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REVIEW OF CLAY-DRUG HYBRID MATERIALS FOR BIOMEDICAL APPLICATIONS: ADMINISTRATION ROUTES

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Abstract—Focus here is placed on the pharmaceutical and biomedical applications of novel clay-drug hybrid materials categorized by methods of administration. Clay minerals have been used for many years as pharmaceutical and medicinal ingredients for therapeutic purposes. A number of studies have attempted to explore clay-drug hybrid materials for biomedical applications with desired functions, such as sustained release, increased solubility, enhanced adsorption, mucoadhesion, biocompatibility, targeting, *etc*. The present review attempts not only to summarize the state-of-the-art of clay-drug hybrid materials and their advantages, depending on the methods of administration, but also to deal with challenges and future perspectives of clay mineral-based hybrids for biomedical applications.

Key Words—Administration Methods, Biocompatibility, Biomedical Applications, Clay-drug Hybrid, Mucoadhesion, Pharmaceutical Applications, Sustained Release, Targeting.

INTRODUCTION

Much attention has been paid to clay minerals, since the early days of humankind, for various purposes because they are abundant in nature and inexpensive, and because they have unique structural properties (Carretero, 2002; Choy *et al.*, 2007). Clay minerals are, in general, hydrated alumino-silicates containing alkaline and alkaline earth metals. Among the layered clay minerals (phyllosilicates), only some of them, including kaolin, talc (*sensu lato*), smectites, and fibrous clays can be used as excipients in the formulation of different dosage forms such as solid, liquid, or semisolid. The application of each clay mineral is determined by the individual intrinsic properties derived from the structure type (1:1 or 2:1 layer type) and chemical composition.

The kaolin group of minerals, including kaolinite (Kln) and halloysite, has a 1:1 layer-type structure, in which the layer is composed of a tetrahedral silica sheet and an octahedral alumina sheet combined in a unit, and the layers are stacked along the *c* axis by hydrogen bonding interaction. Although Kln also has a relatively small specific surface area (SSA) compared to other types of clay minerals, some reports have dealt with its rapid rate of exchange reaction and good adsorption properties on the surface for small molecules such as proteins, bacteria, and viruses (Barral *et al.*, 2008; Rutkai and Kristóf, 2008). Talc (Tlc) is a 2:1 phyllosilicate composed of an edge-linked $MgO_4(OH)_2$ octahedral sheet located between two corner-linked tetrahedral silica sheets through sharing of oxygen atoms. Talc is an excellent adsorbent due to its large adsorption capacity for hydrophilic and hydrophobic substances (López-Galindo *et al.*, 2007; Rotenberg *et al.*, 2011; Jadhav *et al.*, 2013). Smectite (Sme) is an expandable 2:1 phyllosilicate with a layer charge of −0.2 to −0.6 per formula unit. Each individual layer is composed of a sheet of octahedrally coordinated aluminum, magnesium, or iron atoms with oxygen ligands and hydroxyl groups, which is sandwiched between two sheets of tetrahedral silicons coordinated with oxygen atoms. Smectite is subdivided into dioctahedral and trioctahedral Sme, depending on the number and the nature of octahedral cations. When the octahedrally and/or tetrahedrally coordinated elements are substituted by cations of lower valence such as Mg^{2+} and/or Al^{3+}, respectively, a cation exchange capacity (CEC) develops due to the formation of a negative layer charge and its distribution upon substitution. Not only because of its large CEC, surface area, and swellability, but also because of its biocompatibility, Sme has been recommended frequently for biomedical applications, especially pharmaceutics (Gamiz *et al.*, 1992; Aguzzi *et al.*,

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2007; Park *et al.*, 2008). Palygorskite and sepiolite are 2:1 phyllosilicates and, unlike other clay minerals, have a fibrous morphology. They contain a continuous two-dimensional tetrahedral sheet, but differ from other layer silicates in that they lack continuous octahedral sheets, which can be considered as ribbons of 2:1 phyllosilicate structure. Each ribbon is linked to the next ribbon by inversion of SiO_4 tetrahedra along a set of Si−O bonds. Such micron-sized needle-like fibrous clays have been used widely as an adsorbent because their structures contain micropores and they have a large SSA (40−180 m^2/g) compared to that of the kaolinite (5−40 m^2/g). Palygorskite and sepiolite are also amenable to assembly with a polymer matrix through hydrogen bonding, making them suitable for pharmaceutical formulations (Viseras and López-Galindo, 1999; Lopéz-Galindo and Viseras, 2004). The properties of these various types of clay minerals make them suitable for biomedical applications because they are abundant and have plentiful surface space which is reactive with many biological, organic, and inorganic substances.

Clay minerals have long been used as folk remedies for various purposes, such as relief from diarrhea, blood clotting, wound healing, *etc*. (Chang *et al.*, 2007; Williams *et al*., 2008; Li *et al.*, 2012; Alavi *et al.*, 2014). For example, peloid, mud used therapeutically, is administered locally to alleviate joint pain and recover bone-muscle damage, by slowly elevating the local temperature of the underlying tissues without causing damage (Ferrand and Yvon, 1991; Cara *et al.*, 2000a, 2000b). Medicinal clays have also been used in curing ulcers, preventing infections, and even treating some allergies in the body (Poensin *et al.*, 2003; Veniale *et al.*, 2004). Moreover, clay minerals have been adjusted to improve pharmaceutical properties depending on the medical application required. The hydrophilic surface can be rendered hydrophobic by different treatments, including ion exchange with quaternary ammonium compounds; the resulting organoclays are compatible with polymers and can be used to prepare organoclay-polymer composites. Such organoclays, either individually or in combination with polymers, have been used widely in the formulation of biomedical applications (Ghadiri *et al.*, 2015).

New organic-inorganic hybrid materials are currently being developed for biomedical applications, beginning with clay minerals combined with drugs intended for targeted purposes (Choy *et al.*, 1999, 2000; Yang *et al.*, 2003; Choy *et al.*, 2006; Oh *et al.*, 2006; Kim *et al.*, 2008; Lim *et al.*, 2011; Wang *et al.*, 2013). Because clay minerals are efficient and safe transporters, they may provide a new paradigm in the field of drug delivery systems (DDS) compared to other inorganic materials (Aguzzi *et al.*, 2007; Suresh *et al.*, 2010; Viseras *et al.*, 2010; de Sousa Rodrigues *et al.*, 2013). Drug delivery systems have many advantages, *e.g.* reduced side effects from the drug due to sustained release and better patient compliance through reduced dose frequency. For many types of controlled-release formulations, immediately upon placement in the release medium a large initial bolus of drug is released uncontrollably before it can reach a stable release rate (*i.e.* 'initial burst' or 'burst release'), which can result in toxicity. Drug formulations for controlling the release rate of the drug (*i.e.* delayed release, extended release, or sustained release) can achieve the dual target of reduced toxicity and better compliance along with enhanced drug efficacy.

The incorporation of drug molecules into clay minerals has received a great deal of attention for biomedical applications because clay-drug hybrids are distinguished from simple physical mixtures of each component. Various polar or cationic species can be combined with clay minerals by physical adsorption or intercalation to form clay-drug hybrid materials which have the large SSA or CEC of clay minerals.

Organic drug molecules stabilized in the interlayer space of clay minerals could be oriented with a mono-layer, bi-layers, or pseudo-triple layers, or a paraffin-like mono-layer or bi-layer arrangement (Bergaya and Lagaly, 2013), depending not only on the CEC of the clay minerals but also on the amount of drug loaded, resulting in controlled-release and sustained-release properties (Abdel-Mohsen *et al.*, 2001; Takahashi *et al.*, 2005; Jung *et al.*, 2008a; Lvov *et al.*, 2008; Joshi *et al.*, 2009). In addition, clay minerals have been utilized as formulation additives in order to enhance the solubility of poorly soluble drugs (Jung *et al.*, 2008b; Dornelas *et al.*, 2011; Lim *et al.*, 2011) to improve the photo/dispersion/thermal stability of fragile bioactive molecules (El-Nahhal *et al.*, 1999; Cypes *et al.*, 2003; Takahashi *et al.*, 2005; Pongjanyakul *et al.*, 2009), and to provide mucoadhesive properties for increasing retention time in the gastro-intestinal (GI) tract and the preocular surface (Dobrozsi, 2003; Hua *et al.*, 2010; Salcedo *et al.*, 2012). The fascinating features of clay-drug hybrid materials allow the potential to develop efficient DDS.

In the present review, DDS with clay-drug hybrid materials are categorized based on the methods of administration, and their advantages and therapeutic effects are summarized. The challenges and future prospects of clay-drug hybrids are described in terms of biomedical applications.

BIOMEDICAL APPLICATIONS OF CLAY MINERALS

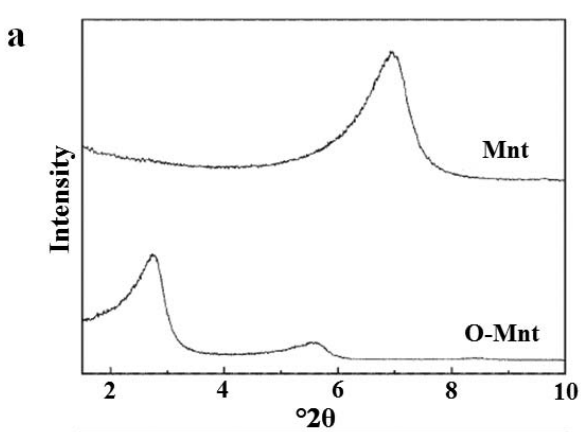
Clay minerals have been used widely as ingredients for pharmaceutical formulations, as indicated by the US Food and Drug Administration (FDA) 'Inactive Ingredient Database' (Table 1). For example, the Na forms of Sme are effective in laxatives, stimulating defecation through osmosis, and their Ca forms can be used as anti-diarrhea agents, *via* oral administration, due to strong adsorbent properties (Alestig *et al.*, 1979;

Ippoliti, 1998; Carretero, 2002). In addition, clay minerals are well known as emulsifying, gelling, and thickening agents in pharmaceutical formulations for oral medication (Bolger, 1995; Viseras and López-Galindo, 1999; Abend and Lagaly, 2000), because those clay minerals can absorb water or oils and modulate the viscosity of formulations. When used as ingredients for improved organoleptic qualities in pharmacological formulations, clay minerals can mask unpleasant tastes or smells of drugs and prevent unwanted changes in their intrinsic colors and physico-chemical properties through the stabilization effects of the inorganic matrix and modulation of drug-release properties (Lee *et al.*, 2012; Oh *et al.*, 2013; Ambrogi *et al.*, 2014).

Clay minerals have also been employed for many years in dermatology to protect the skin from external physical and chemical substances, to palliate joint inflammations, and to cure skin diseases (Ferrand and Yvon, 1991; Cara *et al.*, 2000a, 2000b). Clay minerals have also been utilized as anti-bacterial agents for wound healing (Clark *et al.*, 1998; Meng *et al.*, 2009; Williams and Haydel, 2010; Wei *et al.*, 2011; Hsu *et al.*, 2012), and as fillers in the fabrication of transdermal patches (Tan and Pfister, 1999). This strategy has been developed further in order to provide good adhesion to the skin without pain or damage to the outermost skin layer, the stratum corneum, when detaching or removing the patches, because of the hydrophilic property of the clay minerals.

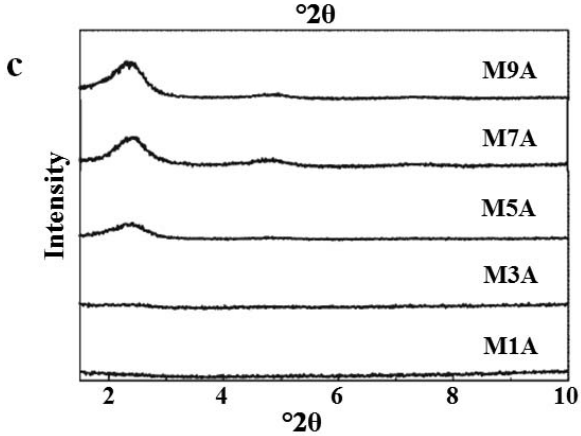
In the case of the local administration of clay minerals for bone-related biomedical applications, a novel type of bone-cement composite, consisting of organomodified montmorillonite (O-Mnt) with poly (methyl methacrylate) (PMMA), was reported by Wang *et al.* (2006). To prepare O-Mnt, octadecylammonium ions were intercalated into the interlayer space of Mnt by ion-exchange reaction in such a way that the hydrophobicity of Mnt could be established and the interlamellar space of Mnt expanded. The *d* spacing increased considerably from 1.28 to 3.1 nm after ion exchange reaction, indicating that the octadecylammonium ions had entered and expanded the interlayer space of the clay (Figure 1a). Well ordered second (5.68º) and third (8.58º) order peaks corresponding to (002) and (003) reflections, respectively, were observed.

An aqueous suspension of between 1 and 9 wt.% of O-Mnt was blended with a biocompatible PMMA through a melt-blending process (Isayev and Palsule,



b

Sample	Clay content (%)	Blending time (min)
M1A	1	10
M3A	3	10
M5A	5	10
M7A	7	10
M9A	9	10
M1B	1	20
M3B	3	20
M5B	5	20
M7B	7	20
M9B	9	20



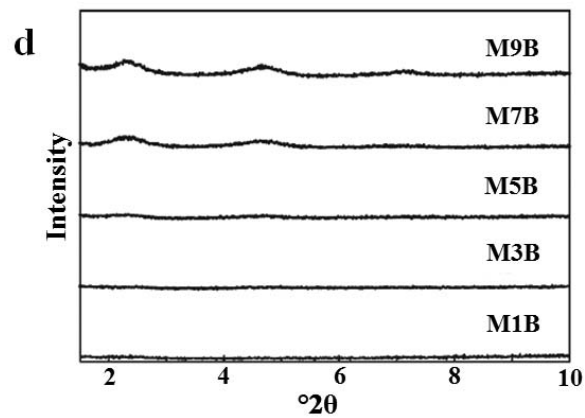


Figure 1. (a) XRD patterns of Mnt and O-Mnt. (b) Sample list of O-Mnt/PMMA composites corresponding to clay content and blending time. (c,d) XRD patterns of O-Mnt/PMMA composites with (c) 10 min and (d) 20 min of blending time. (Image reproduced here from Wang *et al.*, 2006, with the permission of John Wiley & Sons.)

Table 1. Clay minerals as ingredients for pharmaceutical formulations corresponding to routes of administration.

Route of administration	Issue	Delivery system	Mechanism	Reference
Oral				
	Gastrointestinal protectant	Prolonged delivery	Adsorption	Alestig *et al.* (1979), Takahashi *et al.* (2005), Bergaya and Lagaly (2013)
	Laxatives, antidiarrhea	Prolonged delivery	Osmosis	Alestig *et al.* (1979), Ippoliti (1998), Murray (2000), Carretero (2002), Classen *et al.* (2003)
	Release pattern	Sustained/ Controlled/ Extended/ Retarded delivery	Adsorption/Desorption Intercalation/ Deintercalation	Albert *et al.* (1978), Cypes *et al.* (2003), Levis and Deasy (2003), Byrne and Deasy (2005), Jung *et al.* (2008a), Forsgren *et al.* (2010), Hua *et al.* (2010), Dornelas *et al.* (2011), Mostafavi *et al.* (2011)
	Solubility	Improved solubility	Adsorption Intercalation	Jung *et al.* (2008), Park *et al.* (2008)
	Stability	Improved stability	Adsorption Intercalation	El-Nahhal *et al.* (1999), Ambrogi *et al.* (2014)
	Site-specific drug delivery	Site-specific/ Programmed/ Target delivery	Enteric coating Mucoadhesion Targetability Activation by environmental stimuli (pH, temperature)	Dobrozsi (2003), Dong and Feng (2005), Sun *et al.* (2008), Feng *et al.* (2009), Hua *et al.* (2010), Salcedo *et al.* (2012), de Sousa Rodrigues *et al.* (2013)
	Improved organoleptic qualities	Site-specific delivery	Enteric coating Mucoadhesion Intercalation	Lee *et al.* (2012), Jadhav *et al.* (2013), Oh *et al.* (2013)
	Formulation additives	Sustained/ Controlled/ Extended/ Retarded delivery	Intercalation Exfoliation Electrostatic interaction	Bolger (1995), Viseras and Lopez-Galindo (1999), Abend and Lagaly (2000), Takahashi *et al.* (2005)
Transdermal				
	Aesthetic medicine	Topical delivery	Adsorption Promoted sebaceous secretions Protections of external physical or chemical substances Alleviation of pain Antibacterial effect Wound healing	Ferrand and Yvon (1991), Clark *et al.* (1998), Cara *et al.* (2000), Poensin *et al.* (2003), Veniale *et al.* (2004), Chang *et al.* (2007), Barral *et al.* (2008), Rutkai and Kristóf (2008), Hsu *et al.* (2012), Alavi *et al.* (2014)
	Solubility	Improved solubility	Adsorption Intercalation	Ito *et al.* (2001), Jo *et al.* (2006), Bonina *et al.* (2007), Ha and Xanthos (2011)
	Stability	Improved stability	Adsorption Intercalation	Jo *et al.* (2006), Bonina *et al.* (2007), Pongjanyakul *et al.* (2009)
	Release pattern	Sustained/ Controlled/ Extended/ Retarded delivery	Adsorption/Desorption Intercalation/ Deintercalation Penetration of drug by diffusion	Ito *et al.* (2001), Bonina *et al.* (2007), Shaikh *et al.* (2007). Meng *et al.* (2009), Pongjanyakul *et al.* (2009), Ha and Xanthos (2011)
	Fillers	Sustained/ Controlled/ Extended/ Retarded delivery	Intercalation Exfoliation Electrostatic interaction	Tan and Pfister (1999), Jo *et al.* (2006), Ha and Xanthos (2011), Irmukhametova *et al.* (2014)

Table 1 (*contd.*)

Route of administration	Issue	Delivery system	Mechanism	Reference
Local				
	Local anesthetic	Sustained/ Controlled/ Extended/ Retarded delivery	Adsorption/Desorption Intercalation/ Deintercalation	Abdel-Mohsen *et al.* (2001)
	Implanted devices			Kelly *et al.* (2004), Pongjanyakul and Suksri (2009), da Silva *et al.* (2011), Pinto *et al.* (2011), Sharifzadeh (2013)
	Stability	Improved stability	Adsorption Intercalation	Pongjanyakul and Suksri (2009)
	Fillers	Sustained/ Controlled/ Extended/ Retarded delivery	Intercalation Exfoliation Electrostatic interaction	Kelly *et al.* (2004), Wang *et al.* (2006), Da Silva *et al.* (2009, 2011), Pinto *et al.* (2011), Sharifzadeh (2013)
	Passive coating layer		Dispersion Transmission rate of water	Wittchow (2014)

2011) at 200ºC at 60 rpm in a mixer (Brabender, plasticorder PL-2100-5) for 10 min.

The sample list of O-Mnt/PMMA composites corresponding to clay content and blending time are summarized in Figure 1b. For small proportions of O-Mnt (1 or 3 wt.%), no X-ray diffraction (XRD) peaks were observed over the scanning range 0.5–10º2θ because the clay contents in these composites were too small to generate sufficient diffraction intensity (Figure 1c). On the other hand, the diffraction peaks for other composites containing 5, 7, and 9 wt.% O-Mnt were all located at 2.3º2θ corresponding to a *d* value of 3.8 nm. The entangled polymer chain of PMMA was inserted into the interlayer space of the O-Mnt, resulting in an expansion of the *d* spacing by >25% compared to that of the unaltered O-Mnt. As the blending time increased from 10 to 20 min, a pronounced exfoliation of O-Mnt occurred gradually with rather flat and very small humps at the same position (Figure 1d). As nanoscale mixing was established, the degree of interactions between organic and inorganic increased as a result of extensive interfacial contacts. The O-Mnt/PMMA composites prepared showed not only a significant enhancement in terms of thermal stability without degradation of PMMA, but also significant improvement in the mechanical properties such as impact strength, which are, in general, very desirable in typical formulations for bone cements. In particular, the thermal degradation temperature and impact strength of O-Mnt/PMMA composites were increased by 1.13 and 1.66 times, respectively, compared to those of pure PMMA. In addition, the O-Mnt/PMMA composites showed an improved cell growth on the bone-cement surface, as confirmed by colorimetric assay for assessing cell metabolic activity. These newly designed bone-cement composites were, therefore, able to meet all of the requirements for orthopedic applications.

Biodegradable polymers and their clay composites are used in anti-corrosion coatings on the surfaces of bio-corrodible implant devices, specifically stents (Wittchow, 2014). In general, the implantation of stents is one of the most effective treatments for vascular diseases as it offers the opportunity to support hollow or damaged organs. Stents made of corrodible magnesium or its alloys offered limited biomedical application because of rapid degradation under physiological conditions. Biodegradable polymer-clay composites offer promise in terms of passive coating layers of biocorrodible stents. With the aid of clay minerals, the transmission rate of water, which is the key factor in terms of the passive coating layer, was reduced dramatically below the transmission-rate value of standardized water vapor: 50 g/m^2 per day. The implant device could be protected from degradation under biological conditions thanks to the polymer-clay composite coating.

DRUG-DELIVERY ROUTES OF CLAY-DRUG HYBRIDS

Recently, new strategies have emerged to investigate the potential of clay minerals as inorganic drug carriers because of their unique properties such as biocompatibility, increased solubility, adsorption, muco-adhesiveness, sustained release, and targeting (Figure 2a). An attempt is made here to describe DDS with clay-drug hybrid materials, depending on their routes of administration (Figure 2b).

Oral administration

Many efforts have been made to develop clay-drug hybrids by intercalating or absorbing drug molecules into clay minerals for orally administered DDS. The representative dosage forms for oral administration

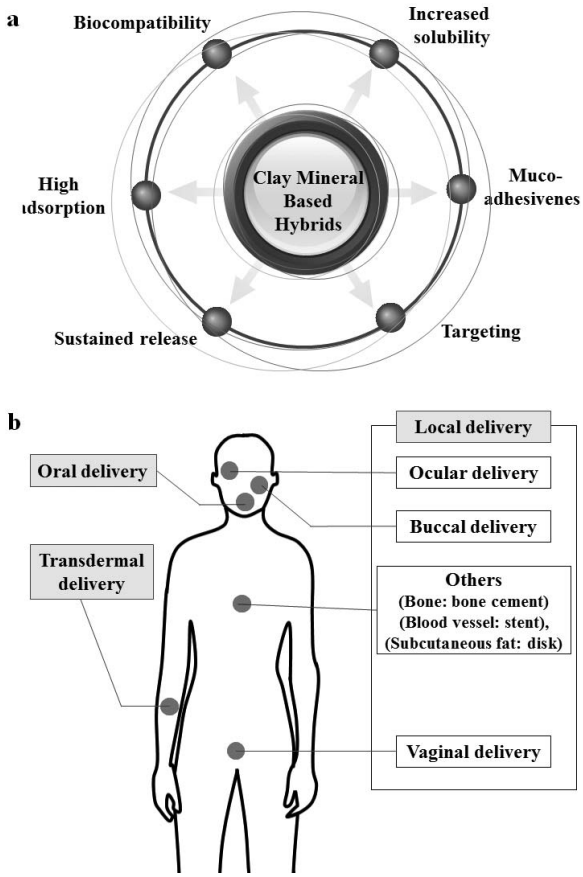


Figure 2. (a) Featured properties of clay hybrids and (b) possible routes of administration for drug-delivery systems.

include powder, suspension, capsule, tablet, gum, and pellet. The effects on the bioavailability of orally administered clindamycin with kaolin-pectin antidiarrheal suspension by pharmacokinetic techniques, in terms of the amount, lag time, and half-time of drug adsorption were evaluated by Albert *et al.* (1978). Although the suspension of kaolin-pectin had no effects on the total amount of drug absorption, the half-time of drug absorption was extended by a factor of ~20 due to the fact that drug molecules adsorbed on the kaolin-pectin could be released in a sustained manner.

In a similar study, halloysite, a naturally occurring microtubular aluminosilicate, could encapsulate a highly water-soluble drug (diltiazem HCl) in order to induce a sustained drug-release property. The release of diltiazem HCl was examined by dissolution testing in pH 6.8 buffer media, simulating conditions in the small intestine. The drug release by halloysite was retarded only slightly with an evident 'large burst' effect compared to that of unaltered diltiazem HCl. The highly water-soluble nature of the drug and simple entrapment in halloysite meant that the clay did not have an adequate sustained-release property. In an attempt to prolong the release of diltazem HCl from the halloysite, *in situ* polymerization with various alkylcyanoacrylate monomers and drug-loaded halloysite hybrids in a non-aqueous solvent was carried out for 8 h. Among three different formulations, the diltiazem HCl-halloysite hybrid coated with poly-iso-butyl cyanoacrylate was found to be most effective, showing a reduced 'initial burst' effect and achieving sustained release, where the release kinetics was best fitted by a 'square-root of time' dependence. The poly-iso-butyl cyanoacrylate was added as a coating to the surface of the drug-encapsulated halloysite by *in situ* polymerization, and this retarded drug release significantly.

Another approach to extend the drug release was made by using kaolinite or halloysite pellets through extrusion-spheronization or cryopelletization, and subsequently drug molecules were loaded by a vacuum impregnation technique (Byrne and Deasy, 2005; Forsgren *et al.*, 2010). The drug molecules loaded in the pellets exhibited a prolonged-release profile following an 'initial burst' release due to entrapment within the porous architecture of the pellets. The pelletized porous clays in an oral dosage form could lead to extended drug release, which depends not only on the pH of the release medium, but also on the design of the porous architecture including the porosity and the pore size. In the case of halloysite pellets, the drug release was further prolonged due to the entrapment of the drug molecules within the halloysite microtubules.

Several attempts have also been made to develop orally administered clay-drug hybrids for chemotherapy. Generally, an intact form of chemotherapeutic agent often causes adverse side effects due to non-site-specific adsorption in the body. In order to reduce the perceived toxicity of 5-fluorouracil (5-FU) and to achieve controlled release for colorectal cancer therapy, 5-FU/Mnt hybrid was prepared by intercalating 1.185 wt.% of 5-FU, as the initial concentration under pH 11.6 at 80ºC for 2 h, into Mnt (Lin *et al.*, 2002; Kevadiya *et al.*, 2012; Jin *et al.*, 2014). The total loading amount of 5-FU in Mnt was determined to be ~87.5 mg/g of Mnt, which was proved by thermogravimetric analysis. The 5-FU/Mnt hybrid was expected to achieve *in situ* release for colorectal cancer therapy.

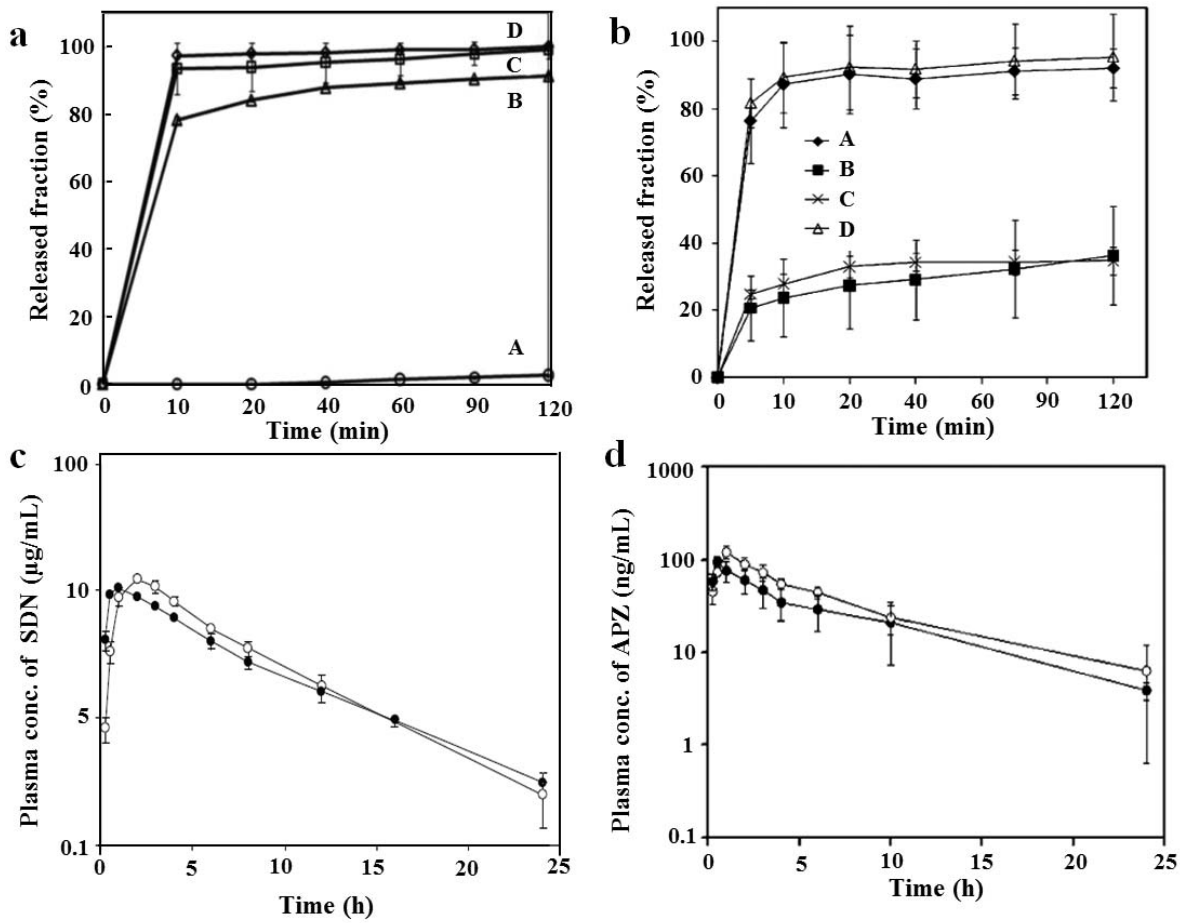
In terms of the bioavailability of orally administered anticancer drugs, attempts were made (Dong and Feng, 2005) to develop bioadhesive poly(D,L-lactide-co-glycolide)/montmorillonite nanoparticles (PLGA/Mnt NPs) based on the emulsion solvent evaporation method. When the NPs were formulated with Mnt as a matrix additive material, Mnt could not only play a role as the co-emulsifier in the synthesis of the NPs, but also influence the particle morphology and encapsulation efficiency. Above all, the mucoadhesiveness of Mnt enabled a marked increase in the cellular uptake efficiency of the bare PLGA NPs in two human colon-derived cell lines, by 57−177% for Caco-2 cells and by 11−55% for HT-29 cells, depending on the amount of

Mnt in the fluorescent-loaded PLGA/Mnt NPs. Based on these results, one might expect increased residence times for drug-loaded PLGA/Mnt NPs in the GI tract mucus/epithelial surface and thus promote the bioavailability of orally administered anticancer drugs.

Work on the PLGA/Mnt NPs by Sun *et al.* (2008) has allowed advanced target drug delivery by surface decoration with the human epidermal growth factor receptor-2 (HER2) antibody, Trastuzumab, for breast cancer chemotherapy. This multi-functional formulation reduced the adverse side effects of the model anticancer drug employed, paclitaxel (Pac), and promoted synergistic therapeutic effects by achieving targeted delivery. The HER2-decorated paclitaxel-PLGA/Mnt NPs (Pac-PLGA/Mnt-HER2 NPs) were analyzed by X-ray photoelectron spectroscopy and sodium dodecyl sulfate polyacrylamide gel electrophoresis analysis to evaluate the presence and stability of Trastuzumab on the PLGA/Mnt-HER2 NPs, respectively. *In vitro* internalization of two different fluorescent-loaded PLGA/Mnt NPs, with or without antibody, demonstrated that the surface-modified NPs displayed much greater cellular uptake efficiency on SK-BR-3 breast cancer cells, as expressed by fluorescence strength. Trastuzumab decoration enhanced the cellular uptake by SK-BR-3 breast cancer cells, which is known to be HER2 positive. To compare the therapeutic effects of the commercially available paclitaxel agent (Taxol®), Pac-PLGA/Mnt NPs, and Pac-PLGA/Mnt-HER NPs, *in vitro* cytotoxicity assay was carried out on the same cell line. The antibody-decorated NPs showed therapeutic effects which were 12.74 and 13.11 times greater than those of Pac-PLGA/Mnt NPs and Taxol®, respectively, as estimated by the level of half maximum inhibitory concentration (IC_{50}), the concentration of a drug that is required for 50% inhibition *in vitro*, after 24 h of incubation.

Following those PLGA/Mnt NPs studies, Feng *et al.* (2009) introduced d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), a water-soluble derivative of natural vitamin E formed by esterification of vitamin E succinate with polyethylene glycol (PEG), into poly(-lactide)/montmorillonite nanoparticles (PLA/Mnt NPs). The newly designed TPGS-PLA/Mnt NPs displayed substantial emulsification effects, which resulted in greater drug encapsulation efficiency and cellular adhesion properties. Without targeting effects, the IC_{50} values of the formulated TPGS-PLA/Mnt NPs were found to be about three times more effective in terms of therapeutic effects on a human breast adenocarcinoma cell (MCF-7) than those of Taxotere®, which is used clinically. In addition, *in vivo* pharmacokinetic studies on normal Sprague-Dawley rats revealed that orally administrated TPGS-PLA/Mnt NPs achieved half-lives which were 26.4 times greater, and improved bioavailability by a factor of ~25 compared to Taxotere® administered by intravenous injection. Interestingly, a single dose of the NPs formulated as an oral medication had sustained chemotherapeutic efficacy for about 3 weeks, as compared to 22 h for the intravenously administered Taxotere®.

A new concept related to an organoleptic development with clay minerals has emerged in pharmaceutics. Specifically, taste-masking formulations with clay minerals to block the unpleasant taste of drugs have been studied intensively because such drugs often face limitations in terms of formulation design, and have poor patient compliance. Sildenafil (SDN) and Aripiprazole (APZ) were intercalated into Mnt by cation exchange reaction to yield clay-drug hybrids, and subsequently coated with a cationic polymer, polyvinylacetal diethylamino acetate (AEA), by a spray-drying process to further improve the taste-blocking efficiency and also control the drug-release kinetics (Lee *et al.*, 2012; Oh *et al.*, 2013). Both AEA-coated SDN-Mnt and APZ-Mnt hybrids suppressed the drug-release rate to a significant extent (4.70 ± 0.53% for SDN and <1% for APZ) at neutral pH after 2 min, suggesting that they have potential to mask the bitter or unpleasant taste of drugs in the buccal cavity. Under simulated gastric-fluid conditions (pH 1.2), the release profiles of SDN from the SDN-Mnt and AEA-coated SDN-Mnt were examined and compared with those of intact SDN and the clinically used drug, Viagra® (Figure 3a). Predictably, intact SDN and Viagra® displayed substantial initial burst release of 90% SDN within 10 min and their cumulative release amounts reached 99% in 2 h due to the high solubility of SDN in the acidic conditions. On the other hand, SDN could not be released effectively from the SDN-Mnt (<3%) because of strong ionic interaction between the intercalated SDN and Mnt in the acidic conditions. Remarkably, ~75% of SDN was discharged from AEA-coated SDN-Mnt within 10 min and reached 90% by 2 h because dissolved cationic AEA at low pH was exchanged with SDN in the interlayer space of Mnt and enlarged the interlayer spacing to facilitate drug diffusion toward the release media. With regard to APZ, the drug-release rate for AEA-coated APZ-Mnt increased significantly with the help of AEA, compared to the APZ-Mnt (Figure 3b). The drug-release patterns revealed that both AEA-coated drug-Mnt hybrids were considered as good formulations for preventing the unpleasant taste of drugs and had similar drug efficacy to alternatives used in clinical environments. In addition, these pharmaceutical formulations proved useful for improving *in vivo* pharmacokinetics and bioavailability, as verified by comparison with the drugs currently in clinical use (Figure 3c–e). For the AEA-coated SDN–Mnt hybrid, the maximum concentration (C_{max}) and area under the curve from 0 h to infinity ($AUC_{0-\infty}$) were 1.1× and 1.2× larger than those obtained with Viagra® ($AUC_{0-\infty}$ = 69.2 ± 3.19 μg h/mL; C_{max} = 10.5 ± 0.64 μg/mL). In the case of the AEA-coated APZ–Mnt hybrid, a ~20% increase of *in vivo* drug bioavailability was shown as compared to



e

Parameters	Viagra®	AEA-coated SDN-Mnt	Abilify®	AEA-coated APZ-Mnt
$AUC_{0-\infty}$ (μg h/mL)	6.92 ± 3.19	78.8 ± 2.32*	(609 ± 196)	(847 ± 193)*
C_{max} (μg/mL)	10.5 ± 0.641	12.4 ± 0.67*	(96 ± 11)	(121 ± 19)*
T_{max} (h)	1.00	2.33 ± 5.77	0.50	1.00
$t_{1/2}$ (h)	5.00 ± 0.074	4.13 ± 0.79	(6.72 ± 2.03)	(6.53 ± 3.29)
V_d/F (L)	31. 3 ± 1.19	22.7 ± 4.49*	(54 ± 28)	(33.1 ± 11.2)
Cl/F (L/h)	4.34 ± 0.205	3.81 ± 0.11*	(5.43 ± 1.56)	(3.75 ± 0.81)*

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from 0 to infinity; C_{max} = maximum plasma concentration; T_{max} = time required to reach C_{max}; $t_{1/2}$ = elimination half-life; V_d/F = apparent volume of distribution; Cl/F = total clearance; * = statistically significant difference ($p < 0.05$).

Figure 3. (a) *In vitro* release profiles of SDN of (A) SDN-Mnt, (B) AEA-coated SDN-Mnt, (C) Viagra®, and (D) intact SDN in simulated gastric fluid (pH 1.2). (b) *In vitro* release profiles of APZ from (A) Abilify®, (B) intact APZ, (C) APZ-Mnt, and (D) AEA-coated APZ-Mnt in simulated gastric fluid (pH 1.2). (c) Plot of mean plasma concentration-time curves of SDN after oral administration of Viagra® (●) and AEA-coated SDN-Mnt (○) to beagle dogs at a dosage of 20 mg/kg. (d) Plots of mean plasma concentration-time curves of APZ after oral administration of Abilify® (●) and AEA-coated APZ-Mnt (○) to rats at a dosage of 10 mg/kg. (e) Pharmacokinetic parameters of drugs after oral administration of Viagra®, AEA-coated SDN-Mnt, Abilify®, and AEA-coated APZ-Mnt. (Reprinted from Lee *et al.* (2012) and Oh *et al.* (2013); with the permission of John Wiley & Sons.)

Abilify®. The clay-drug hybrid coated with a cationic macromolecule demonstrated, therefore, potential for blocking the unpleasant taste of the drug, as well as for enhancing the bioavailability of the drug.

In summary, clay minerals with the benefits featured have been applied widely in oral DDS. Clay minerals, as drug delivery vehicles, play important roles in terms of enhancing the bioavailability of drug molecules and these

roles are functions of the characteristics of clay-drug hybrids: (1) increased solubility; (2) substantial emulsification effects; (3) significant encapsulation efficiency; (4) controlled-release profile in a manner of sustained or extended release; (5) cell adhesion and cellular uptake efficiency; (6) muco-adhesiveness; and (7) blocking the unpleasant taste of drugs. Clay minerals offer promise, therefore, as inorganic biomaterials and can provide novel perspectives for developing oral drug delivery.

Transdermal administration

Clay minerals have been employed as pharmaceutical ingredients or drug carriers for transdermal drug delivery systems (TDDS) (Wokovich *et al.*, 2006; Kim *et al.*, 2013) as well being used to release the drug at a controlled rate to systemic circulation through passive diffusion across the skin. The TDDS allows the user to maintain a drug concentration in the plasma which is within therapeutically effective levels over an extended period of time, while avoiding first-pass metabolism by the liver and GI tract. Simple administration with this non-invasive dosage can lead to improved patient compliance, and can be terminated easily at any point by removal of the patch or the type of dosage form. Finally, this type of DDS allows for self-medication.

Many related studies on TDDS have revealed that the main factors relating to the skin permeability of drug molecules, such as a concentration gradient, distribution coefficient, and diffusion coefficient, can be controlled simply by combining with clay minerals. In particular, clay minerals as drug-delivery vehicles can enhance the solubility of poorly soluble drugs with the drug intercalated and then deintercalated out of the interlayer space of the clay at a molecular level (Jung *et al.*, 2008b; Park *et al.*, 2008; Ha and Xanthos, 2011). Clay minerals can be formulated into many kinds of dosage forms, such as powder, gel, cream, ointment, film, bandage, and patch for transdermal administration.

An indomethacin-montmorillonite (IDM-Mnt) complex was reported by Ito *et al.* (2001) to be effective at increasing the skin permeability of the drug, as evaluated by the *in vitro* Franz cell diffusion method. Such results are not surprising because IDM in an IDM-Mnt complex became almost three times more soluble than the intact form due to the stabilization of IDM on the surface of Mnt by hydrogen bonding. The molecular arrangement of poorly soluble IDM in the IDM-Mnt complex prevented the recrystallization of IDM itself, and the hydrophilic surface of the complex also resulted in an enhancement of dispersibility of the complex in aqueous solution. The solubility of IDM, therefore, stabilized on Mnt in an amorphous form, was greatly improved, and the transdermal efficacy of IDM was enhanced.

One example of a transdermal drug, salicylic acid (SA), was incorporated into natural bentonite for gradual drug release *via* the transdermal route (Bonina *et al.*, 2007). Note that the clay minerals were employed to stabilize the photo-unstable drug under ultraviolet radiation, increasing the drug solubility, and retarding the release rate. Using a Franz diffusion-cell method, the aqueous suspension of a model clay-drug hybrid was confirmed to suppress significantly the 'initial burst' release of SA and showed sustained drug-release kinetics. Although only 1.4% of the SA adsorbed by the bentonite had penetrated through the skin after 23 h, the sustained release behavior of the model hybrid systems could be suitable for real transdermal application.

In a US patent application by Jo *et al.* (2006), a newly designed transdermal formulation was disclosed. The clay-drug hybrid, piroxicam (PR), intercalated at a molecular level in the interlayer space of the clay mineral, was mixed with an adhesive polymer and adsorption enhancer. In this transdermal patch system, the solubility and physicochemical stability, as well as the dispersibility of the PR, were greatly enhanced by combining with magnesium aluminum silicate (MAS), which consequently prevented recrystallization of the drug. For stability test, the patches containing MAS-PR hybrid were stored under accelerating conditions at 40ºC and 75% relative humidity in a light-blocked state. The permeability of PR in the patches was maintained in stable fashion without recrystallization even after 6 months of the storage. In addition, the permeability of PR in the patches was enhanced by a factor of two or more in comparison with that of commercially available Trast™ patches, even though the clay-drug hybrid patch contained only half of the amount of PR. The clay-drug hybrid materials are expected to be more prominent in terms of TDDS because they could not only overcome various intrinsic demerits of intact drugs, but could also confer excellent skin permeability to drug molecules.

To control the chemical stability and release behavior of drug molecules, a similar approach was carried out by changing the pH of the synthetic medium (Pongjanyakul *et al.*, 2009). Depending on the pH value, some drugs can be in a cationic, anionic, or neutral form. In the case of the protonated cationic drug, ion exchange can occur with negatively charged clay minerals. For example, nicotine (NCT), a volatile and alkaline liquid used widely in smoking-cessation therapy and which possesses two pk_a values (pk_{a1} = 3.04 and pk_{a2} = 7.84), results in differently charged NCT under different pH conditions. When the protonated NCT was incorporated into MAS, a mixture of Mnt and saponite (Sap), under acidic (pH 4) and neutral (pH 7) conditions, NCT encased in NCT-MAS hybrid became thermodynamically more stable than the intact form of NCT, giving rise to a reduction in evaporation. Differential scanning calorimetry (DSC) analysis showed that a broad endothermic peak for the evaporation of NCT was shifted from 147ºC to 215ºC after intercalation of NCT into MAS. In addition, a broad exothermic peak at ~300ºC was observed in the MAS-NCT hybrid due to a decomposition of intercalated NCT, which was not

observed in the DSC thermogram of intact NCT. In addition, NCT molecules stabilized in MAS were released biphasically, in which an 'initial burst' release occurred, followed by a slow release; the release profile was well fitted to both the particle diffusion-controlled model and Higuchi's model (Singhvi and Singh, 2011). Specifically, while 54% NCT was released rapidly from a physical mixture of NCT and MAS within 2 min, the release of NCT from MAS-NCT hybrid was reduced significantly to 36%. The $T_{60\%}$ (time to reach 60% NCT release) value of NCT release from the MAS-NCT hybrid was eight times greater than that of the physical mixture. The MAS-NCT hybrid may be a good model case for transdermal drug delivery due to its enhanced thermal stability and sustained release behavior.

A new TDDS, by Shaikh *et al.* (2007), suggested incorporating organomodified clay (OC) hybrids into polydimethyl siloxane (PDMS) to attain OC-based pressure sensitive adhesive (PSA) formulations (OC-PDMS). The hydrophobic surface property of organo-modified clay minerals can facilitate the formation of clay-polymer composites and eventually improve mechanical properties such as the shear strength of the polymer composites. Moreover, the hydrophilic surface property of PDMS adhesives, terminated with −OH groups, could result in strong hydrogen bonding with the clay platelets, giving rise to an enhanced dispersion in an aqueous matrix. Based on the strategy above, an optimized level of OC additives to the polymer matrix for a transdermal PSA formulation was found by Shaikh *et al.* (2007) to realize controlled drug-release kinetics, enhanced adhesive properties, and reinforced shear strength. By adding 2% and 5% of OC, the 'initial burst' of drug release was suppressed reasonably well, and as a consequence, the total drug release decreased by ~50 and 75% after 10 days, respectively. This was surely due to the fact that the clay platelets were well dispersed in the PSA composites, resulting in controlled release of drug molecules. In addition, measurement of the shear adhesion failure temperature (SAFT) and shear strength presented significant improvements in the adhesion properties of OC-PDMS composites. The SAFT (21%) and shear strength (265%) were determined to be enhanced for the 1% OC-loaded PSA composite due to the reinforcement effect of homogeneously dispersed clay minerals. Such OC-PSA formulations would be applicable for TDDS, because they could not only provide a steady and extended penetration of the drug in blood, leading to the minimization of the adverse side effects such as toxicity, but also improve adhesive property and mechanical strength.

To sum up, clay minerals play important roles not only as pharmaceutical ingredients for improving the adhesion and mechanical properties of the TDDS formulations, but also as transdermal drug delivery carriers for enhancing solubility, physicochemical stability, and dispersibility of drug molecules. Due to the combination of drug molecules with clay minerals, clay-drug hybrids provide a steady and prolonged penetration of drug molecules through the skin with their controlled-release properties, resulting in improved drug efficacy and minimized side effects of drugs. Clay-drug hybrids could be suggested, therefore, as promising TDDS for improving drug bioavailability.

Local administration

Many attempts have been made in recent decades (Hubbell, 1996; Khang *et al.*, 2003; Krisanapiboon *et al.*, 2006; Noel *et al.*, 2008; Bhattarai *et al.*, 2010) to develop local drug delivery systems (LDDS). This concept was examined mainly in order to deliver therapeutic agents directly to the desired target organs and/or cells, to decrease concomitant secondary systemic complications, and to simultaneously increase drug efficacy compared to use of the other routes of DDS (Tsourvakas, 2012). Clay-drug hybrids have been suggested as promising candidates for LDDS, not only for the reasons mentioned above but also due to featured advantages such as maintained effective concentrations of drugs for healing and minimized systemic side effects. All of the positive points of clay-drug hybrid formulations were conferred by the sustained drug-release property in that they could reduce the frequency of drug administration for patient compliance. Dosage forms with clay minerals for local administration include film and tablet for buccal drug delivery, local injection for periodontal treatment, bone cement, film or implant devices for ocular drug delivery, vaginal ring, and stent.

Lidocaine (LDC) has been used widely as a local anesthetic due to its low toxicity and relatively high potency, but the remedial effect of LDC lasts no more than 30 min (Görner *et al.*, 1999; Padula *et al.*, 2003). In order to prolong the medicinal effect of LDC, it was intercalated into the interlayer space of Mnt by means of an ion-exchange reaction under an acidic pH (5−6) (Abdel-Mohsen *et al.*, 2001). The pH was an important factor in influencing intercalative ion-exchange reactions between LDC and Mnt because the number of ionic species of LDC changed under different pH values. The optimized LDC-Mnt hybrid provided long-lasting local anesthetic activity of the LDC with sustained-release kinetics.

The NCT-absorbed sodium alginate-magnesium aluminum silicate (SA-MAS)-based film was suggested by Pongjanyakul and Suksri (2009) to have significant potential for use as a buccal delivery system. The SA-MAS films were prepared for loading large amounts of NCT and achieving a sustained permeation rate, as compared to native SA film. At acidic and neutral pH, the protonated NCT molecules could be strongly bound with the negatively charged film through electrostatic interaction. The incorporation of MAS, a mixture of Mnt and Sap, into the SA films at pH 10 increased the NCT content in the film from 4.5 to 6.9% (w/w) and decreased

the NCT permeation rate from 5.61 ± 1.17 to 1.64 ± 0.33% cm^{-2} $min^{-0.5}$, compared to those of the SA film. The NCT-loaded SA-MAS films fabricated at pH 5 and pH 7 showed greater loading of NCT (10.5% and 8.4%, respectively) and smaller permeation rates (1.23 and 1.45% cm^{-2} $min^{-0.5}$, respectively) than those of NCT-loaded SA-MAS film prepared at pH 10. On the other hand, the detachment force of all NCT-loaded SA-MAS films was reduced significantly regardless of the preparation pH, compared to that of the SA film. The interaction between the MAS and hydroxyl and/or carboxyl groups of SA resulted in low water uptake and swelling of the composite films and decreased mobility and flexibility of SA molecules, which eventually reduced physical entanglements of SA and mucus. Although the NCT-loaded SA-MAS film showed a weaker bioadhesive property than the NCT-loaded SA film, the clay mineral-loaded film was still bioadhesive enough for adhesion on the mucosal membrane. Given these results, the buccal drug delivery formulation with clay minerals could be expected to suppress the intrinsic volatility of NCT and enhance bioavailability of NCT when applied to mucosal membranes.

One of the most interesting biomedical applications for clay-drug hybrids would probably be as an implant material with a drug-delivery function. Such an implant material could deliver active ingredients to specific organs, such as teeth, bone, subcutaneous fat, eye, vagina, and blood vessel. A local drug-delivery formulation was envisioned by Kelly *et al.* (2004) for periodontal disease using two components. The chitosan-tetracycline-halloysite hybrid prepared was formulated with thermo-responsive polymer (poloxamer 407), tissue adhesives (polyethylene glycol (PEG) and octyl cyanoacrylate (OCA)), and water for further improvement of retention in the gingival and periodontal pocket, defined as the presence of an abnormal depth of the gingival sulcus at which the gingival tissue contacts the tooth. The optimized formulation (Poloxamer 407 20% (w/w), PEG 20,000 0.5% (w/w), OCA 1% (w/w), and 200 mg/mL chitosan-tetracycline-halloysite hybrid) was determined after careful denaturalization tests of the syringeability to facilitate ease of administration to the periodontal pocket, as well as the thermal stability to maintain a high storage modulus upon achieving body temperature. This formulation was very stable *in vitro* for at least 9 months at room temperature (20ºC) with no changes in syringeability (45.53 N) or gelling temperature (24.9ºC). Preliminary *in vivo* tests using a wound pocket creation model in dogs were carried out to estimate the amount of drug release and the retentive ability of the formulation. The drug was found to be delivered easily to the target site at a locally effective level (average drug concentration = 21.24 μg/100 mg) and retained in the pocket for up to 6 weeks.

In order to treat chronic inflammatory diseases, clay-drug hybrid-based polyurethane (PU) implants have been developed (Da Silva *et al.*, 2009; Pinto *et al.*, 2011). Biodegradable PU has been investigated extensively due to its great biocompatibility, chemical versatility, and superior mechanical properties. Da Silva *et al.* (2009) incorporated 5 wt.% of Mnt into aqueous polyurethane dispersions (PUD) in order to control the biodegradability of PUD and the release rate of the drug incorporated. Disc-type implantable devices, 1 mm thick and 4.5 mm in diameter, were fabricated successfully by casting PUD composites containing dexamethasone acetate (ACT) and Mnt, and then implanted into the subcutaneous fat on the back of mice to examine *in vivo* drug release rate and biocompatibility. Prior to *in vivo* evaluations, *in vitro* degradation of PUD and PUD-Mnt composite and *in vitro* release profiles of ACT from ACT-loaded PUD and PUD-Mnt composite were analyzed. The increased mass loss of PUD-Mnt composite was associated with its greater hydrophilicity than PUD because of the clay mineral incorporated. Hydrophilic Mnt effectively allowed the penetration and diffusion of water in the polymer chains, which increased the hydrolysis rate of the ester bonds in PCL segments in the PUD composite. *In vitro* drug-release tests showed that ~18% and 29% of ACT were released during the first 10 weeks by PUD and the PUD-Mnt composite, respectively, by a diffusion process through pre-existent channels and pores. Then, their release rates were enhanced significantly by hydrolytic degradation of the PUD and PUD-Mnt composites between the 10^{th} and 20^{th} weeks of the dissolution test. In the final stage of release, a slower release rate of ACT was observed for both PUD and PUD-Mnt composites as a consequence of reduced drug concentrations in the implantable discs. Given those positive results, the incorporation of the clay mineral appears to be advantageous in terms of achieving controlled long-term drug delivery with implantable devices. Moreover, any mild inflammatory response observed in the tissues adjacent to the implants in the initial state was resolved completely within a 2-week period. The extent of neutrophil accumulation, assessed by myeloperoxidase (MPO) activity, decreased substantially during the first week of the implantation period, which indicated that the inflammatory response was resolved quickly. The PU implants fabricated with the clay-drug hybrid thus seemed feasible as local drug delivery devices for the treatment of chronic inflammatory diseases.

As an extension of advanced clay-drug-polymer composites for implant devices, Da Silva *et al.* (2011) investigated ocular implants for posterior segment ocular disease, such as uveitis, inflammation of the uvea. This kind of disease cannot be cured easily by means of topical eye drops or oral drug medication because the administration of such medications does not allow effective penetration of the drugs through the natural barriers of the body. An attempt was made to immobilize dexamethasone acetate, a type of corticoid used for the treatment of uveitis, into biodegradable PU composites

containing clay minerals, which were obtained by delaminating Mnt within a PU aqueous dispersion. The Mnt was employed to adjust the mechanical properties of PU to match the ocular soft tissues. The elastic modulus of intact PU was improved by a factor of ~10 by the addition of Mnt, which could not be achieved easily by simply changing the ratio between the soft and hard segments of PU. In addition, well distributed Mnt in the PU composites played an important role as a reservoir and transporter of the therapeutic ingredient at the desired site, which may contribute greatly to overcoming the low permeability of the drug. Thus, the drug was released constantly from PU-containing Mnt for 371 days by diffusion, together with the degradation mechanism of PU. Finally, to evaluate *in vitro* cytotoxicity of the composites, human retinal pigment epithelial cells were cultured directly with PU and PU-Mnt implants for 7 days. Then, MTT (3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide) tetrazolium assay was conducted for assessing cell metabolic activity. The cellular oxidoreductase enzymes of viable cells are able to reduce or convert MTT to a purple-

Table 2. Biomedical applications with clay mineral-based hybrids.

Layer type	— Clay mineral — Group	Octahedral character (species)	Route of administration	Dosage form	Reference
1:1	Serpentine-Kaolin	Dioctahedral (Kaolinite, halloysite)	Oral	Solid (tablets, capsule, powder) Liquid (suspension, emulsion)	Albert *et al.* (1978), Alestig *et al.* (1979), Carretero (2002)
			Topical	Film and patches	Sablotsky and Gentile (1994), Carretero (2002)
			Local	Power and polymer mixtures	Carretero (2002), Vergaro *et al.* (2010)
2:1	Talc-Pyrophyllite	Trioctahedral (Talc)	Oral	Solid (tablets, capsules, powders) Liquid (suspensions, emulsions)	Carretero (2002), Sohi *et al.* (2004), Viseras *et al.* (2010)
			Buccal Sublingual	Chewing gums and tablets	Raju *et al.* (2011), Jadhav *et al.* (2013)
			Topical	Creams, ointments, and powders	Gupte and Bogardus (1987), Carretero (2002), López-Galindo *et al.* (2007)
			Rectal	Suspensions, tablets	Jadhav *et al.* (2013)
	Smectite	Dioctahedral (Montmorillonite)	Oral	Solid (tablets, capsules, powders) Liquid (suspensions, emulsions)	Carretero (2002), Chang *et al.* (2007), Park *et al.* (2008)
			Topical	Creams, ointments, and powders	Ito *et al.* (2001), Carretero (2002)
			Transdermal	Films and patches	Abdel-Mohsen *et al.* (2001), Carretero (2002)
			Rectal	Suspensions, tablets	Classen *et al.* (2003), Suresh *et al.* (2010), de Sousa Rodrigues *et al.* (2013)
			Vaginal	Ointments, creams, gels	Sharifzadeh (2013)
		Trioctahedral (Saponite, Hectorite)	Oral	Solid (tablets, capsules powders) Liquid (suspensions, emulsions)	Carretero and Pozo (2010)
	Sepiolite-Palygorskite	Dioctahedral (Palygorskite) Trioctahedral (Sepiolite)	Oral	Solid (tablets, capsules, powders) Liquid (suspensions, emulsions)	Viseras and Lopez-Galindo (1999), Carretero and Pozo (2010)
			Topical	Emulsions, creams, lotions, suspensions	Galán (1996), López-Galindo and Viseras (2004), Carretero and Pozo (2010)
			Rectal	Suspensions, tablets	Viseras *et al.* (2010), Almeida (2013)
			Vaginal	Tablets, ointments, cream	Singer and Galán, (2011)

colored formazan, which is a marker of only the viable cells. The viability of the cells upon culturing with PU and PU-Mnt was confirmed to be 95.23 ± 6.41% and 96.24 ± 5.09, respectively, compared to the negative control. All experimental results indicated that the biocompatible dexamethasone acetate-loaded PU-Mnt composite could be applicable as a suitable substrate for ocular implant devices.

The synthesis and characterization of a hydrogel containing polyacrylamide/sodium carboxymethyl cellulose/Mnt nanocomposite was attempted by Sharifzadeh (2013) in order to fabricate a vaginal ring for LDDS. By adding sodium carboxymethyl cellulose to a hydrogel, the swelling behavior was improved gradually, but the mechanical strength was reduced. To resolve this defect, Mnt was added to the hydrogel for its rigid structure with optimum swelling property. With the aid of Mnt, extended drug release was achieved for ~15 days under simulated local conditions by reducing the 'initial burst' of the drug. This composite, containing clay minerals, may be a possible candidate for vaginal DDS.

Briefly, a clay-drug hybrid could be formulated in many different types of dosage forms for LDDS with the properties featured. At desired sites, the drug could be delivered directly by achieving an effective drug concentration for a long time and minimizing the systemic side effects of the drug which were accompanied by the sustained release property of the clay-drug hybrid. The locally administered clay-drug hybrid allows the user to reduce the frequency of medicine delivery and to increase patient compliance in this regard.

CHALLENGES AND FUTURE PERSPECTIVES OF CLAY-DRUG HYBIDS

Clay minerals as formulation additives and drug carriers have been applied by a variety of routes including oral, transdermal, and local administration (Table 2). Depending on the routes of administration of clay minerals for biomedical applications, clay minerals can be selected in order to control key parameters including size, swellability, CEC, SSA, mucoadhesiveness, dispersibility, and drug-release rate. In addition, the hybridization reaction of the drug with clay minerals, whatever the physical adsorption or intercalation, results not only in enhanced solubility and physicochemical stability of drug molecules, but also offers a controlled and sustained drug-release rate, and eventually achieves improved bioavailability due to efficient drug delivery. The advanced developments of clay-drug hybrid systems *via* various routes of administration will allow medication to be deployed to specifically targeted parts of the body (organs or cells). Although the field of clay-drug hybrid systems has experienced significant growth over the past decade, many challenges remain. From general prospects, clay-drug hybrid systems seemed to be very effective and to work well *in vitro*, but some fail in *in vivo* due to complications involved in real biological conditions. Also, toxicology studies are required to determine whether the clay-drug hybrid or polymer-clay-drug composites can be applied in clinical environments. The gene delivery and programed DDS, *i.e*. targetability and/or environmental stimuli responsiveness, with clay minerals are further challenges. Innovative design in terms of formulations with clay-drug hybrids advance clinical use and consequently open new drug-delivery markets. Finally, research on clay minerals will expand their applications in biomedical fields, such as regenerative tissue engineering, theranosis, personalized medicine, pharmaceutics, implants, *etc*.

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