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REVIEW

Application of montmorillonite in bentonite as a pharmaceutical excipient in drug delivery systems

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Abstract Montmorillonite is a multifunctional clay mineral and a major component of bentonite. Montmorillonite has been used in various industrial and pharmaceutical fields due to its unique characteristics, which include swelling and adsorption. The high adsorption capacity of montmorillonite contributes to increase drug entrapment and sustained-release of drugs. Montmorillonite generally sustains drug release in many formulations by strongly adsorbing to the drug. In addition, montmorillonite enhances the dissolution rate and bioavailability of hydrophobic drugs. Moreover, montmorillonite was applied to form composites with other polymer-based delivery systems. Thus, montmorillonite could be applied to formulate diverse drug delivery systems to control and/ or improve the pharmaceutical properties of drugs, including solubility, dissolution rate, and absorption. In this review, perspectives of applying montmorillonite as a pharmaceutical excipient in drug delivery systems are discussed.

Keywords Bentonite · Montmorillonite · Adsorption · Cationic exchange · Sustained release · Delivery system · Drug release

Introduction

Montmorillonite is a major active component of bentonite and a multifunctional clay mineral with unique properties, such as swelling and adsorption. These characteristics, have allowed montmorillonite to be widely used in medical and industrial applications (Eisenhour and Brown 2009; Carretero and Pozo 2010). Moreover, it has been applied to develop diverse drug delivery systems to overcome the pharmaceutical disadvantages of drugs, including low solubility and poor pharmacokinetic properties (low bioavailability and short biological half-life) (McNerny et al. 2010; Savjani et al. 2012; Griffin et al. 2013; Mould et al. 2015). Considering these characteristics of montmorillonite, applying this clay mineral to drug delivery systems could be a promising approach to improve the therapeutic efficacy of drugs in the body via sustained release of hydrophilic drugs or solubilization of hydrophobic drugs. Moreover, montmorillonite enhances the function of original formulations of various drug carriers. In this review, basic information about montmorillonite, including its physicochemical characteristics, will be introduced, and perspectives for various applications of montmorillonite as a pharmaceutical excipient in drug delivery systems will be discussed in more detail.

Bentonite and montmorillonite

Bentonite is a natural clay containing clay minerals in the smectite group that was formed by devitrification of volcanic ash that fell into water (Eisenhour and Brown 2009). Bentonite was named after Fort Benton near Rock River, Wyoming, USA where it was originally found, by W.C. Knight in 1898. This clay has excellent swelling,

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adsorption, and colloidal properties. Because of these characteristics, bentonite has been used in many industrial applications, including as foundry bond clay, drilling mud, adhesives, sealants, bleaching agents, pet-waste absorbents, and desiccants (Önal 2006; Eisenhour and Brown 2009). For example, bentonite has sufficient green strength to be used as a bonding agent for sand-based molds used in metal casting (Clem and Doehler 1963). The clay-dispersed fluid acts as drilling mud because of its drill-lubricating activity and protection of the trench wall from collapse. In addition, the moisture-absorbing activity of this clay makes it useful as a desiccant.

Raw bentonite is composed of diverse mineral substances, such as quartz, cristobalite, feldspars, zeolites, and several kinds of clay minerals. Above all, the major component of bentonite is montmorillonite, which is a dioctahedral smectite. The swelling and adsorption properties of bentonite originate from montmorillonite. Pure montmorillonite is necessary for the medical applications, and it can be obtained by purifying raw bentonite.

Montmorillonite is a porous clay mineral composed of a 2:1-layered structure with exchangeable cations between the layers (Önal 2006). The thickness and breadth of each nanoclay sheet are around 1 and 100–1000 nm, respectively (Mahesh et al. 2011). The 2:1 layer consists of two tetrahedral silica sheets sandwiching an octahedral sheet of alumina (Fig. 1). In this layer, substituting the Si^{4+} in the silica tetrahedral sheets to Al^{3+} and the Al^{3+} in the alumina octahedral sheets to Mg^{2+} produces a net negative charge, which is usually balanced by adsorption of cations, such as Li^+, Na^+, and Ca^{2+}, between the layers (Rolfe et al. 1960; Önal 2006). These cations can be easily replaced by other organic or inorganic cations, which is related to the unique hydrophilicity, swelling, adsorption, and fluidity properties of montmorillonite (Chen et al. 2000).
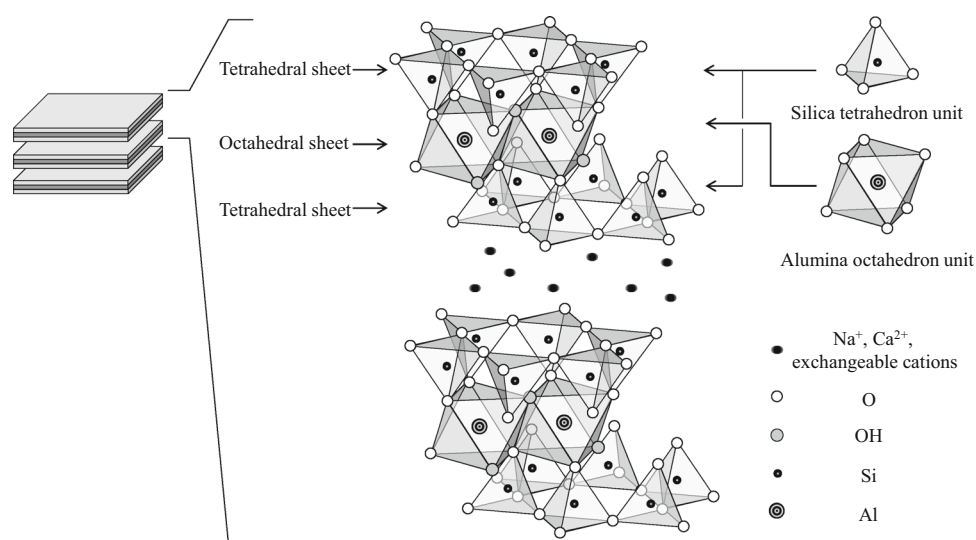
Sodium montmorillonite versus calcium montmorillonite

The characteristics of montmorillonite can be altered based on the cations adsorbed in the interlayers, such as sodium and calcium. Industrial bentonite mainly contains either sodium montmorillonite or calcium montmorillonite, which have different physical properties, so each montmorillonite-based bentonite is used in different fields. Sodium montmorillonite can expand its original volume by absorbing a large volume of water, and its swelling capacity is higher than that of calcium montmorillonite. In addition, sodium montmorillonite has great colloidal and rheological properties, so it has been used in many industrial applications, including drilling mud and sealants (Clem and Doehler 1963; Gleason et al. 1997). On the other hand, calcium montmorillonite has less swelling capability than that of sodium montmorillonite. However, it has excellent green strength among mineral binders, so it is useful as a bonding agent in foundry molding sands (Clem and Doehler 1963). In addition, it has strong adsorption activity against various solutions and oils, so calcium montmorillonite also has medical applications, such as detoxification (Jiang et al. 2012).

Physical properties of montmorillonite: swelling and adsorption

One of the unique physical properties of montmorillonite is that it exhibits a hydrophilic property and swells with water. As the surface of a montmorillonite sheet has a negative charge, H_3O^+ from autoionization of water easily infiltrates into the interlayer (Song et al. 2005). This hydrophilicity contributes to the swelling of

Fig. 1 Molecular structure of montmorillonite

Tetrahedral sheet →
Octahedral sheet →
Tetrahedral sheet →

← Silica tetrahedron unit

Alumina octahedron unit

• Na^+, Ca^{2+}, exchangeable cations
○ O
◉ OH
• Si
◎ Al

montmorillonite. The physical state of montmorillonite changes from an anhydrous solid to a hydrated material, semi-rigid plastic, gel, and suspension with increasing water content (Norrish 1954; Low 1979, 1980; Malfoy et al. 2003). The change in physical state from an anhydrous solid to a gel is called swelling (Komine and Ogata 1994, 1996). Sodium montmorillonite has the capability to increase its volume up to 20 times by absorbing water (Norrish 1954). The swelling occurs as ions are hydrated when water enters the 2:1 layers and is followed by osmotic absorption of water. This swelling pattern depends on the mineralogy, size, negative charge, and hydration energy of exchangeable cations (Norrish 1954; Baker et al. 1995; Xu et al. 2003).

Another characteristic of montmorillonite is adsorption. Because montmorillonite has the 2:1 layers, which contain exchangeable cations, several molecules intercalate between the interlayers by ion exchange. Various polar molecules, such as short chain alcohols, glycerol, carbohydrates, ethylene glycols, ethylene glycol monoethyl ether (2-ethoxyethanol), aliphatic and aromatic amines, and organic dyes, are adsorbed strongly on the surface of the montmorillonite layers (Mikhail et al. 1979; Lagaly et al. 1984; Tsai et al. 2004). On the other hand, non-polar molecules, such as nitrogen, argon, and ethane, are not incorporated on montmorillonite. To be specific, these molecules are adsorbed on the surface but cannot infiltrate the interlayers. Because of this limitation, interlayer volume and surface area obtained by adsorption of non-polar molecules are less than the theoretical values (Lopez-Gonzalez and Deitz 1952; Gregg et al. 1967; Vicente et al. 1996).

Medical uses for montmorillonite

Bentonite can be used is an intact form for many industrial purposes. However, bentonite must be purified to montmorillonite for use in the food and pharmaceutical industries. As montmorillonite has swelling, rheological, moisture-retaining, and adsorption characteristics, it has been widely studied as an active ingredient in medicine.

First, montmorillonite has adsorption properties to remove toxic heavy metals and can be used as a healing agent. Natural clays, such as montmorillonite, can adsorb metals (As, Cd, Pb, Mn, Ni, and Cr) from aqueous solution (Bhattacharyya and Gupta 2008).

In addition to metals, montmorillonite can adsorb unwanted anions, such as fluoride, in water. Montmorillonite incorporated with magnesium adsorbs fluoride, resulting in a decrease in fluoride concentration in drinking water below the standard level (Thakre et al. 2010). Montmorillonite also has detoxification and anti-viral abilities. Clay materials, including sodium montmorillonite, have the ability to adsorb

bovine rotaviruses and coronaviruses (Clark et al. 1998). In other cases, montmorillonite effectively adsorbed aflatoxin B1 and released <16 % of the quantity adsorbed (Desheng et al. 2005). Adsorption of aflatoxin onto montmorillonite reduces its toxic effect (Shi et al. 2005). Other toxic substances, such as nitroaromatic compounds, are strongly adsorbed by smectite clay, including montmorillonite (Haderlein and Schwarzenbach 1993; Boyd et al. 2001; Li et al. 2004; Roberts et al. 2007). With this adsorption activity, a clay mineral group which has the montmorillonite structure, dioctahedral smectite (SMECTA®) has been developed and is commercially available for treating of acute infectious diarrhea (Khediri et al. 2011).

This clay can also be used as an intestinal-healing agent or probiotic-protecting agent. In one report, the survival rate of *Lactobacillus casei* immobilized onto sodium montmorillonite increased under gastrointestinal conditions (Li et al. 2014). In addition, beidellitic montmorillonite, which has gas absorption and coating features, has a discomfort-relieving effect in patients suffering from constipation-predominant irritable bowel syndrome (C-IBS) (Ducrotté et al. 2005). Although symptoms did not improve in all patients with IBS, this result indicates that montmorillonite is an alternative to reduce discomfort and abdominal pain of patients with C-IBS.

Montmorillonite has also been used effectively to treat dermal problems, such as contact dermatitis. One study showed that montmorillonite is more effective and more quickly for improved diaper dermatitis than the topical agent calendula (Mahmoudi et al. 2015). In addition, bentonite has been used as a base for cutaneous therapy, by stabilizing zinc ointment or emulsifying oil and water (Hopkins 1946).

Factors affecting adsorption of drugs onto montmorillonite

Various drugs are adsorbed onto montmorillonite by interacting with the surface of the clay sheets. These adsorptive interactions differ depending on the drug type but the main mechanism is cationic exchange (McGinity and Lach 1976). The surface of montmorillonite sheet is negatively charged, so the surface charge is balanced by exchangeable cations. In particular, cationic drugs are adsorbed onto montmorillonite by these electrostatic interactions. Anionic or organic drugs do not have a strong affinity with montmorillonite compared to that of cationic drugs, but these types of drugs can adsorb weakly to the clay through other interactions, including hydrogen bonding and van der Waals forces (Aguzzi et al. 2007).

Several factors determine the adsorption extent of drugs onto the montmorillonite interlayers. The first factor is

solvent pH. Generally, the charge of a drug molecule depends on the pH of the solvent to control adsorption and desorption of the drug. For example, the adsorption of vitamin B6 and fluoride on montmorillonite decreases as pH is increased (Karthikeyan et al. 2005; Joshi et al. 2009b). In addition, sotalol and hydralazine show the optimum pH of adsorption, and the degree of adsorption decreases by modifying pH (Sánchez-Camazano et al. 1987; Sánchez-Martín et al. 1988). In these cases, the decrease of adsorption can be explained by loss of electrostatic interactions and competition with H^+. This pH-dependent adsorptive property is closely associated with release of the drug from montmorillonite.

The second factor is temperature of the solution. Temperature slightly alters drug adsorption, depending on the drug, but it is not significant compared to pH. In one study, the quantity of vitamin B6 adsorbed on montmorillonite decreased gradually with increasing reaction temperature, whereas that of fluoride exhibited the opposite result (Karthikeyan et al. 2005; Joshi et al. 2009b).

The third factor is ionic strength. Although it is not applicable to all drugs, the sorption coefficient (K_d) tends to decrease with increasing ionic strength (Figueroa et al. 2004).

Another factor that affects the degree of adsorption is the initial drug concentration. Usually, more drug is adsorbed onto montmorillonite in proportion to increases in the initial drug concentration. However, the drug becomes saturated at a certain concentration, and the quantity adsorbed does not increase further (Sánchez-Camazano et al. 1987; Sánchez-Martín et al. 1988; Joshi et al. 2009b). Similar to other clay minerals, montmorillonite has cation exchange capacity (CEC), which is the equivalent amount of exchangeable cations in one kilogram (Önal 2006).

In addition to adsorptive interactions, drugs can degrade in the montmorillonite interlayer. For example, digoxin intercalated into montmorillonite degrades rapidly compared to that of intact digoxin (Porubcan et al. 1979) because the digoxin molecules and protons are concentrated in the montmorillonite interlayers by adsorption and ion exchange, resulting in a condensed acid-catalyst effect and increased rate of degradation. Dexamethasone also degrades in montmorillonite because of the catalyzing effect of iron in the clay (Forteza et al. 1989).

Effect of montmorillonite on drug pharmacokinetics

Co-administration of montmorillonite with drugs often decreases oral bioavailability (Aguzzi et al. 2007). When the macrolide antibiotic tylosin was orally administered with montmorillonite, area under the curve decreased below 20 % of that of a group receiving an equal dose without montmorillonite (Devreese et al. 2012). In addition, formation of amphetamine-montmorillonite complex reduces bioavailability of amphetamine in human volunteers (McGinity and Lack 1977; Aguzzi et al. 2007). Because of the strong interactions between drugs and montmorillonite, adsorption of drugs onto montmorillonite results in low dissolution and low concentration of the drug in the gastrointestinal tract. As a result, intestinal absorption rate decreases, leading to poor bioavailability, which can prevent sufficient gastrointestinal absorption of the drugs, but adsorption can be a benefit because of the decreased absorption of toxins. Montmorillonite effectively adsorbs toxins, such as aflatoxin and nitroaromatic compounds (Haderlein and Schwarzenbach 1993; Boyd et al. 2001; Li et al. 2004; Desheng et al. 2005; Roberts et al. 2007), which can decrease adverse effects via reduced bioavailability (Shi et al. 2005).

Catalytic degradation by montmorillonite can also alter bioavailability. As described in a previous chapter, digoxin and dexamethasone are degraded by the increased acid-catalyst effect and structural iron in clay, respectively, after adsorption onto montmorillonite (Porubcan et al. 1979; Forteza et al. 1989). These degradation mechanisms reduce the absolute amount of drug, causing decreased gastrointestinal absorption.

Adsorption onto montmorillonite can also change other pharmacokinetic properties, including distribution of the drug in organs. For example, encapsulating glutathione into montmorillonite increases its oral bioavailability and liver content (Baek et al. 2012). In this case, glutathione and montmorillonite hybridized, which protected the glutathione from hydrolysis in the intestines, enhanced oral bioavailability, and elevated glutathione liver concentration.

Montmorillonite also affects cellular uptake of drugs. In one study, cellular uptake of a particle system was enhanced by incorporating montmorillonite (Dong and Feng 2005). That study reported that paclitaxel-loaded montmorillonite/poly(lactic-co-glycolic acid) nanoparticles increased drug uptake in two human colon derived cell lines (Caco-2 and HT-29 cells) compared to that of montmorillonite-free nanoparticles. They claimed that incorporating montmorillonite into the formulation strengthened the interactions with cells via increased van der Waals forces and hydrogen bonding, suggesting that drug-loaded nanoparticles with montmorillonite may strongly interact with the mucus/epithelial surface of the gastrointestinal tract and enhance cellular affinity.

Montmorillonite also modifies excretion of drugs. For example, montmorillonite-adsorbed amphetamine decreases urinary excretion rate compared to that of the original amphetamine formulation (McGinity and Lack 1977). Amphetamine is a cationic drug, so it strongly intercalates

with montmorillonite, which slows down release of the drug and decreases absorption and excretion.

In many cases, the most common effect of montmorillonite on pharmacokinetics is related to a decrease in drug release rate and bioavailability, caused by adsorption of the drug onto montmorillonite. However, increased or stable bioavailability has been reported with some drugs. As explained above, glutathione adsorbed onto montmorillonite has increased oral bioavailability (Baek et al. 2012). In addition, bioavailability and dissolution rate of the poorly soluble drug phenytoin are enhanced by adsorption onto montmorillonite (Koleman et al. 2008). Montmorillonite can improve dissolution of hydrophobic drugs with a large surface area and hydrophilicity (Aguzzi et al. 2007).

Application of montmorillonite in controlled drug delivery systems

Although drugs have specific therapeutic effects, they also have pharmaceutical limitations, such as poor absorption, rapid elimination, and low bioavailability. Insufficient bioavailability can be caused by low solubility and/or poor permeation (Savjani et al. 2012). High solubility and rapid absorption of a drug result in high bioavailability; however, this also shortens the duration of drug action (Griffin et al. 2013). Moreover, toxicity can occur due to rapid release of a drug, non-selectivity, or rapid exposure to the drug. Most anticancer agents show nonspecific toxicity and a narrow therapeutic index (McNerny et al. 2010; Mould et al. 2015). Besides these limitations, drug stability is an important issue to be considered. For example, protein and peptide drugs can be easily degraded by enzymes in the gastrointestinal tract (Shaji and Patole 2008).

To overcome these drawbacks, various types of polymer-based drug delivery systems have been studied. Enhanced drug stability and controlled release profile can be acquired by encapsulating drugs with a carrier system.
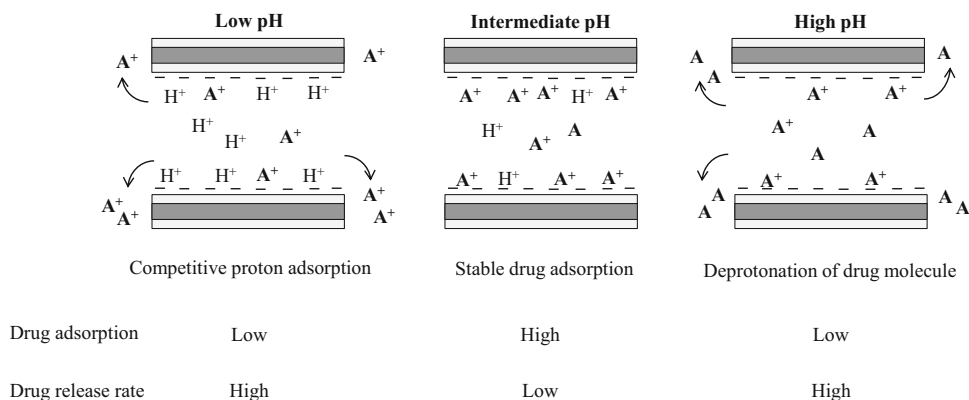
It is also possible to reduce drug toxicity and prolong duration of action by preparing a sustained-release formulation (Grant et al. 1994; Kim et al. 1996). Moreover, a solubilizing effect can be achieved by applying a carrier system to hydrophobic drugs, which enhances bioavailability.

Similar to other polymers, montmorillonite has been investigated in drug delivery systems. The adsorption property of montmorillonite usually contributes to enhance drug entrapment and sustained-release. In addition, montmorillonite affects the physical and mechanical properties of the formulation, including elasticity and tensile strength of a gel or film.

Drug-montmorillonite complexes

Many attempts have been made to encapsulate drugs into montmorillonite to modify the release pattern of the original drug (Sánchez-Camazano et al. 1987; Lin et al. 2002; Joshi et al. 2009a; Madurai et al. 2011; Ravishanker et al. 2013; Jain and Datta 2014b; Bello et al. 2015). Mixing in an aqueous phase is commonly used to prepare a drug-intercalated montmorillonite complex (Aguzzi et al. 2007). This method is usually used to intercalate a hydrophilic drug. When montmorillonite is dispersed in a drug solution, the dissolved drug molecules are adsorbed onto the montmorillonite and exchanged with cations in the interlayer. The drug-montmorillonite complex is obtained by collecting and drying the solid-phase after reaching equilibrium. Drug-clay complexes have also been attempted under dry conditions. Heating a drug with montmorillonite above the melting point of the drug without the aqueous phase or grinding both substances homogeneously have been attempted and are effective for adsorbing hydrophobic drugs (Del Hoyo et al. 1996; Aguzzi et al. 2007). Captopril-adsorbed montmorillonite formulations have been tested to evaluate three different intercalation methods (dissolving, melting, and grinding) (Madurai et al. 2011). As a result, the dissolution and melting methods

Fig. 2 Effect of pH on intercalation of cationic drug molecules on the montmorillonite surface

	Low pH	Intermediate pH	High pH
	Competitive proton adsorption	Stable drug adsorption	Deprotonation of drug molecule
Drug adsorption	Low	High	Low
Drug release rate	High	Low	High

showed similar properties. However, formulations prepared by grinding exhibited significantly lower drug loading and sustained release profile.

The pH value of the aqueous phase is an important factor for drug adsorption when preparing a drug-clay complex using the dissolution method (Fig. 2). Each drug usually has an optimum pH value for adsorption, and extreme acidic or basic conditions cause insufficient drug intercalation (Sánchez-Camazano et al. 1987; Joshi et al. 2009a). In the case of cationic drugs, these problems are dependent on the pKa value. Most drug molecules exist as cations in the acidic-neutral pH range below the pKa value and can be strongly adsorbed to the montmorillonite interlayer. However, competition between cationic drug molecules and abundant H^+ protons occurs at very low pH, resulting in low adsorption. Moreover, deprotonated drug molecules mainly exist in an uncharged form in the basic pH range above the pKa value, which results in decreased intercalation. In particular, zwitterions, such as sotalol, are anionic under basic conditions, which further disturbs drug adsorption to montmorillonite (Sánchez-Camazano et al. 1987). However, higher drug encapsulation has been accomplished under extremely basic conditions. The highest 5-fluorouracil intercalation percentage is obtained at a pH of 11–12 (Lin et al. 2002). It was speculated that opening of the interlayer in the basic condition contributed to drug intercalation.

The drug-montmorillonite complex shows a sustained in vitro release profile compared to that of intact drugs (Bothiraja et al. 2014; Jain and Datta 2014b; Kaur and Datta 2014). For example, a diclofenac-loaded clay complex exhibits a relatively slower release rate than that of the pure drug under all pH conditions (pH 1.2 and 7.4) (Kaur and Datta 2014). After cationic exchange in the clay interlayer, infiltrated drug molecules strongly interact with the montmorillonite layers electrostatically. This interaction makes the drug molecules difficult to desorb, resulting in a sustained release profile. Although the release rate of water-soluble drugs usually decreases with montmorillonite, the opposite effect can be observed with hydrophobic drugs. As explained previously, montmorillonite has a large surface area and hydrophilicity which enhances drug wettability; thus, these properties increase the dissolution rate of hydrophobic drugs (Aguzzi et al. 2007). For example, phenytoin, which is poorly water soluble, adsorbs to montmorillonite and shows an increased drug dissolution rate and enhanced bioavailability (Koleman et al. 2008). In addition, enhanced release of other hydrophobic drugs, including griseofulvin, indomethacin, and prednisolone has been reported (McGinity and Harris 1980).

Besides the effects of montmorillonite, an important factor controlling drug release rate is the pH of the release medium. In many cases, the dissolution rate of the drug-clay complex increases under higher pH (Joshi et al. 2009a, c; Madurai et al. 2011; Kaur and Datta 2014). For example, a vitamin B_1-loaded montmorillonite complex is released twice as fast at pH 7.4 than at pH 1.2 (Joshi et al. 2009c). This tendency can be explained by the change in the charge interaction, similar to adsorptive tendency. A cationic drug has a positive charge under acidic conditions and shows high affinity with the negatively charged montmorillonite interlayer. However, drug molecules lose charge by deprotonation when pH increases and are easily released from the interlayer. Anionic drugs have much weaker interactions with the clay interlayer compared to that of cationic drugs (McGinity and Lach 1976). Although anionic drugs detach easily from the montmorillonite, their solubility is very low under acidic conditions, which slows release (Kaur and Datta 2014). The electrostatic repulsion between negatively charged drug molecules and interlayer surface occurs under more basic conditions, which increases the release rate.

Fig. 3 Comparison of electrostatic interactions of montmorillonite with chitosan and alginate

Montmorillonite

Chitosan

Intercalation with planar part

Alginate

Intercalation with edge part
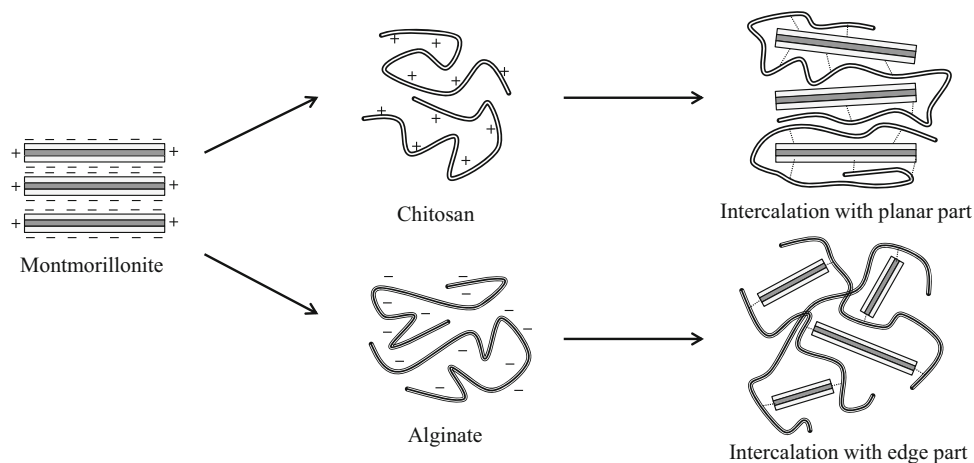
On the other hand, some exceptions exhibit higher release rates under a low pH condition (Sánchez-Camazano et al. 1987; Jain and Datta 2014b). For example, faster venlafaxine release is observed under a more acidic condition when the drug is adsorbed to montmorillonite (Jain and Datta 2014b). If the pKa value of a drug is high enough to have positive charges in a large pH range, only the competition of protons influences drug dissolution. Similar to the drug intercalation process, adsorbed drug molecules can be exchanged with excessive protons under extremely acidic conditions, which increases the drug release rate.

Montmorillonite-based tablets have been prepared using this dissolution-controlling function (Ravishanker et al. 2013). A solid dispersion of ritonavir and montmorillonite mixture was compressed into tablets and showed an enhanced dissolution rate compared to that of plain tablets.

As explained above, montmorillonite can be used as a drug carrier based on its adsorption properties. However, this clay has some limitations to be used independently, including insufficient encapsulation of organic molecules and incomplete drug release from the clay. These defects can be overcome by incorporating other polymers, polysaccharides, polyesters, or surfactants. Moreover synergistic effects of both excipients are observed by preparing new composites containing montmorillonite and other polymers.

Chitosan formulations

Chitosan is a polysaccharide composed of D-glucosamine and N-acetylglucosamine that is obtained from N-deacetylation of chitin. Chitosan is biocompatible, biodegradable, and non-toxic and has been studied as a carrier for drug delivery systems (Muzzarelli et al. 1988; Calvo et al. 1997; Depan et al. 2009; Hua et al. 2010a). In addition, because chitosan exhibits a positive charge, it can interact with negatively charged mucin (Ludwig 2005) to show a mucoadhesive property, which contributes to increased drug residence time (Schipper et al. 1996; Hou et al. 2015).

Chitosan has been formulated with montmorillonite to prepare hybrid composites (Lin et al. 2005; Depan et al. 2009; Monvisade and Siriphannon 2009; Abdeen and Salahuddin 2013; Bothiraja et al. 2014). Because chitosan is positively charged, it adsorbs to the negatively charged montmorillonite interlayer (Fig. 3). The paclitaxel release rate further decreases after coating drug-loaded montmorillonite with chitosan, and anticancer activity improves (Bothiraja et al. 2014). As both montmorillonite and chitosan have adhesive properties, increased cell surface-adhesive activity seems to improve the therapeutic effect. The ibuprofen release rate decreases when chitosan is intercalated to montmorillonite, compared to that of the original chitosan formulation (Depan et al. 2009).

Several attempts have been made to prepare a chitosan/montmorillonite hydrogel using a high viscosity chitosan solution (Liu et al. 2008; Hua et al. 2010b; Cojocariu et al. 2012a, b). In many cases, increasing the montmorillonite content decreases the drug release rate. In addition, incorporating montmorillonite decreases swellability of formulation (Cojocariu et al. 2012a; Abdeen and Salahuddin 2013). An ofloxacin-loaded chitosan hydrogel shows fast drug release under a low pH condition, but montmorillonite decreased the release rate (Hua et al. 2010b). Considering these results, intercalation with montmorillonite may prevent disintegration of chitosan at low pH, resulting in sustained release. Besides the direct effect of montmorillonite on controlling release profiles, it has also been used to improve the electrosensitive performance of a hydrogel. The release rate of an electrosensitive hydrogel is reversibly increases in an electric field, but responsiveness can be decreased gradually by repeated electrical stimulation (Liu et al. 2008). However, incorporating montmorillonite in a chitosan hydrogel contributes to maintain regular responsiveness and reversibility.

Moreover, a montmorillonite-chitosan composite has been used to fabricate particulate formulations, such as nanoparticles, microspheres, and beads (Wang et al. 2008; Hua et al. 2010a; Yan et al. 2013; Hou et al. 2015). Similar to other formulations, montmorillonite usually increases drug encapsulation and sustained drug release. Generally,
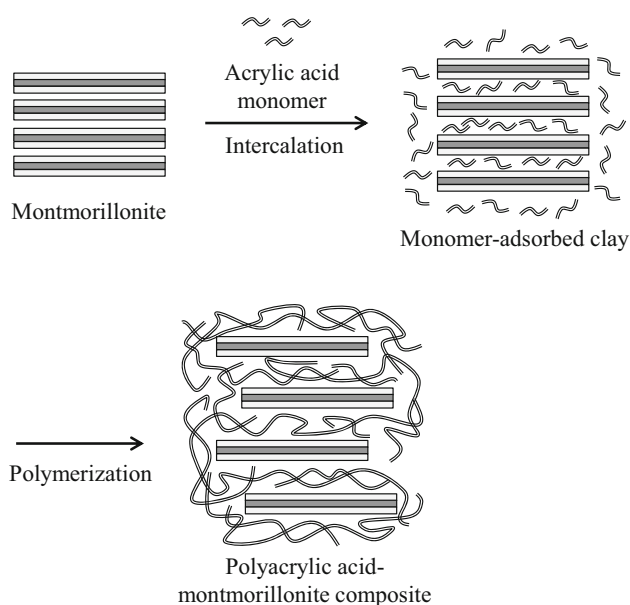

Fig. 4 Formation of a montmorillonite-polyacrylic acid composite by polymerization of intercalated acrylic acid monomers

the release rate of a drug-clay complex increases under high pH, but this tendency can be changed by the physicochemical properties of chitosan. Unlike montmorillonite, chitosan has a positive charge, so chitosan-based formulations disintegrate under a low pH condition, which increases drug release (Hua et al. 2010a, b). Ofloxacin-loaded chitosan-montmorillonite microspheres show a biphasic release pattern at pH 1.2, characterized by rapid release from the chitosan matrix and sustained release from the montmorillonite interlayer (Hua et al. 2010a).

Alginate formulations

Alginate is obtained from brown algae or bacteria and is a polysaccharide composed of β-D-mannuronic acid and α-L-guluronic acid (Yang et al. 2007; Pongjanyakul and Suksri 2009). Similar to chitosan, alginate is biodegradable and mucoadhesive and has drug release-modifying activity, so it has been used in controlled drug delivery systems (El-Kamel et al. 2002; Tønnesen and Karlsen 2002; Shi et al. 2006). However, in contrast to chitosan, alginate has carboxyl groups, so it has a negative charge. Dissolved alginate forms a hydrogel by crosslinking the carboxyl groups with divalent cations, including Ca^{2+} or Zn^{2+} (Chen et al. 2004; Nho et al. 2014). Alginate can be used to fabricate drug-loaded gel-based beads using this gelation mechanism. Generally, alginate beads show faster drug release under a higher pH, so alginate is useful to prepare pH-sensitive drug carriers. However, this hydrophilic matrix does not sufficiently encapsulate water-soluble drugs because the drug is quickly released from the alginate phase during the crosslinking step (Iliescu et al. 2014).

Moreover, the beads disintegrate easily in a high pH environment, which causes rapid drug release, so it cannot be used as a sustained release system.

To overcome these drawbacks, alginate-montmorillonite-based hydrogel formulations have been proposed (Oh et al. 2009; Kevadiya et al. 2010a, b; Iliescu et al. 2011; Jeong and Jung 2013; Liu et al. 2013; Yan et al. 2013; Iliescu et al. 2014). Unlike chitosan, alginate does not intercalate with the montmorillonite interlayer. However, as the edges of the montmorillonite layer are positively charged, they interact with alginate electrostatically to enhance rigidity of the alginate matrix (Fig. 3) (Kevadiya et al. 2010a, b; Iliescu et al. 2014). Similar to the chitosan-montmorillonite composite, montmorillonite enhances drug encapsulation and decreases drug release rate from an alginate matrix because of its adsorption property (Oh et al. 2009; Kevadiya et al. 2010b; Jeong and Jung 2013; Yan et al. 2013). Even after incorporating montmorillonite, an alginate-based formulation shows more rapid drug release in a neutral condition than that in an acidic condition (Oh et al. 2009; Jeong and Jung 2013; Liu et al. 2013) because the protonated carboxyl group of alginate maintains intermolecular hydrogen bonds under low pH (Jeong and Jung 2013). However, the negatively charged carboxyl group loses a hydrogen bond in neutral pH and is affected by the intermolecular repulsive force (Mahkam et al. 2015). This phenomenon induces swelling and disintegration of the alginate formulation, which cause rapid drug release.

Montmorillonite has also been applied to alginate-based films (Pongjanyakul and Suksri 2009; Alboofetileh et al. 2013; Prasetia et al. 2013). Clay changes the physical–

Table 1 Examples of polymers used to prepare montmorillonite-based drug delivery systems

Polymer	Formulation	References
Chitosan	Complex Hydrogel Nanoparticle Microspheres Beads	Lin et al. (2005), Liu et al. (2008), Wang et al. (2008), Depan et al. (2009), Monvisade and Siriphannon (2009), Hua et al. (2010a, b), Cojocariu et al. (2012a, b), Abdeen and Salahuddin (2013), Yan et al. (2013), Bothiraja et al. (2014) and Hou et al. (2015)
Alginate	Gel-based beads Microspheres Film	Oh et al. (2009), Pongjanyakul and Suksri (2009), Kevadiya et al. (2010a, b), Iliescu et al. (2011), Alboofetileh et al. (2013), Jeong and Jung (2013), Liu et al. (2013), Prasetia et al. (2013), Yan et al. (2013) and Iliescu et al. (2014)
Polyacrylic acid	Complex Hydrogel Film	Lee and Chen (2004), Thatiparti et al. (2010, Bhattacharya et al. (2011) and Hosseinzadeh et al. (2011)
Polyester	Complex Nanoparticles	Feng et al. (2009), Campbell et al. (2010) and Jain and Datta (b)
Starch	Nanoparticles	Banik et al. (2013) and Namazi and Belali (2015)
Poloxamer	Complex	Datta and Kaur (2014)

Fig. 5 Adsorption of an anionic drug with cationic polymer-intercalated montmorillonite
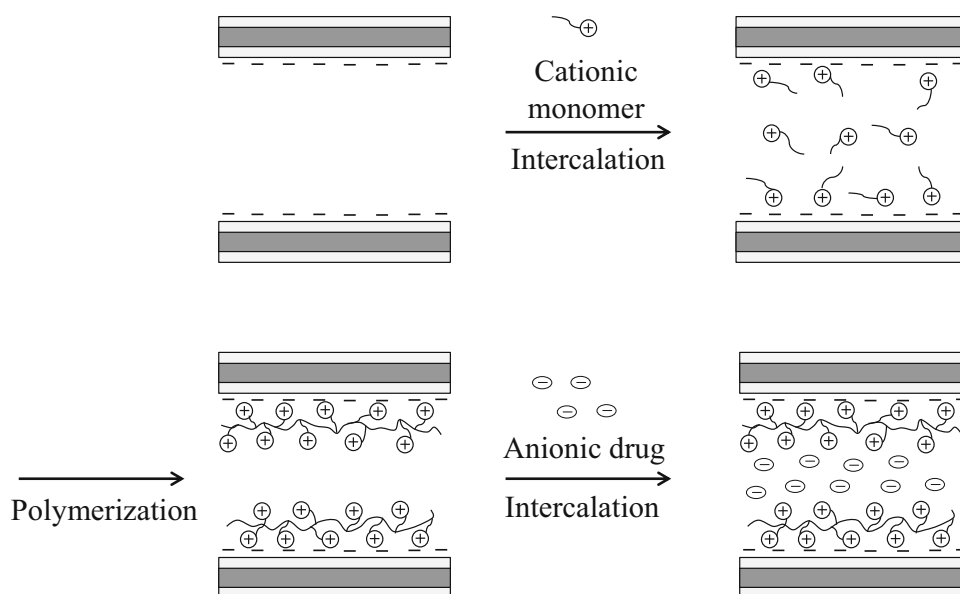
mechanical properties of films. For example, montmorillonite increases tear resistance and tensile strength and decreases percent elongation (Prasetia et al. 2013). In addition, the dissolution rate of the film or drug also decreases after incorporating montmorillonite (Pongjanyakul and Suksri 2009; Prasetia et al. 2013).

Poly(acrylic acid) formulations

Synthesized and natural polymers have also been used to develop drug delivery systems. For example, poly(acrylic acid), which is fabricated by polymerizing acrylic acid, has been studied as a hydrogel formulation because of its water absorption and mucoadhesive properties (Nho et al. 2014; Calixto et al. 2015). In addition, several methods, including crosslinking and hydrogen bond formation with other polymers, have been attempted to modify the original properties of poly(acrylic acid), including mechanical strength and the swelling effect (Katono et al. 1991; Elliott et al. 2004).

Montmorillonite has been applied with acrylic acid and its derivatives to design a newly structured drug carrier system (Lee and Chen 2004; Thatiparti et al. 2010; Bhattacharya et al. 2011; Hosseinzadeh et al. 2011). One interesting approach is to polymerize acrylic acid monomers in a montmorillonite suspension, rather than mixing poly(acrylic acid) with montmorillonite (Fig. 4) (Lee and Chen 2004). They reported that gel strength of the prepared hydrogel increased and release of a cationic drug decreased. Moreover, similar to alginate film, incorporating montmorillonite increased tensile strength and decreased degradation and drug release rates of a polyester polyol acrylate-based film (Thatiparti et al. 2010). Polyamide and polyacrylamide have also been studied as montmorillonite-mixed formulations (Kevadiya et al. 2013; Salahuddin et al. 2014).

Montmorillonite is sometimes modified with other cationic molecules prior to polymerization to prepare the polymer-montmorillonite composites explained above. For example, 3-acrylamidopropyl trimethylammonium chloride has been intercalated into the montmorillonite interlayer (Lee and Chen 2004). This modified montmorillonite is well exfoliated by efficient crosslinking with other acrylate monomers, and the exfoliation contributes to increase montmorillonite surface area and enhance interactions with the gel matrix. In another study, dodecylamine was intercalated to increase hydrophobicity of the montmorillonite interlayer (Thatiparti et al. 2010). Then, the hydrophobic monomer infiltrated well into this organo-modified clay, resulting in well-mixed composite (Table 1).

Polyester formulations

Polyesters, including polyglycolic acid, polylactic acid, polycaprolactone, and poly(lactic-co-glycolic acid) are biodegradable, biocompatible, and thermoplastic polymers that can be prepared by ring-opening polymerization of cyclic diesters (Athanasiou et al. 1996; Dinarvand et al. 2011). Because of their hydrolytic degradation and nontoxicity, polyesters are useful for various biomedical applications (Gentile et al. 2014). As these polymers are hydrophobic, they are usually used for controlled delivery of water-insoluble drugs (Dinarvand et al. 2011). Many studies have introduced montmorillonite into polyester-based formulations to control drug release of the original formulation (Feng et al. 2009; Campbell et al. 2010; Jain and Datta 2014a). In these reports, incorporating montmorillonite always delays drug release. Moreover,

montmorillonite enhances cellular uptake and cytotoxicity of docetaxel-loaded polylactic acid-based nanoparticles, indicating that the clay interacts with cells by hydrogen bonding or van der Waals forces (Lavie and Stotzky 1986; Feng et al. 2009).

Formulation as pharmaceutical additives

Montmorillonite have been formulated with various pharmaceutical excipients, including solubilizers and other polysaccharides. Intercalation of organic molecules increases when montmorillonite is added to a polysaccharide formulation (i.e., guar gum) (Mansa and Detellier 2013). Soy flour and starch have been used with montmorillonite to prepare biodegradable nanoparticles with a sustained release profile (Banik et al. 2013; Namazi and Belali 2015). Poloxamer has been added as a solubilizer to modify the montmorillonite interlayer (Datta and Kaur 2014). Interestingly, the release rate of diclofenac from montmorillonite decreased after incorporating poloxamer 188. It was speculated that the majority of the drug was successfully intercalated into montmorillonite after adding the poloxamer, resulting in sustained drug release. Moreover, an attempt to adsorb an anionic instead of a cationic drug into montmorillonite has been made. The anionic drug was successfully loaded into the interlayer by intercalating cationic monomers into the interlayer of the clay prior to adsorption of drug molecules (Fig. 5) (Mahkam et al. 2015). In this study, an intercalated anionic drug (i.e., naproxen) showed an increased release rate under a high pH condition because of the electrostatic repulsive forces from deprotonated COO^- groups. Furthermore, incorporating montmorillonite into methylcellulose/pectin-based films is more effective than montmorillonite-free films for transdermal drug delivery applications (Saha et al. 2016).

Conclusion and perspectives

Montmorillonite is a clay mineral in bentonite that is useful in various pharmaceutical applications. This clay exhibits representative characteristics, such as swelling and adsorption, and these properties contribute to improve and/ or modify drug delivery systems. Montmorillonite forms composites with various polymers, such as chitosan, alginate, and polyacrylic acid, thereby modifying the characteristics of the polymers, release patterns, and mechanical properties. Moreover, surface modifications of the montmorillonite sheet have been attempted to encapsulate noncationic drugs or to prepare composite formulations with other polymers. In general, montmorillonite sustains drug release of many formulations by strongly adsorbing drug molecules. However, montmorillonite also enhances dissolution rate and bioavailability of hydrophobic drugs. Because of the cationic exchanging activity, the adsorption and release pattern of drugs from montmorillonite-incorporated formulations are mainly affected by pH. Thus, montmorillonite is a promising material for use as a pharmaceutical excipient in diverse drug delivery systems.

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