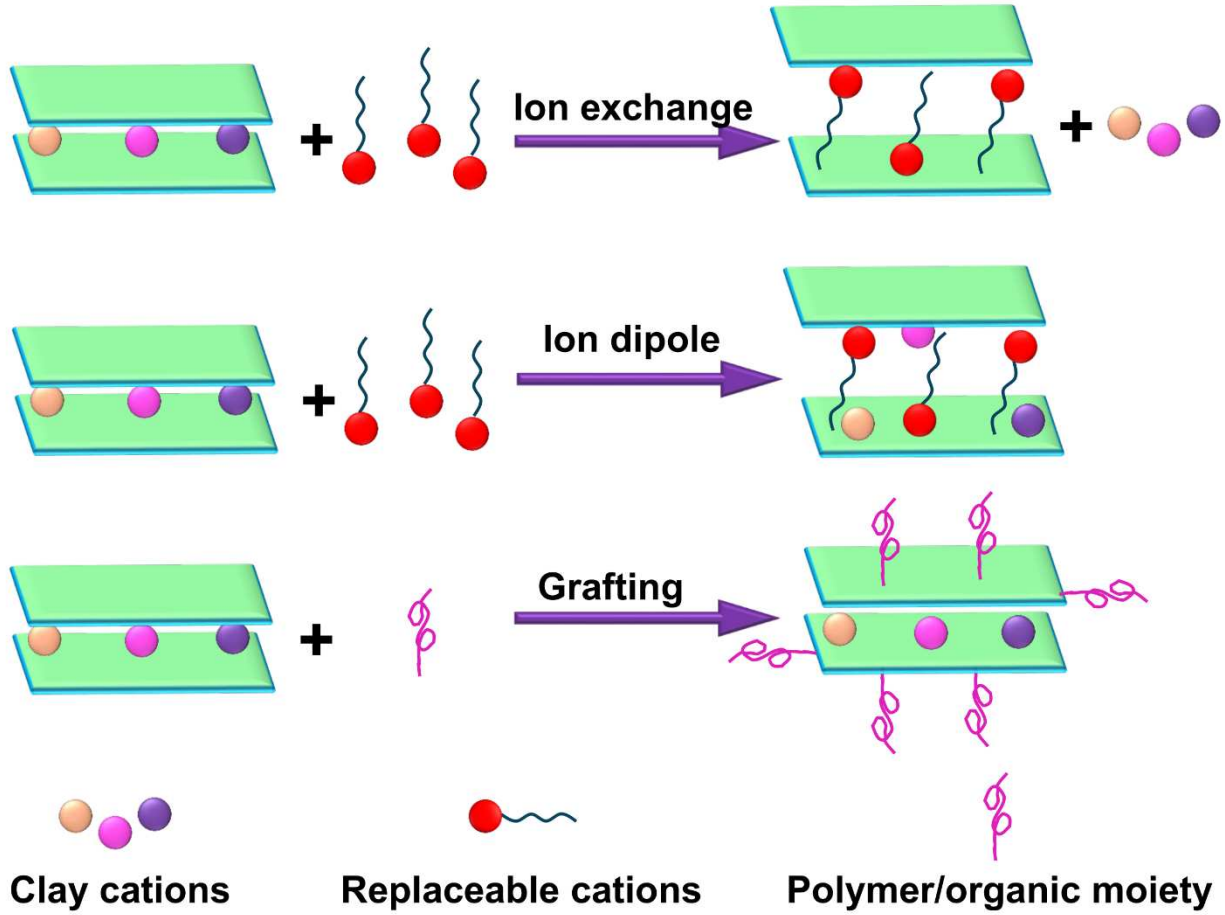


Figure 3. Schematic illustration of synthesis of nanocomposite via (a) *in situ* polymerization, (b) solution intercalation and (c) melt intercalation method. Reproduced from [64] with permission from Elsevier B.V.



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978 **Figure 4.** Schematic illustration of ion exchange, ion dipole and grafting intercalation methods.

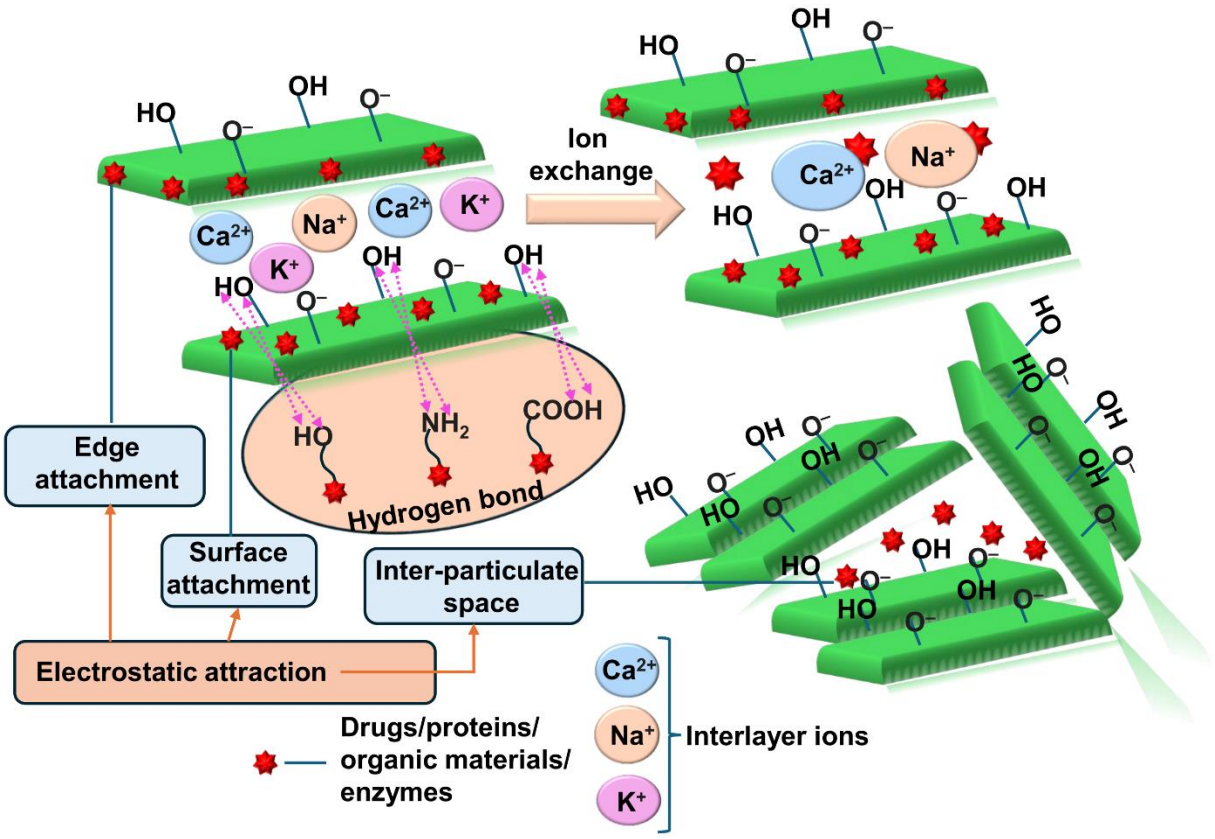

Figure 5. Adsorption of biomolecules, drugs, and organic materials occurs on clay minerals at surface sites, edge sites, inter-particulate sites, and through the exchange of interlayer ions.

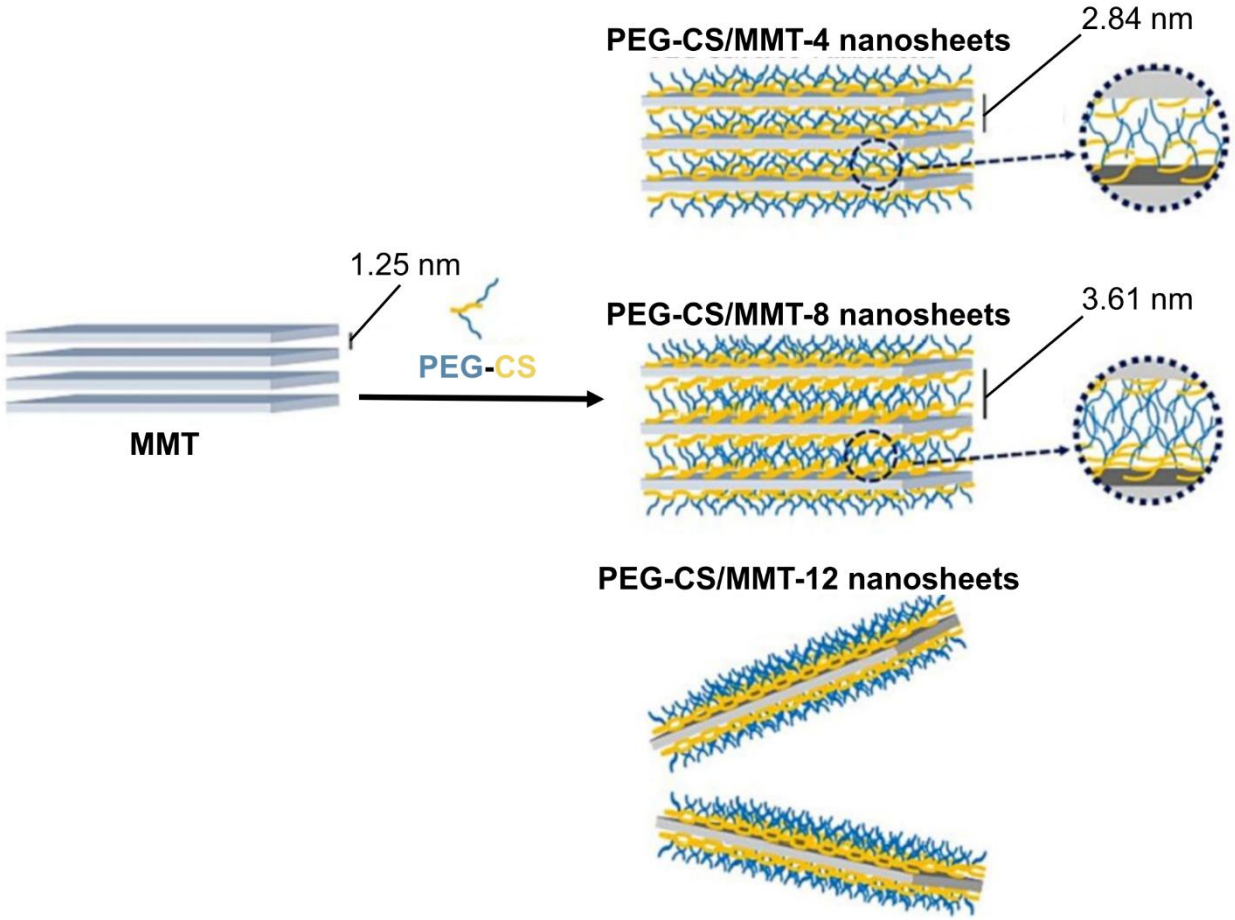

Figure 6. Schematic representation of variations in microstructures of PEG-CS/MMT nanosheets across varying mass ratios of PEG-CS to MMT. Reproduced from [105] with permission from Elsevier B.V.

Table 1. Basic properties of MMT and halloysite mineral sources.

Clay mineral	Property				Ref.
	Structural formula	CEC meq/100g	SSA m^2/g	Interlayer material	
MMT STx-1	$(Ca_{0.27}Na_{0.04}K_{0.01})[Al_{2.41}Fe(III)_{0.09}Mn_{tr}Mg_{0.71}Ti_{0.03}][Si_{8.00}]O_{20}(OH)_4$	84.4	83.79	Hydrated exchangeable cations	[9, 12]
Na-MMT SWy-1	$(Ca_{0.12}Na_{0.32}K_{0.05})[Al_{3.01}Fe(III)_{0.41}Mn_{0.01}Mg_{0.54}Ti_{0.02}][Si_{7.98}Al_{0.02}]O_{20}(OH)_4$	76.4	31.82	Hydrated exchangeable cations	[9, 12]
Halloysite	$Al_2Si_2O_5(OH)_4 \cdot nH_2O$	2-60	50-60	Water	[9-11]

991 **Table 2.** Examples of CS/clay nanocomposites reported for drug delivery.

Nanocomposite	Application	Performance	Ref.
CS/polyvinyl alcohol/Na^+ MMT nanocomposite film	Controlled release of 5-fluorouracil	The drug loading efficiency of the nanocomposite film increases with higher clay content and is accompanied by an enhanced drug release rate.	[85]
CS-MMT nanocomposite	Sustained release of vancomycin and gentamicin	By optimizing voltage, distance, and flow rate, composite nanospheres with uniform size were fabricated. These nanospheres demonstrated significant antibacterial activity with no cytotoxicity.	[86]
MMT/N-(carboxyacyl) CS coated magnetic nanoparticle	Controlled release of paracetamol	The composites exhibited greater swelling and higher drug release rates at pH 7.4 compared to pH 1.4.	[87]
CS/MMT nanocomposite	Controlled release of curcumin	The nanocomposites demonstrated antioxidant activity and pH-responsive drug release behavior.	[88]
Poly(lactic-co-glycolic acid)-lysine-proline-valine/MMT/CS nanoparticle	Targeted delivery of cyclosporine A (CyA)	The nanoparticles adhered to inflamed colonic tissue. They improved the therapeutic efficacy of CyA in a dextran sulfate sodium (DSS)-induced colitis mouse model, significantly improving colon length and body weight.	[89]
Fe_2O_3/CS/MMT nanocomposite	Controlled release of quercetin	The nanocomposites exhibited high drug loading efficiency.	[90]
Na^+ MMT/CS composite bead	Sustained release and antibacterial applications of chlorhexidine	The beads controlled the initial burst release of the loaded drug and demonstrated mucoadhesive properties.	[91]
CS/MMT nanocomposite	pH-responsive release of ciprofluxcacin	The nanocomposites were pH-responsive, showing an increase in the drug release rate under an external magnetic field.	[92]
CS-coated HNT	Controlled release of khellin	The application of the CS coating enhanced the regulation of the drug release rate.	[93]
CS/alginate-coated sulfuric acid-functionalized HNT	Sustained release of ibuprofen	The presence of the polyelectrolyte coating enabled sustained and pH-responsive drug release.	[94]
CS/HNT nanocomposite film	Sustained release of norfloxacin	The film remained stable under various humidity conditions and exhibited notable antibacterial properties.	[95]
CS-grafted HNT	Controlled release of doxorubicin	The CS-grafted HNTs provided controlled drug release and demonstrated high biocompatibility.	[96]

Acetic acid-treated HNT/CS nanocomposite	Sustained release of aceclofenac	Acid etching of the HNTs enhanced lumen enlargement and, when combined with CS functionalization, improved drug loading efficiency.	[97]

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