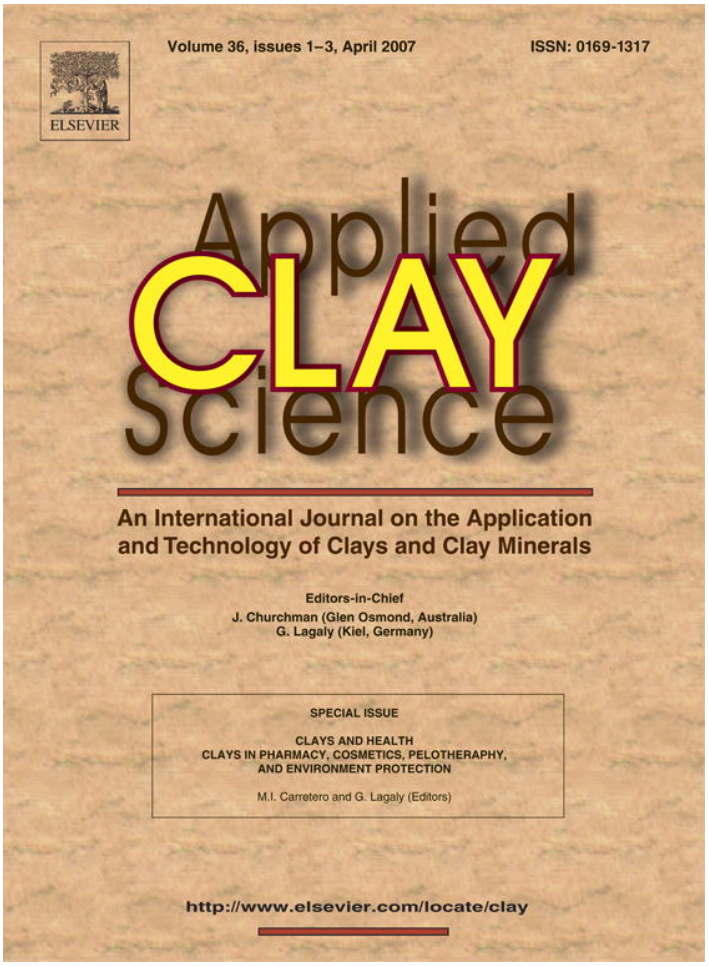

Available online at www.sciencedirect.com
ScienceDirect
Applied Clay Science 36 (2007) 122–132
Applied CLAY Science
www.elsevier.com/locate/clay

Clay minerals and layered double hydroxides for novel biological applications

Jin-Ho Choy *, Soo-Jin Choi, Jae-Min Oh, Taeun Park

Center for Intelligent Nano-Bio Materials, Division of Nanoscience and Department of Chemistry, Ewha Womans University, Seoul 120-750, Republic of Korea

Received 19 April 2006; received in revised form 6 May 2006; accepted 9 July 2006
Available online 13 October 2006

Abstract

This review is focused on the pharmaceutical and biological applications of clays, clay minerals and layered double hydroxides (LDHs). Novel nanohybrids of clay mineral-/ or LDH-biomaterials, including vitamins, drugs, and DNA strands are discussed for possible future developments in cosmetics, pharmaceutics, medicine as well as information storage.

Keywords: Biological applications; Biomaterials; Clay minerals; Layered double hydroxides (LDHs); DNA; Drugs; Inorganic–bio hybrid systems; Vitamins

1. Introduction

A great deal of attention has been focused on clay minerals since the earliest days of civilization due to their abundance in nature and unlimited potentials (Theng, 1974; Reichle, 1986; Cavani et al., 1991; Ogawa and Kuroda, 1995; Kim et al., 1998; Vaccari, 1998). In particular, the usage of clay minerals for curative and protective purpose is as old as mankind itself (Robertson, 1996; Carretero, 2002; Veniale et al., 2004). The local or generalized application of thermal muds called peloids has been done in terms of pelotherapy to recover rheumatism, arthritis, and bone-muscle traumatic damages (Ferrand and Yvon, 1991; Veniale et al., 2004). Medicinal clays have been widely used in medicine and properly administered clays can purify the blood, reduce or even eliminate infection, heal ulcers, and even rid the body of certain allergies (Gorchakov et al., 2001). Cutaneous chemotherapy based on clay minerals for the treatments of seborrhoeic skin as antimicrobial and antifungal agents has also been developed. Nowadays, the importance of cellular delivery of various drugs and bio-active molecules in medicine leads to advanced development in novel area of chemistry–biology–material sciences. Studies on both natural and synthetic clay minerals including layered double hydroxides (LDHs) for biological applications are extensively carried out. Among them, researches on novel nano-bio hybrids that combine efficient and safe transport carriers and biological molecules provide a new paradigm. Clay minerals possess excellent properties such as low or null toxicity, good biocompatibility, and promise for controlled release, thus give rise to the incessant interest to their development for biological purposes, for example, pharmaceutical, cosmetic, and even medical ones.

* Corresponding author. Tel.: +82 02 3277 4305; fax: +82 02 3277 4340.
E-mail address: jhchoy@ewha.ac.kr (J.-H. Choy).

0169-1317/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.clay.2006.07.007

2. Clay minerals

2.1. Pharmaceutical applications

The properties which make clay minerals useful in pharmaceutical applications are the high adsorption ability, high internal surface area, high cation exchange capacity, interlayer reactions, chemical inertness, and low or null toxicity (Gamiz et al., 1992; Bolger, 1995; Lin et al., 2002; Carretero, 2002). Smectites have been widely used as both active principle and excipient in pharmaceutical formulations (Cornejo et al., 1983; Ferrand and Yvon, 1991; Poensin et al., 2003). Sodium smectites can act by osmosis to encourage defecation as laxatives, and calcium smectites are used to eliminate the excess water in the feces as antidiarrhoeaics. In addition, smectites are applied as dermatological protectors to mechanically protect the skin against external physical or chemical substances. Smectites and bentonite are widely used in spas in mixed form with water due to their absorption/adsorption capacity, high cation exchange, plastic properties, and cooling index (Summa and Tateo, 1998; Cara et al., 2000; Poensin et al., 2003). The effects of clay minerals in spas are to treat dermatological disease and alleviate joint pain caused by sport traumatism and rheumatic inflammations. Moreover, they can acts as an anti-inflammatory agent. Clay minerals are used as excipients in pharmacological applications to improve the organoleptic properties, for example, taste, smell, and color, or the physical and chemical ones, and to facilitate and promote the pharmacological formulations. They are used as lubricants and agents to disperse easily and effectively active principles based on their ability to swell in the presence of water and to buffer abrupt change of acidity. Also, their colloidal properties make them useful as emulsifying, gelling and thickening agents to avoid the segregation of the components of the pharmaceutical formulations. Contrary to these traditional applications of clay minerals, novel attempts have recently been explored to develop new potentials as drug carrier, protecting matrix, release controlling agents, and chemical modifiers.

A new technology, hybridization of drugs with the clay minerals, has very recently received a great deal of intention for pharmacological applications of cationic clays. Traditional applications mainly rely on the inherent physical, rheological, and chemical properties of the clay (McGinity and Lach, 1977; Lin et al., 2002), whereas the inorganic and organic hybrids lead to interesting properties distinguished from those of each component in simple physical mixtures. Hybridization can offer the fascinating features such as protected delivery, controlled release, enhanced water solubility, increased dispersion ability, and the feasibility of target delivery (White and Hem, 1983; McCarter and Broussean, 1990; Castela-Papin et al., 1999; Ito et al., 2001; del Hugo et al., 2001).

A great number of studies on hybridization of drug and clay minerals have focused on preparation, modification, and characterization of surfactant-clay minerals to facilitate the advanced formulation of various drugs (Wilson, 1987; Ito et al., 2001; Lee and Fu, 2003). However, only a few studies have been done on direct complexation of drug with clay minerals. Ito et al. (2001) reported that the complexation of indomethacin, an anti-inflammatory and an analgesic agent, with smectite enhanced its penetration rate through skin and increased stability of amorphous indomethacin as well as water solubility. Lin et al. (2002) attempted to intercalate 5-fluorouracil, an effective chemotherapeutic agent for colorectal cancer, into montmorillonite to diminish its severe side effect through its release *in situ*. Lee and Fu (2003) also found that release properties of drug could be controlled by their loading into nanocomposites of *N*-isopropylacryamide and montmorillonite. Release property of loaded drug could be controlled by handling electrostatic interaction between the drug molecules and clay layers. Electrostatic attraction decreases the release ratio, while electrostatic repulsion increases the release ratio. In our laboratory, poor water soluble itraconazole, an antifungal agent, was hybridized with smectites, which led to remarkable improvement of water solubility and bioavailability of the drug (Fig. 1). The molecular arrangement of itraconazole within the interlayer space prevents the recrystallization of itraconazole molecules and the hydrophilic surface of drug–clay nanocomposites enhanced the water-dispersibility of drug composites, therefore water solubility of drug greatly improved. Furthermore, additional coating with polymers like hydroxypropylmethyl cellulose (HPMC) or hydroxypropyl cellulose (HPC) adjusts the electrostatic interaction between drug and clay, thus control the release property.

2.2. Cosmetic applications and aesthetic medicines

Clay minerals have been widely employed as thickeners and emulsion stabilizers in cosmetics (Elmore, 2003; Ray and Okamoto, 2003). They are also used as active principles in cosmetics because of their high adsorptive capacity of substances such as greases, toxins, etc. They can be applied as antiperspirants to give the skin opacity, remove shine and cover blemishes. For

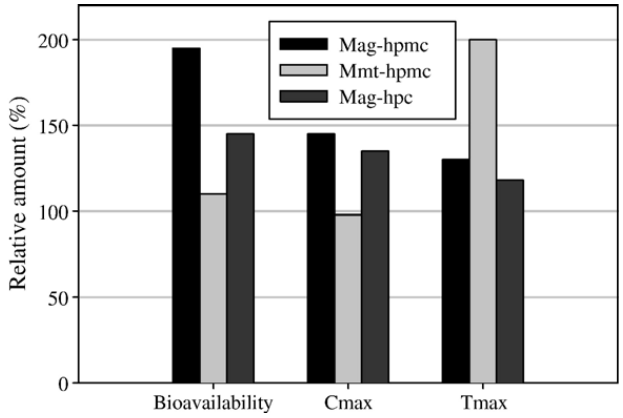

Fig. 1. Effect of clay minerals on pharmacokinetic parameters of itraconazole after oral administration. After magnabrite (Mag) or Montmorillonite(Mmt) was reacted with itraconazole (Itra) at a mass ratio 0.7/0.3, the resulted solid was coated with either HPMC or HPC at a solid/polymer mass 0.7/ 0.3. The parameters were compared with those of commercial Sporanox (maximum blood concentration (Cmax) : 223 μg/L; time to reach Cmax (Tmax) : 1.8 h).

the purpose of aesthetic medicine in cosmetic products, geotherapy, pelotherapy, and paramuds, the cationic clays are also used as active principles or excipients. For example, the geotherapy is mainly used for facial treatments to treat dermatological problems such as blackhead, spots, acne, seborrhea, etc. and to promote perspiration and sebaceous secretions. Paramuds are used to moisturize the skin and act as anti-inflammatory. These applications are mainly based on high cation exchange capacity, excellent swelling property, remarkable hydration ability, and structural plasticity of the cationic clays.

2.3. Agricultural and environmental applications

Attempts to incorporate clay minerals in animal feeds have been carried out for multiple purposes. They act as an anti-caking and palletizing aid in no medicated feeds and as a consolidating additive of feces (Ferrario et al., 2000). They are also used as an adsorbent of gastrointestinal gases and toxins involved in human and animal disease including mycotoxins, aflatoxins, and cyanobacterial hepatoxins (Abdel-Wahhab et al., 1998; Ferrario et al., 2000; Huwig et al., 2001). Increasing attention has been given to detoxication of various toxins by smectites. Inactivation of viruses and bacteria by adsorption has also been attempted, suggesting unlimited potential of clay minerals in prevention of virus infection as well as bacterial contamination (Mayura et al., 1998; Clark et al., 1998; Vacca et al., 2005; Zou et al., 2006).

Serious environmental problems arise from the use of pesticides. Application of clays and clay minerals in pesticide formulations is currently attracting considerable interest (Armstrong et al., 2000; Brown et al., 2001; Maxwell et al., 2002; Hocine et al., 2004; Sanchez-Martin et al., 2006). To increase pesticide efficiency and to reduce their leaching into the environment like air and water, it has been suggested that reversible binding of the pesticide on clay minerals would be one of the feasible solutions. Many studies have been focused on adsorption of pesticides by clay minerals for their removal from water and immobilization in soils. Slow-release formulations were prepared with organo-clays, e. g. benzyl trimethylammonium bentonites increased the adsorption of alachlor and metolachlor (El-Nahhal et al., 1988, 1999; Carrizosa et al., 2000). (see also Zadaka et al., 2007-this issue; Rytwo et al., 2007-this issue).

Clays can be also used to effectively protect unstable pesticides against volatilization and photodegradation that lead to increasing frequency and dose of herbicide treatment.

3. Layered double hydroxides (LDHs)

LDHs have a wide range of chemical compositions and their layer structure exhibits a variety of stacking faults to generate many different polytypes. They exhibit various particle sizes according to the synthetic route while the surface area values are generally lower than 100 $m^2\ g^{-1}$. They also possess higher layer charge densities (2–5 meq/g), which results in strong electrostatic forces between the brucite-type sheets and the anions, thus swelling is more difficult than for clay minerals. LDHs particularly prefer multivalent anions within their interlayer space due to strong electrostatic interaction and therefore LDHs bearing monovalent anions like nitrate or chloride ions are good precursors for exchange reactions (Miyata, 1983; Yamaoka et al., 1989). The solubility of LDHs as hydroxides is highly pH-dependent (Bish, 1980). LDHs are widely applicable not only to develop various supramolecular structures and heterogeneous hybrid systems, but also to stabilize and protect biomolecules.

3.1. Pharmaceutical applications

Pharmaceutical applications of LDHs mainly rely on acid buffering effect and anion exchange property. Hydrotalcite-derived antacidic and antipeptic formulations are representative of their applications in pharcameutics. Synthetic hyrotalcite was suggested to have barrier properties similar to those of gastric mucous, and to afford mucosal protection by its ability to maintain or mimic the barrier properties of gastric mucous gel.

Hydrotalcite has also found pharmaceutical applications as an ingredient in sustained-release pharmaceuticals containing nifedipine, for stabilizing pharmaceutical composition, and for preparing aluminum magnesium salts of antipyretic, analgesic and anti-inflammatory drugs. Unfortunately, LDHs are not widely employed in pharmaceutics contrary to natural clay minerals. However, recent advance in hybridization technique and increasing interest on interdisciplinary researches have brought out a strong increase in the attention to their pharmaceutical potentials.

LDHs can intercalate many important biomolecules with negative charge such as oligomers, single or double stranded DNA, and simple molecules like nucleotides (Choy et al., 1997, 1999, 2000, 2001). Especially, the single or double stranded DNAs have a great deal of application potentials in various fields, expanding from gene therapy to biosensing and even high density information storage. However, DNA strands are very susceptible to degradation and denaturation occurring during manufacture processes and storage. Pioneering works have been carried out by Choy et al. (1999) They clearly demonstrated that biomolecules such as CMP, AMP, GMP and even DNA are bound by LDHs by anion exchange, yielding heterostructured nanohybrids (Fig. 2). The intercalated DNA was safely protected against harsh condition including strong alkaline, weak acidic environments, and DNase attack. It could be also recovered very easily by exposing DNA–LDH hybrids to an acidic condition due to the solubility of LDHs in acid, implying promising potential of LDHs in biological applications.

Choy et al. (2000) also developed LDHs as nonviral vectors for delivery of antisense oligonucleotides. The antisense of *myc* cancer gene was intercalated into LDH and transferred into HL-60 cells, the human promyelocytic leukemia cell line. The *myc* gene encodes a transcription factor, which plays a prominent role in a variety of commonly occurring human cancers. The effect of As-*myc*-LDH hybrid on the growth of HL-60

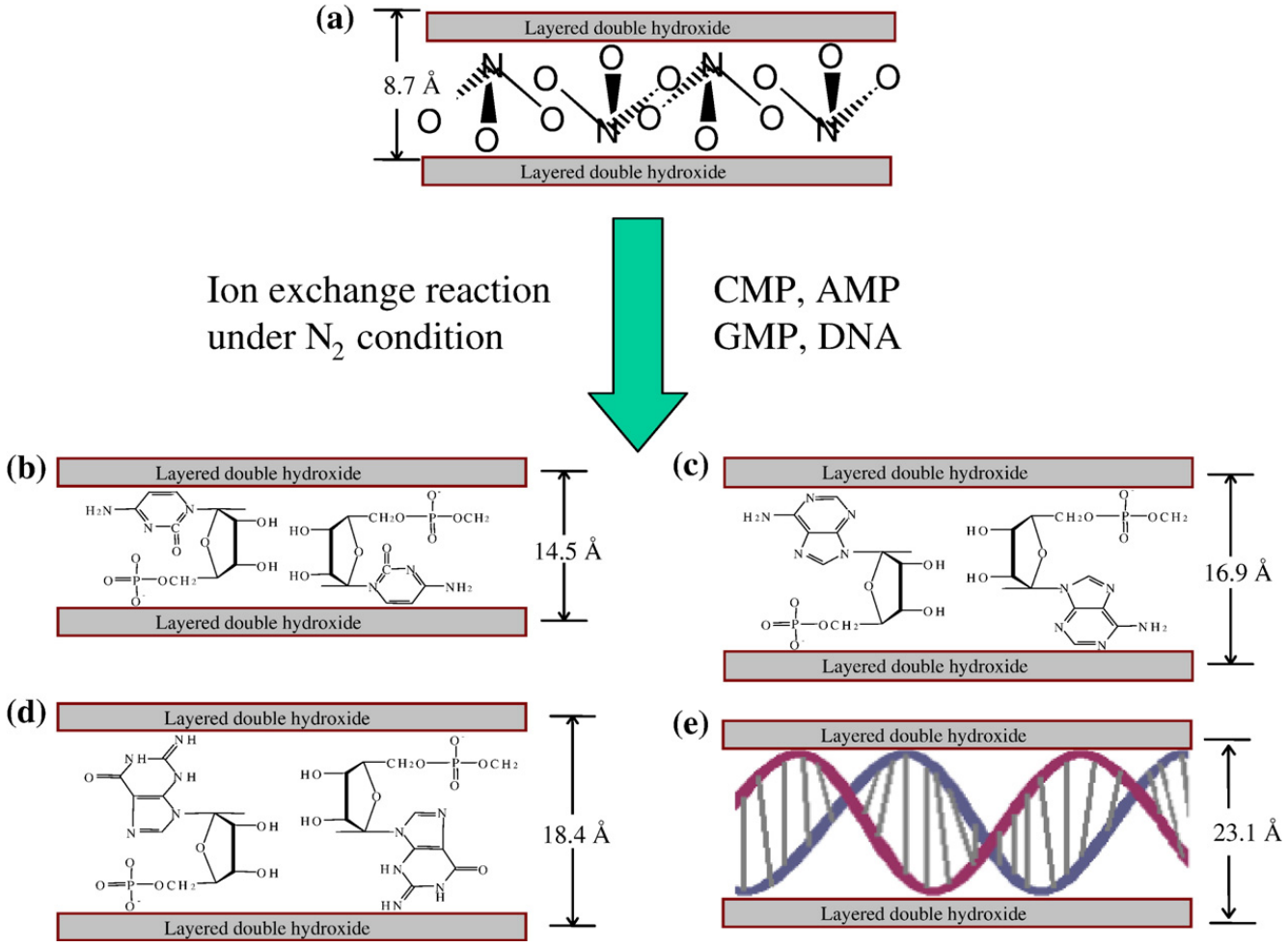

Fig. 2. Various biomolecule–LDH hybrids obtained by intercalation reaction (a) the pristine MgAl–LDH, (b) CMP–LDH hybrid, (c) AMP–LDH hybrid, (d) GMP–LDH hybrid, and (e) DNA–LDH hybrid.

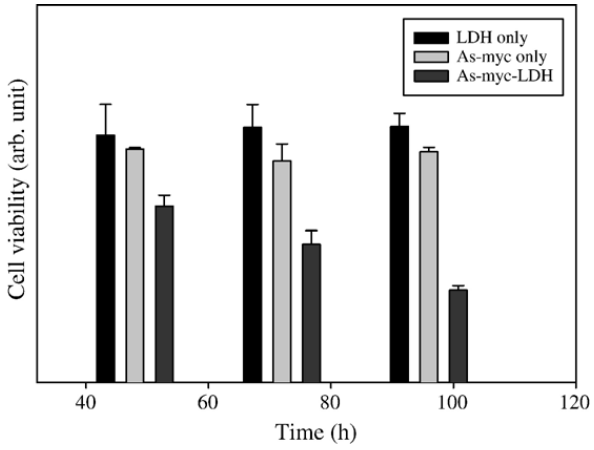

Fig. 3. Cell viability test for HL-60 cells treated with 20 uM of LDH, As-*myc*, and As-*myc*-LDH with respect to given incubation time.

cells was considerably higher than that of As-*myc* only (about 65% of inhibition versus 88% after 4 days) in a time dependent manner. It is worth to note that LDH itself did not affect cell growth, suggesting its good biocompatibility. It is, therefore, concluded that the suppression effect of cancer cell growth only results from As-*myc*-LDH (Fig. 3).

The molecules intercalated into LDHs can be easily released by carbonate ions, which possess extremely high affinity with the LDH layers. Furthermore, LDH can be prepared from biocompatible compositions with arbitrarily tailored physical and chemical properties, which is a great advantage distinguished over other inorganic matrices and clay minerals. LDHs are also completely decomposed by acidic body fluids. A schematic illustration is shown in Fig. 4.

Application of DNA–LDH hybrids for information storage was proposed by Choy et al. (2004a). It has been suggested that the genetic code system using the base units of DNA strand could overcome low creditability and confidentiality, which are the main problems of the current coding system. Furthermore, a large amount of information can be incorporated into a short DNA without any concern about forgery. However, the development of a genetic code system was retarded due to the inherent problems of naked DNA strands, including instability, flocculation property, and difficult recovery. Engineered double stranded DNA coding genetic information was intercalated into LDHs as a practical genetic molecular code system. This system consists of four distinct procedures: encoding, encrypting, decrypting, and decoding (Fig. 5).

At first, in the encoding step, double stranded DNA with 100 base pairs was engineered to contain primer–buffer–code–buffer–primer parts. Since the primer part is essential to amplify DNA, its sequence ensures the security of the molecular code. The confidential code part is intentionally inserted between the additional buffer parts to reinforce security. The code part is

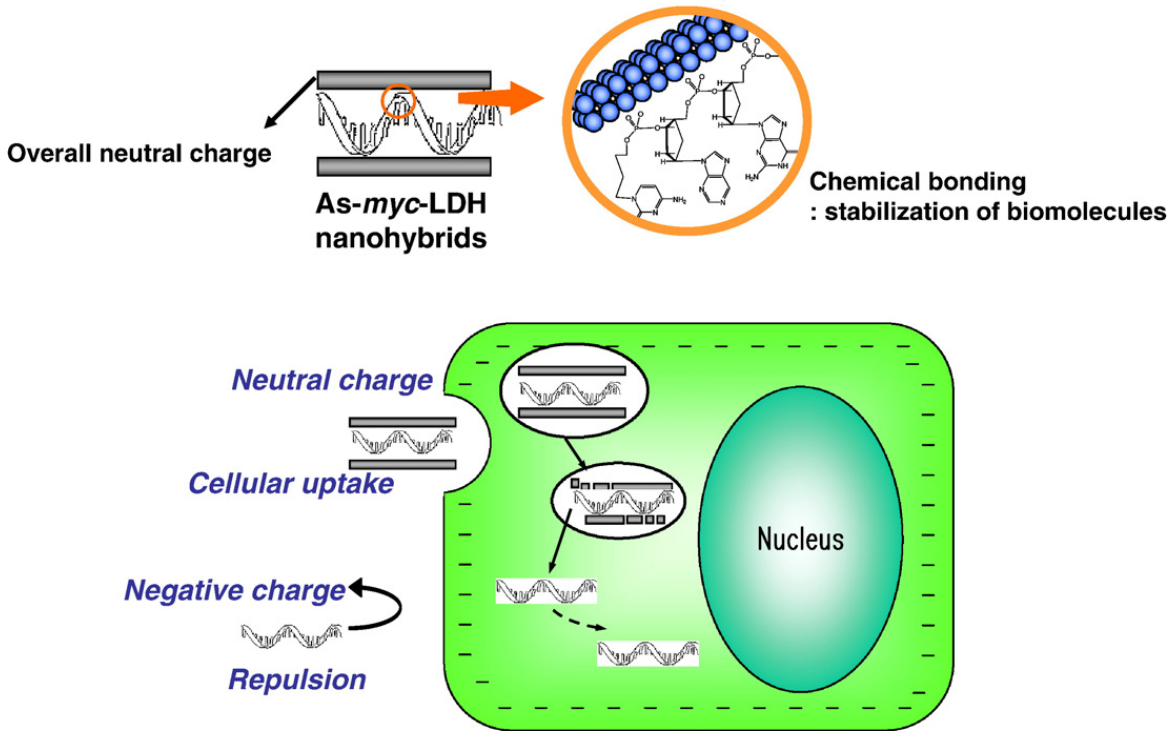

Fig. 4. Schematic diagram for cellular uptake of As-*myc*-LDH nanohybrids compared to that of As-*myc* only.

located in the center and each of the three base pairs could be assigned to one alphabet character as shown in the Table inserted in Fig. 5, which could be standardized by a global criterion. In the second encrypting step, the DNA strands were intercalated into LDHs by anion exchange. In the third decrypting step, the DNA–LDH nanohybrid was collected and simply acidified to pH=2. The acidified solution was then treated with the polypyrrole coated maghemite (PPY-MAG) nanohybrid to separate DNA molecules by the strong interaction between PPY and DNA strands, and finally DNA containing PPY-MG nanohybrids were gathered through magnetic decantation. In the final decoding step, PPY-MAG nanohybrid retaining the retrieved DNA strands was directly subjected to PCR amplification. It should be noted that the data stored in DNA strands are very compact, unique, and uncopyable. Genetic and biological information can be almost permanently conserved in this DNA barcode system. Therefore, this system provides a new concept of molecular and genetic information storage with high security and confidentiality and opens novel perspectives in future-oriented data storages. However, it still remains to elucidate if the DNA molecules can be easily recovered from DNA–LDH hybrid and to shorten decoding time for practical use of this DNA barcode system.

These fascinating results have evolved into the advanced concepts of LDHs for pharmaceutical application, inorganic drug delivery vector system. Recently, Choy et al. (2004b) reported a successful application of anticancer drug methotrexate (MTX)-LDH hybrid in cancer treatment *in vitro*. They demonstrated that the cell proliferation of the osteosarcoma cell culture line, Saos-2, is more strongly suppressed by treatment with a MTX–LDH hybrid, showing higher DNA damage than for MTX only. It is noted here that LDH does not exert any appreciable toxic effects on both normal and cancer cells. In addition to the evaluation of no cytotoxicity of LDHs *in vitro*, Kwak et al. (2004) and Kriven et al. (2004) further evaluated the safety of LDH for adult male Sparague Dawley rats *in vivo*, and found that LDHs, when vein-injected, have any significant effects on tissues and organs below a dose rate of 100 mg/kg by intravenous injection. Reversely, extravascular injected LDHs are locally irritating and

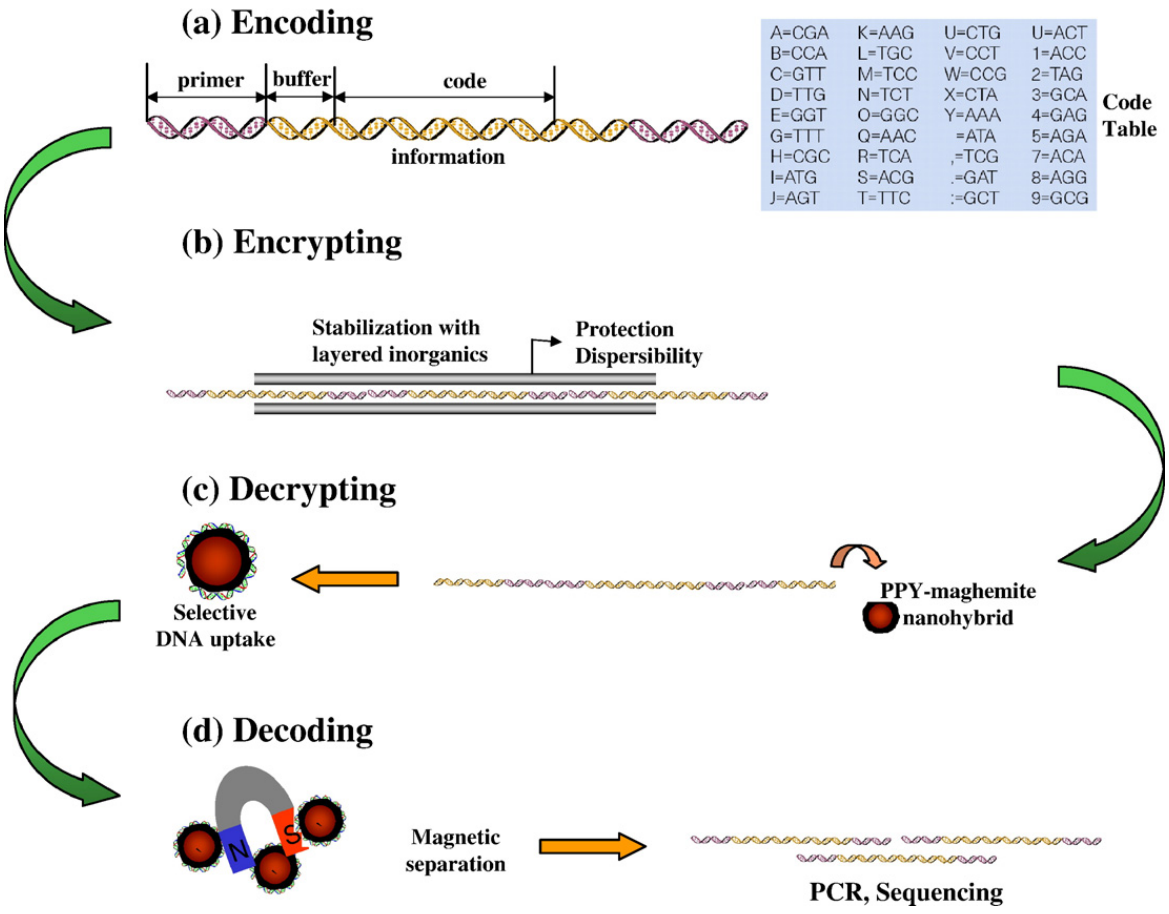

Fig. 5. Schematic illustration of genetic code system.

elicit an inflammatory response around the precipitated particles at a dose rate of more than 200 mg/kg. Quite recent research of Oh et al. (2006) on anticancer efficacy of MTX through MTX–LDH nanohybrid system *in vitro* clearly revealed that MTX–LDH shows the same drug efficacy to the MTX only in spite of the low concentration by about 5000 times in the two osteosarcoma cell lines, Saos-2 and MG-63, indicating such a high cancer suppression effect of MTX–LDH hybrid is surely due to the excellent delivery efficiency and controlled release of inorganic delivery vector, LDHs.

The pioneering works of Choy and coworker have led to a rapid increase in the research not only on various hybrid systems of LDHs with polymers and anions, but also pharmaceutical applications of LDHs (Khan et al., 2001; Ambrogi et al., 2001, 2003; Li et al., 2004; Desigaux et al., 2006). Khan et al. (2001) reported that several pharmaceutically active compounds such as diclofenac, gemfibrozil, ibuprofen, and naproxen, etc. could be reversibly intercalated into LDH for their storage and controlled release. Ambrogi et al. (2001) showed that the hybridization of LDH with anti-inflammatory drug ibuprofen exhibits a high anti-inflammatory activity in a controlled release manner and significantly enhances water solubility. Ambrogi et al. (2003) further focused on the hybridization of LDH with the nonsteroidal anti-inflammatory drugs including indomethacin, tiaprofenic acid, and ketoprofen. They suggested that the fast dissolution of LDHs in acidic medium could release intercalated drugs in ionic form, which lack of crystallinity, resulting in the enhancement of solubility. In fact, good water solubility plays a crucial role in drug bioavailability, especially in the case of poorly soluble drugs the water solubility is directly related with the efficient dose delivery and undesirable side effects. Li et al. (2004) also developed anti-inflammatory drug fenbufen–LDH hybrids and showed that these drug-inorganic hybrid materials can be used as an effective drug delivery system due to their controlled release capacity. Desigaux et al. (2006) recently found that a new self-assembly chemical approach can be used to synthesize new labile supramolecular complexes from the association of DNA molecules with LDHs. These degradable DNA–LDH hybrids were taken up by carcinoma HeLa cells. Choy et al. (unpublished data) also demonstrated that edible dyes such as Allura® Red AC ($C_{18}H_{14}N_2O_8S_2^{2-}$), Sunset Yellow FCF ($C_{16}H_{10}N_2O_7S_2^{2-}$), and Brilliant Blue FCF ($C_{37}H_{34}N_2O_9S_3^{2-}$), could be successfully intercalated into Zn–Al LDHs. The edible dyes intercalated into LDH layers exhibit significant enhancement in color development and higher thermal stability compared to their salt forms, suggesting such an organic–inorganic–polymer hybrid system can be applied to various industries. So far, the approach of hybridization with LDHs offers outstanding and fascinating advantages such as simplicity of the preparation, cost effectiveness, high dispersion property, safety, and efficient delivery.

However, current studies on LDHs for pharmaceutical applications still remain as simple intercalation and disintercalation of various drugs in LDHs, although the drugs to be intercalated are widely expanding from simple anionic forms to neutral and zwitterionic forms. Actually, there are very limited reports on activities and efficacy of the intercalated drugs *in vitro* as well as *in vivo*. More profound studies on their practical applications in pharmaceutics must be carried out to develop LDH as a next-generation drug carrier for a broad spectrum of drugs.

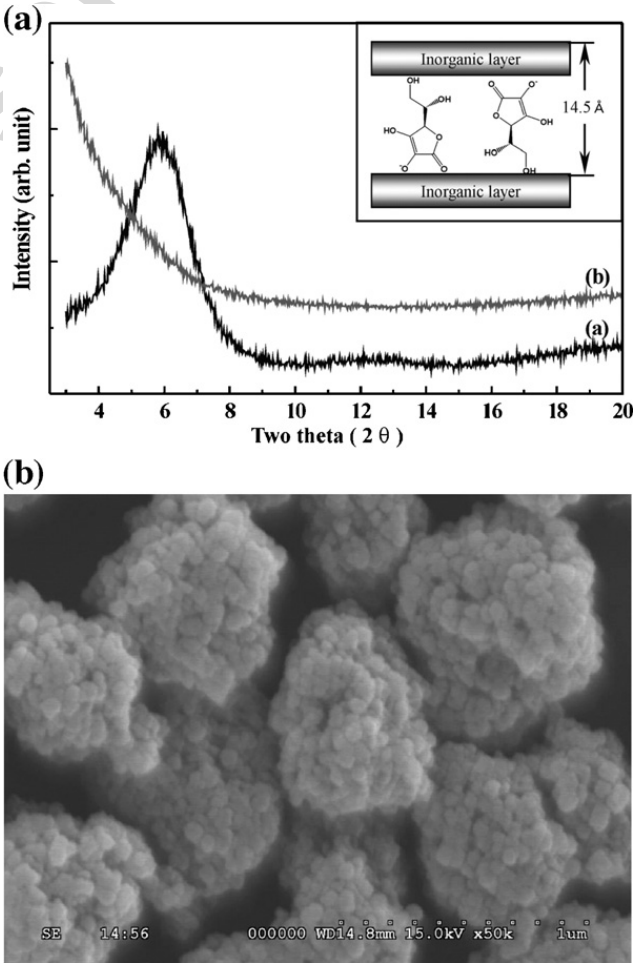

Fig. 6. (a) X-ray powder diffraction patterns of (a) vitamin C-zinc hydroxide hybrid and (b) the silica-coated hybrid. (b) Scanning electron micrograph of the silica-coated hybrid.

3.2. Cosmetic applications

LDHs possess many fascinating features to be also applied to cosmetics like high adsorption capacity, excellent anion exchange ability, and stabilizing potentials. For example, the high adsorption capacity can be used to remove skin exudates and to encapsulate skin sensitive coloring and UV-screening agents, while the anion exchange ability can be useful to protectively deliver active substances for anti-wrinkling and skin regenerating. LDHs stabilize unstable molecules such as retinoic acid, ascorbic acid, and tocopherol, etc. often used in cosmetics and can improve rheological properties of various formulations, especially emulsions. Even if the practical application of LDHs in cosmetics is not much developed, there are some studies to explore the potentials of LDHs for cosmetic purposes.

Hwang et al. (2001) and Yang et al. (2003) reported the intercalation of vitamins A, E, and C into LDHs and zinc basic salts by coprecipitation. The hybrid was then coated with a porous shell of silica to enhance the stability of intercalated vitamins and dispersion property of the hybrid nanoparticles. Fig. 6 shows the X-ray diffraction patterns of the vitamin C–zinc hydroxide hybrid during the first encapsulation process and modification by silica. The vitamin C–inorganic hybrid exhibited a layer character with the basal spacing of 14.5 Å, indicating an intercalate with a 1 : 1 layer sequence along the *c*-axis where vitamin C molecules were encapsulated by the inorganic layers as depicted in the inset.

The intercalated vitamin C was released out of inorganic lattice in high purity without any traces of decomposed species. Skin permeation test showed that the permeation patterns of free vitamin and intercalated vitamin are similar, suggesting the similar penetration mechanisms. Nevertheless, the encapsulated vitamin C by inorganic species showed higher penetration rate than the pure vitamin C. The proposed releasing and delivering mechanism of vitamin C in vitamin C–inorganic hybrid system is schematically represented in Fig. 7. The vitamin C–inorganic hybrid effectively absorbs the skin wastes, serums, and sweats discharged from human skin because of its well developed nanoporous structure. Actually, the present hybrid materials showed a large oil absorption capacity of more than 150%. The absorption of chemical species such as NaCl and fatty acids in sweat and skin wastes into nanopores of the hybrid gave rise to a release of vitamin C from the pore by exchange reaction between them, in such a way the vitamin C could be slowly diffused out from the inorganic shell and delivered into the epidermis in skin.

There are other reports dealing with LDHs for cosmetic applications. bin Hussein et al. (2002) intercalated naphthol blue black into Mg–Al–LDH, which may make its formulation more easy and broad. The attempt to encapsulate the organic human skin UV absorbents into Zn_2Al–LDHs was also reported using 4-hydroxy-3-methoxyenzoic acid, 4-hydroxy-3-methoxycinnamic acid, *p*-aminobenzoic acid, and urocanic acid, etc. (He et al., 2004; Perioli et al., 2006). This research revealed that the catalytic oxidation of the intercalated UV absorbents greatly decreased whereas the UV absorption ability was highly enhanced. The high potential of LDH in cosmetic applications leads to further and active exploitation in the near future.

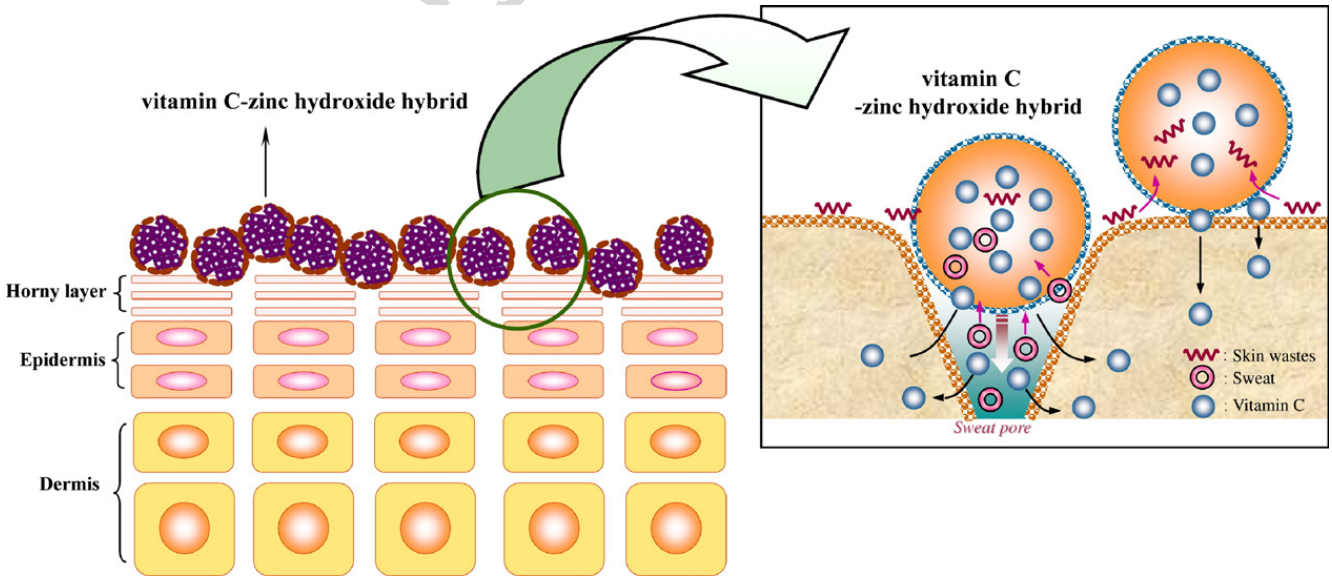

Fig. 7. The proposed releasing and delivering mechanism of vitamin C from the silica coated zinc hydroxide.

3.3. Agricultural and environmental applications

Agricultural applications of LDHs are rarely found contrary to clays. However, LDHs are one of the ideal candidates for a wide range of agricultural applications. Not only their framework could be decomposed into plant nutrients, but also their structure offers interesting features such as accommodation and controlled release of various active anionic agro-substances, high buffering capacity, high water retention ability, and acid neutralizing potential. The important reasons for the retarded development of LDHs in agriculture seem to be due to the fact that clays are naturally abundant and inexpensive so that the need of the development of LDHs for agricultural proposes was not high and urgent. Recently, as serious contamination of soils and water arises from various anionic compounds, and cultivated soils extensively develop acidic property, many attempts to remove anionic ions and pesticides by adsorption to LDHs have steadily increased. A few studies have been carried out to develop the potential of LDHs as plant nutrients, pesticides, growth regulators, and active principle in animal feeds (Olanrewaju et al., 2000; Lakraimi et al., 2000; bin Hussein et al., 2002).

Olanrewaju et al. (2000) synthesized nitrate-LDH at ambient condition without any considerable contamination by carbonate and suggested it as a potential slow-release fertilizer. The plant growth regulator, α-naphthalene acetate, was also intercalated through coprecipitation by bin Hussein et al. (2002) to explore the protected storage and controlled release in natural environments. More attention has been given to pesticide formulation that mainly consists of various organic solvents. Lakraimi et al. (2000) reported that 2,4-dichlorophenoxyacetate, a broad leaf herbicide, intercalated into ZnAl–LDH by ion exchange reaction showed a slow-release pattern. It is, therefore, expected that the application of LDHs in agriculture could be more extensively expanded in near future because their acid neutralizing potential and high anion adsorption capacity are urgently required to this field as a complement to clays.

4. Conclusions

The use of clays in various fields is well known and familiar to mankind, contributing to human health and life. In addition to their traditional applications, many types of clays, clay minerals but also LDHs have been recently applied to diverse commercial products as simple additive or adjuvants. Increasing attention has been recently given to advanced applications, in particular, based on new interdisciplinary fields developed for protective and controlled delivery of various functional compounds. The promising potential of clay minerals and LDHs offers novel perspectives for inorganic–biomaterial hybrids, and practical applications as new delivery systems are not so far.

Acknowledgements

This work was financially supported by the SRC program of MOST/KOSEF through the Center for Intelligent Nano-Bio Materials at Ewha Womans University (grant: R11-2005-008-00000-0).

References

Abdel-Wahhab, M.A., Nada, S.A., Farag, I.M., Abbas, N.F., Amra, H.A., 1998. Potential protective effect of HSCAS and bentonite against dietary aflatoxicosis in rat: with special reference to chromosomal aberrations. Nat. Toxins 6, 211–218.

Ambrogi, V., Fardella, G., Grandolini, G., Perioli, L., 2001. Intercalation compounds of hydrotalcite-like anionic clays with antiinflammatory agents - I. Intercalation and in vitro release of ibuprofen. Int. J. Pharm. 220, 23–32.

Ambrogi, V., Fardella, G., Grandolini, G., Nocchetti, M., Perioli, L., 2003. Effect of hydrotalcite-like compounds on the aqueous solubility of some poorly water-soluble drugs. J. Pharm. Sci. 92, 1407–1418.

Armstrong, A., Aden, K., Amraoui, N., Diekkruger, B., Jarvis, N., Mouvet, C., Nicholls, P., Wittwer, C., 2000. Comparison of the performance of pesticide-leaching models on a cracking clay soil: results using the Brimstone Farm dataset. Agric. Water Manag. 44, 85–104.

bin Hussein, M.Z., Zainal, Z., Yahaya, A.H., Foo, D.W.V., 2002. Controlled release of a plant growth regulator, alpha-naphthaleneacetate from the lamella of Zn–Al-layered double hydroxide nanocomposite. J. Control. Release 82, 417–427.

Bish, D.L., 1980. Anion exchange in takovite: application to other hydroxide minerals. Bull. Mineral. 103, 170–175.

Bolger, R., 1995. Industrial minerals in pharmaceuticals. Ind. Min. 52–63 (August).

Brown, C.D., Fryer, C.J., Walker, A., 2001. Influence of topsoil tilth and soil moisture status on losses of pesticide to drains from a heavy clay soil. Pest Manag. Sci. 57, 1127–1134.

Cavani, F., Trifiro, F., Vaccari, A., 1991. Hydrotalcite-type anionic clays: Preparation, properties and applications. Catal. Today 11, 173–301.

Cara, S., Carcangiu, G., Padalino, G., Palomba, M., Tamanini, M., 2000. The bentonites in pelotherapy: thermal properties of clays pastes from Sardinia (Italy). Appl. Clay Sci. 16, 125–132.

Carretero, M.I., 2002. Clay minerals and their beneficial effects upon human health. A review. Appl. Clay Sci. 21, 155–163.

Carrizosa, M.J., Calderón, M.J., Hermosín, M.C., Cornejo, J., 2000. Organosmectites as sorbent and carrier of the herbicide bentazone. J. Cornejo Sci. Total Environ. 247, 285–293.

Castela-Papin, N., Cai, S., Vatier, J., Keller, F., Souleau, C.H., Farinotti, R., 1999. Drug interaction with diosmectite: a study using the artificial stomach–duodenum model. Int. J. Pharm. 182, 111–119.

Choy, J.H., Kwak, S.Y., Han, Y.S., Kim, B.K., 1997. New organo-montmorillonite complexes with hydrophobic and hydrophilic functions. Mater. Lett. 33, 143–147.

Choy, J.H., Kwak, S.Y., Park, J.S., Jeong, Y.J., Portier, J., 1999. Intercalative nanohybrids of nucleoside monophosphates and DNA in layered metal hydroxide. J. Am. Chem. Soc. 121, 1399–1400.

Choy, J.H., Kwak, S.Y., Jeong, Y.J., Park, J.S., 2000. Inorganic layered double hydroxides as nonviral vectors. Angew Chem., Int. Ed. Engl. 39, 4041–4045.

Choy, J.H., Kwak, S.Y., Park, J.S., Jeong, Y.J., 2001. Cellular uptake behavior of [− 32P] labeled ATP–LDH nanohybrids. J. Mater. Chem. 11, 1671–1674.

Choy, J.H., Jung, J.S., Oh, J.M., Park, M., Jeong, J., Kang, Y.K., Han, O.J., 2004a. Layered double hydroxide as an efficient drug reservoir for folate derivatives. Biomaterials 25, 3059–3064.

Choy, J.H., Oh, J.M., Park, M., Sohn, K.M., Kim, J.W., 2004b. Inorganic–biomolecular hybrid nanomaterials as a genetic molecular code system. Adv. Mater. 16, 1181–1184.

Clark, K.J., Sarr, A.B., Grant, P.G., Phillips, T.D., Woode, G.N., 1998. In vitro studies on the use of clay, clay minerals and charcoal to adsorb bovine rotavirus and bovine coronavirus. Vet. Microbiol. 63, 137–146.

Cornejo, J., Hermosin, M.C., White, J.L., Barnes, J.R., Hem, S.L., 1983. Role of ferric iron in the oxidation of hydrocortisone by sepiolite and palygorskite. Clays Clay Miner. 31, 109–112.

del Hugo, C., Vincente, M.A., RIves, V., 2001. Preparation of drug-montmorillonite UV-radiation compounds by gas–solid adsorption. Clay Miner. 36, 541–546.

Desigaux, L., Belkacem, M.B., Richard, R., Cellier, J., Leone, P., Carion, L., Leroux, F., Taviot-Gueho, C., Pitard, B., 2006. Self-assembly and characterization of layered double hydroxide/DNA hybrids. Nano Lett. 6, 199–204.

Elmore, A.R., 2003. Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int. J. Toxicol. 22 (Suppl 1), 37–102.

El-Nahhal, Y.N., S., Polubesova, T., Margulies, L., Rubin, B., 1988. Leaching, phytotoxicity, and weed control of new formulations of alachlor. J. Agric. Food Chem. 46, 3305–3313.

El-Nahhal, Y., Nir, S., Margulies, L., Rubin, B., 1999. Reduction of photodegradation and volatilization of herbicides in organo-clay formulations. Appl. Clay Sci. 14, 105–119.

Ferrand, T., Yvon, J., 1991. Thermal properties of clay pastes for pelotherapy. Appl. Clay Sci. 6, 21–38.

Ferrario, J.B., Byrne, C.J., Cleverly, D.H., 2000. 2,3,7,8-dibenzo-*p*-dioxins in mined clay products from the United States: evidence for possible natural origin. Environ. Sci. Technol. 34, 4524–4532.

Gamiz, E., Linares, J., Delgado, R., 1992. Assessment of two Spanish bentonites for pharmaceutical uses. Appl. Clay Sci. 6, 359–368.

Gorchakov, V.N., Dragun, G.N., Kolmogorov, Y.P., Smelova, V.A., Tikhonova, L.I., Tysjachnova, Y.V., 2001. The using of SR XRF for estimation of macro-and microelement contents of biological objects at the clay treatment. Nucl. Instrum. Methods Phys. Res., Sect. A, Accel. Spectrom. Detect. Assoc. Equip. 470 (1–2), 437–440.

He, Q., Yin, S., Sato, T., 2004. Synthesis and photochemical properties of zinc–aluminum layered double hydroxide/organic UV ray absorbing molecule/silica nanocomposites. J. Phys. Chem. Solids 65, 395–402.

Hocine, O., Boufatit, A., Khouider, A., 2004. Use of montmorillonite clays as adsorbents of hazardous pollutants. Desalination 167, 141–145.

Huwig, A., Freimund, S., Kappeli, O., Dutler, H., 2001. Mycotoxin detoxication of animal feed by different adsorbents. Toxicol. Lett. 122, 179–188.

Hwang, S.H., Han, Y.S., Choy, J.H., 2001. Intercalation of functional organic molecules with pharmaceutical, cosmeceutical and nutraceutical functions into layered double hydroxies and zinc basic salts. Bull. Korean Chem. Soc. 22, 1019–1022.

Ito, T., Sugafuji, T., Maruyama, M., Ohwac, Y., Takahashic, T., 2001. Skin penetration by indomethacin is enhanced by use of an indomethacin/smectite complex. J. Supramol. Chem. 1, 217–219.

Khan, A.I., Lei, L., Norquist, A.J., O'Hare, D., 2001. Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide. Chem. Commun. 2342–2343.

Kim, S.S., Zhang, W.Z., Pinnavaia, T.J., 1998. Ultrastable mesostructured silica vesicles. Science 282 (5392), 1302–1305.

Kriven, W.M., Kwak, S.Y., Wallig, M.A., Choy, J.H., 2004. Bioresorbable nanoceramics for gene and drug delivery. MRS Bull. 29, 33–37.

Kwak, S.Y., Kriven, W.M., Wallig, M.A., Choy, J.H., 2004. Inorganic delivery vector for intravenous injection. Biomaterials 25, 5995–6001.

Lakraimi, M., Legrouri, A., Barroug, A., De Roy, A., Besse, J.P., 2000. Preparation of a new stable hybrid material by chloride-2,4-dichlorophenoxyacetate ion exchange into the zinc–aluminium–chloride layered double hydroxide. J. Mater. Chem. 10, 1007–1011.

Lee, W.F., Fu, Y.T., 2003. Effect of montmorillonite on the swelling behavior and drug-release behavior of nanocomposite hydrogels. J. Appl. Polym. Sci. 89, 3652–3660.

Li, B., He, J., Evans, D.G., Duan, X., 2004. Inorganic layered double hydroxides as a drug delivery system-intercalation and in vitro release of fenbufen. Appl. Clay Sci. 27, 199–207.

Lin, F.H., Lee, Y.H., Jian, C.H., Wong, J.M., Shieh, M.J., Wang, C.Y., 2002. A study of purified montmorillonite intercalated with 5-fluorouracil as drug carrier. Biomaterials 23, 1981–1987.

Maxwell, D.J., Taylor, J.R., Nie, S.M., 2002. Self-assembled nanoparticle probes for recognition and detection of biomolecules. J. Am. Chem. Soc. 124, 9606–9612.

Mayura, K., Abdel-Wahhab, M.A., McKenzie, K.S., Sarr, A.B., Edwards, J.F., Naguib, K., Phillips, T.D., 1998. Prevention of maternal and developmental toxicity in rats via dietary inclusion of common aflatoxin sorbents: potential for hidden risks. Toxicol. Sci. 41, 175–182.

McCarter, W.J., Broussean, R., 1990. The A.C. responses of hardened cement paste. Cem. Concr. Res. 20, 891–900.

McGinity, J.W., Lach, J.L., 1977. Sustained-release applications of montmorillonite interaction with amphetamine sulfate. J. Pharm. Sci. 66, 63–66.

Miyata, S., 1983. Anion-exchange properties of hydrotalcite-like compounds. Clays Clay Miner. 31, 305–311.

Ogawa, M., Kuroda, K., 1995. Photofunctions of intercalation compounds. Chem. Rev. 95, 399–438.

Oh, J.M., Park, M., Kim, S.T., Jung, J.Y., Kang, Y.G., Chong, J.H., 2006. Efficient delivery of anticancer drug MTX through MTX-LDH nanohybrid system. J. Phys. Chem. Solids 67, 1024–1027.

Olanrewaju, J., Newalkar, B.L., Mancino, C., Komarneni, S., 2000. Simplified synthesis of nitrate form of layered double hydroxide. Mater. Lett. 45, 307–310.

Perioli, L., Ambrogi, V., Bertini, B., Ricci, M., Nocchetti, M., Latterini, L., Rossi, C., 2006. Anionic clays for sunscreen agent

safe use: photoprotection, photostability and prevention of their skin penetration. Eur. J. Pharm. Biopharm. 62, 185–193.

Poensin, D., Carpentier, P.H., Fechoz, C., Gasparini, S., 2003. Effects of mud pack treatment on skin microcirculation. Jt. Bone Spine 70, 367–370.

Ray, S.S., Okamoto, M., 2003. Polymer/layered silicate nanocomposites: a review from preparation to processing. Prog. Polym. Sci. 28, 1539–1641.

Reichle, W.T., 1986. Synthesis of anionic clay minerals (mixed metal hydroxides, hydrotalcite). Solid State Ionics 22, 135–141.

Robertson, R.H.S., 1996. Cadavers, chloreras and clays. Br. Miner. Soc. Bull. 113, 3–7.

Rytwo, G., Kohavi, Y., Botnick, I., Gonen, Y., 2007. Use of CV- and TPP-montmorillonite for the removal of priority pollutants from water. Appl. Clay Sci. 36, 182–190 (this issue). doi:10.1016/j.clay.2006.04.016.

Sanchez-Martin, M.J., Rodriguez-Cruz, M.S., Andrades, M.S., Sanchez-Camazano, M., 2006. Efficiency of different clay minerals modified with a cationic surfactant in the adsorption of pesticides: influence of clay type and pesticide hydrophobicity. Appl. Clay Sci. 31, 216–228.

Summa, V., Tateo, F., 1998. The use of pelitic raw materials in thermal centres: mineralogy, geochemistry, grain size and leaching test. Examples from the Lucania area (southern Italy). Appl. Clay Sci. 12, 403–417.

Theng, K.G., 1974. The Chemistry of Clay-Organic Reactions. Adam Hilger, London, UK.

Vacca, G., Wand, H., Nikolausz, M., Kuschk, P., Kastner, M., 2005. Effect of plants and filter materials on bacteria removal in pilot-scale constructed wetlands. Water Res. 39, 1361–1373.

Vaccari, A., 1998. Preparation and catalytic properties of cationic and anionic clays. Catal. Today 41, 53–71.

Veniale, F., Barberis, E., Carcangiu, G., Morandi, N., Setti, M., Tamanini, M., Tessier, D., 2004. Formulation of muds for pelotherapy: effects of “maturation” by different mineral waters. Appl. Clay Sci. 25, 135–148.

White, J.L., Hem, S.L., 1983. Pharmaceutical aspect of clay–drug interactions. Ind. Eng. Chem. Prod. Res. Dev. 22, 665–671.

Wilson, M.J., 1987. A Handbook of Determinative Methods in Clay Mineralogy. Chapman and Hall, New York, USA.

Yamaoka, T., Abe, M., Tsuji, M., 1989. Synthesis of Cu–Al hydrotalcite like compound and its ion exchange property. Mat. Res. Bull. 24, 1183–1199.

Yang, J.H., Lee, S.Y., Han, Y.S., Park, K.C., Choy, J.H., 2003. Efficient transdermal penetration and improved stability of L-ascorbic acid encapsulated in an inorganic nanocapsule. Bull. Korean Chem. Soc. 24, 499–503.

Zadaka, D., Mishael, Y.G., Polubesova, T., Serban, C., Nir, S., 2007. Modified silicates and porous glass as adsorbents for removal of organic pollutants from water and comparison with activated carbons. Appl. Clay Sci. 36, 174–181 (this issue). doi:10.1016/j.clay.2006.04.012.

Zou, H., Pan, G., Chen, H., Yuan, X., 2006. Removal of cyanobacterial blooms in Taihu Lake using local soils II. Effective removal of *Microcystis aeruginosa* using local soils and sediments modified by chitosan. Environ. Pollut. 141, 201–205.