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Laponite-based nanohybrid for enhanced solubility and controlled release of itraconazole

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Abstract

Laponite, a form of layered aluminosilicates, and itraconazole, a water insoluble drug, were hybridized through an interfacial reaction at the boundary between water and a water-immiscible liquid. The reaction was carried out under a controlled pH to maintain both physical and chemical stability of the drug. The X-ray diffraction patterns and spectroscopic analyses indicated that itraconazole was intercalated into the interlayer space of clay with a lateral monolayer structure. No significant chemical structural change of itraconazole was seen through the formation of the hybrid. The hybrid system exhibited enhanced solubility and controlled release of itraconazole. The released amount of itraconazole could be controlled in the range from 18 to 75%, depending on the kinds of cations in the release media.

Keywords: Itraconazole; Clay; Nanohybrid; Solubility; Controlled release

1. Introduction

Recently, various nanohybrid materials have attracted considerable research interest due to their useful physicochemical properties, which cannot be achieved by the individual components in and of themselves (Choy et al., 1998, 2002; Paek et al., 2005; Kwak et al., 2002). In particular, there has been rapid development of bioinorganic hybrid systems for effective drug delivery (Choy et al., 2004a, 2000, 1999). Bioinorganic hybrid systems can allow controlled delivery of various therapeutic agents into the target tissues/organs with high efficiency. Among a variety of inorganic materials, smectite clays are associated with great potential (Choy et al., 2004b; Lin et al., 2002). The interlayer space of smectite clays could be an effective reservoir for various biomolecules due to their high retention capacity. The molecules, stabilized by electrostatic forces between the inorganic layers, can be protected chemically and biologically from the body's environments and also released the compound of interest in a controlled manner. Most of all, the water solubility of the drug, when intercalated into the clay, can be greatly enhanced because the drug molecules are distributed in ionic form. Therefore, such hybrid system is known to be advantageous especially for the controlled release of the drugs with low solubility.

Itraconazole (ITA) (4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]- 1 -piperazinyl]phenyl]-2, 4-dihydro-2 -(1-methyl-propyl)-3H-1,2,4-triazol-3-one) is a synthetic anti-fungal drug, which is composed of a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs). Three chiral centers are present in each diasteromer which possess a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and molecular weight of 705.64 g/mol (Jain and Sehgal, 2001; Grant and Clissol, 1987). ITA is poorly soluble in aqueous media (less than 1 μg/ml in aqueous solutions at pHs of 1–12.7) with a partition coefficient greater than 5 in octanol/water at pH 6. Thus, in spite of the high antifungal activity, the bioavailability of unformulated crystalline ITA is extremely low (Jung et al., 1999; Verreck et al., 2003). In order to enhance its solubility and dissolution rate, various formulations have been developed, including solid dispersions (Leuner and Dressman, 2000; Verreck et al., 2003), solid solution (Kapsi and Ayres, 2001), and complexes (Peerers et

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al., 2002; Miyake et al., 1999). However, these routes may not prevent the drugs from recrystallization or may not provide for controlled delivery (Choy et al., 2000, 1999, 2004b). In addition, such routes often required complicated procedures.

In this study, we attempted a new approach, the hybridization of ITA with laponite clay, in order to enhance water solubility and facilitate controlled release. Laponite, a plate like synthetic hectorite-type clay, was used as the host clay, which possesses high purity required for the systematic study. To explore the potential of smectite group as an ITA delivery vehicle, this study focused on the characterization of ITA-laponite hybrid along with the release behavior of ITA.

2. Experimental and characterization

2.1. Materials

Laponite (XLG, Laporte Industries Ltd.), synthetic swelling clay with tri-octahedral 2:1 layered structure, has the chemical composition of SiO_2, 59.5%; MgO, 27.5%; LiO_2, 0.8% and Na_2O, 2.8%. Because some of octahedral magnesium ions in the octahedral sheets are substituted by lithium ions, negative layer charges are developed which are compensated by exchangeable sodium ions located in the interlayer space. Its monoclinic crystals (*C*2/*m*) with a dimension of ca. 1 nm × 25 nm have a negative charge density of 0.014 $e^-/Å^2$ (Park et al., 2004; Taco and Stephane, 2000). ITA (Scheme 1) was purchased from Joongwae Pharmaceutical (Seoul, Korea) and was used without further purification (purity > 99.5%). ITA is weakly basic with extremely low solubility in water ($S < 1$ μg/ml in aqueous solutions in a pH range of 1.0–12.7).

2.2. Preparation of ITA-laponite hybrid

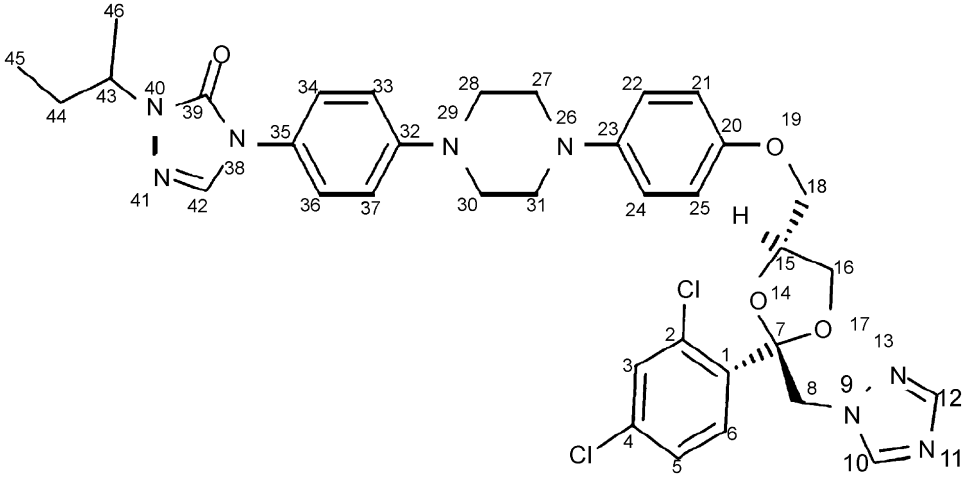
Laponite is dispersed in deionized water at 1.0 wt.% with vigorous agitation at room temperature. The pH of the transparent laponite suspension was adjusted to 4.0 with a 0.1 M HCl solution (Solution 1). ITA at three-fold the cationic exchange capacity (CEC) of laponite was dissolved in methylene chloride (MC) (Solution 2). The CEC refers to the value associated with the capacity of the clay to bind cationic agents. Solutions 1 and 2 were then mixed to result in the ion exchange reaction. The intercalation reaction was carried out at the interface between two immiscible solutions while vigorously stirred for 24 h, which facilitated the diffusion of ITA from the MC solution into the clay suspension. The solid product, ITA-laponite hybrid, was separated by centrifugation, washed with MC several times to remove the excess ITA, dried, and then gently milled in an agate mortar to give a fine hybrid powder with a primary particle size of ∼25 nm.

2.3. Characterization

X-ray diffraction (XRD) patterns were obtained using a diffractometer (a Phillps PW 1830 diffractometer) with graphite-monochromatized and Ni-filtered Cu Kα radiation ($\lambda = 1.5418$ Å). X-ray diffractometer was operated at 40 kV/30 mA in a continuous scan mode at a scanning speed of 0.02° $2\theta\ s^{-1}$ with a slit of 1°. Diffuse reflectance UV–vis spectra were recorded on a Perkin-Elmer Lamda 12 spectrometer equipped with an integrating sphere, 60 mm in diameter, using $BaSO_4$ as a standard. Fourier transform infrared spectra were obtained in the range of 4000–400 cm^{-1} with a Jasco 660 FT-IR spectrometer by the standard KBr disk method. Thermogravimetric (TG) and differential thermal analyses (DTA) were conducted using Rigaku TAS-100 with a heating rate of 10 °C/min in the temperature range from room temperature to 1000 °C in air. Elemental analysis was performed using CE EA-1110 Elemental Analyzer. Morphology was examined by Scanning Electron Microscopy (HITACHI-S 4300) after Pt coating.

2.4. In vitro drug release studies

In vitro drug release was carried out using a USP dissolution apparatus 2 (a paddle stirring method). One gram of the



Scheme 1. Molecular structure of ITA.

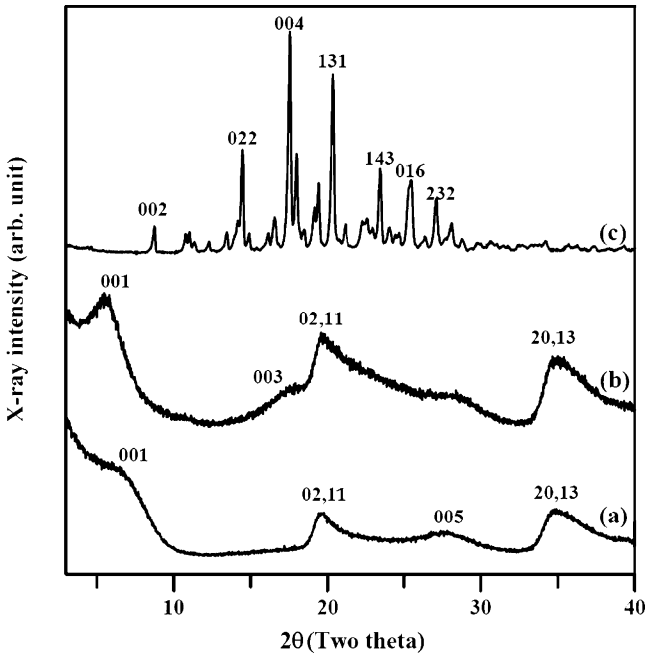


Fig. 1. X-ray diffraction patterns of (a) pristine Na-Laponite, (b) ITA-laponite hybrid, and (c) ITA.

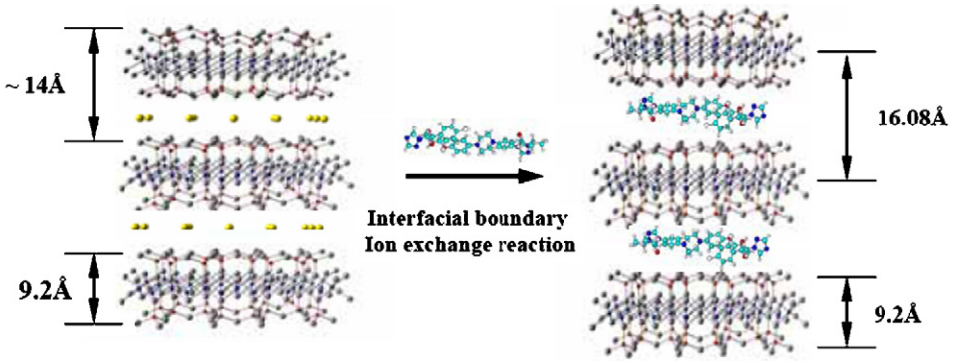
hybrid (equivalent to 89 mg of ITA) was suspended in 900 ml of the aqueous solutions containing various cations (NaCl, $CH_3(CH_2)_3NH_3Cl$, $CH_3(CH_2)_{15}NH_3Cl$ and Eudragit® E-100). The cation (0.034 mol) was dissolved in 1 l of the release media. The pH was maintained at 1.2 and the temperature at 37 ± 1 °C in a water bath incubator. We checked the stability of the ITA by HPLC under the conditions used for the in vitro drug release study and found that there was no significant degradation. Thus, the amount of released ITA was simply determined by UV absorption (Perkin-Elmer Lambda 12 spectrometer) at 258 nm for quick and economic measurements. Tests were carried out in triplicate and the results were recorded as an average.

3. Results

3.1. Powder X-ray diffraction analysis

Fig. 1 shows the powder XRD patterns of the pure laponite, ITA-laponite hybrid, and ITA itself. The unmanipulated laponite exhibited a broad XRD pattern indicating low crystallinity and small particle size (Park et al., 2004). Upon intercalation, the basal spacing significantly expanded from approximately 14 to 16.08 Å, suggesting the replacement of interlayer cation by ITA. Subtracting the silicate layer thickness (9.2 Å) from the basal spacing (16.08 Å) of the ITA-laponite hybrid, the gallery height was estimated to be 6.88 Å (Taco and Stephane, 2000). Interestingly, the gallery height of the hybrid was rather larger than the lateral molecular length of ITA (4.822(2) Å) but much smaller than its longitudinal length (21.0425 Å) (Peeters et al., 1996). The result suggested that intercalated ITA form a monolayer with its longitudinal axis parallel to the layer of laponite (Scheme 2).

It has been reported that the gallery height of the clay treated with various cations did not always coincide with the dimensions of the cation in the free state due to hydration, orientation, packing, and deformation of the cation in interlayer space (Gisking, 1937). To explain such discrepancy, one needs to consider the critical factors associated with forming the interlayer structure, such as electrostatic interaction and steric limitation between the guest species and charged sites of clay layer. Scheme 1 shows the first and second protonation sites of ITA, N26 and N29, respectively. Due to the locations of two charged sites, ITA tended to be configured not in a longitudinal orientation but in a lateral one in the interlayer (Inkamann and Holzgrabe, 1999). Theoretically, the more favorable conformation of ITA in the hybrid should be as a bilayer rather than a monolayer due to the equivalent charge of ITA. To propose a more reasonable interlayer structure, we examined steric influences. Steric limitation is usually generated by the equivalent area (A_e) of clay lattices and the area demand (A_c) of intercalated molecules. The equivalent area (A_e) available for a monolayer cation in the interlayer space can be estimated from the equation $A_e = ab/2\xi$, where a and b are lattice parameters and ξ is the layer charge (Aray et al., 2003; Yang et al., 2001). The laponite exhibited the equivalent area of about 60.24 $Å^2$ per unit charge while the area demand of ITA molecule (A_c) was 101.47 $Å^2$. The fact that A_c is sufficiently larger than A_e could suggest that the interlayered ITA molecules formed parallel arrangement in the gallery space of the interlayer. If the area of ITA molecules is larger than the equivalent area, the monolayer rearranges into a bilayer to avoid steric hindrance. Moreover, the affinity between ITA molecules is stronger than that between ITA and the laponite layer due to hydrophobic properties of ITA. It should be noted that the bent V-shaped



Scheme 2. Schematic description for ITA-laponite hybrid.

monolayer or pseudobilayer structure was highly probable for ITA in the interlayer space, which could explain a larger gallery height than the lateral dimension of ITA molecules.

In addition, ITA molecules, when intercalated, were homogeneously distributed at the molecular level in the interlayer space of laponite without forming large particles with a crystalline structure. As shown in Fig 1b, the characteristic triclinic (P-1) crystalline peaks of ITA disappeared in the hybrid. According to the Noyes–Whitney relationship, the dissolution of a solid could be improved by increasing its surface area or by increasing the saturation solubility of the drug. The increased dissolution rate may therefore, suggests that the intercalated ITA would possess a significantly improved solubility compared to the pure crystalline ITA. The previous studies also showed the enhancement of the ITA solubility when prepared as spray drying tablet (SD-T) incorporated with AEA® and Eudragit® E-100 (Jung et al., 1999).

3.2. Ultraviolet visible (UV) spectroscopy analysis

A UV spectrum of the hybrid was compared with that of ITA both in aqueous solution and in solid state as shown in Fig. 2. The spectrum of ITA solid shows two bands at 240 and 311 nm. The former may be associated with the $n \rightarrow \pi^*$ transition of the $N_2C{=}O$ group and the latter to the $\pi \rightarrow \pi^*$ transition (Heinz-Helmut, 1992). The spectrum of ITA in aqueous solution shows blue shifts of their bands to 225 and 257 nm compared to solid ITA due to the isolation caused by polar solvent and protonation.

The hybrid exhibits a unique UV absorption characteristics different from that of solid ITA. It was found that the spectrum of hybrid was very similar to that of ITA in an aqueous solution at pH 1.2. This indicated that the intercalated ITA was stabilized between clay layers as a protonated form, leading to enhanced water solubility.

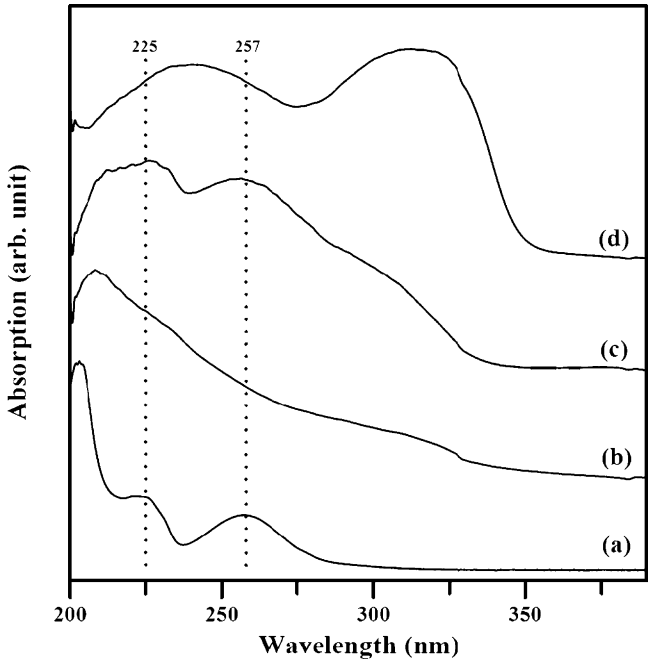


Fig. 2. Ultraviolet spectra of (a) ITA in solution (pH 1.2 buffer solution), (b) solid Na-laponite, (c) solid ITA-laponite hybrid and (d) solid ITA (1/(%R)).

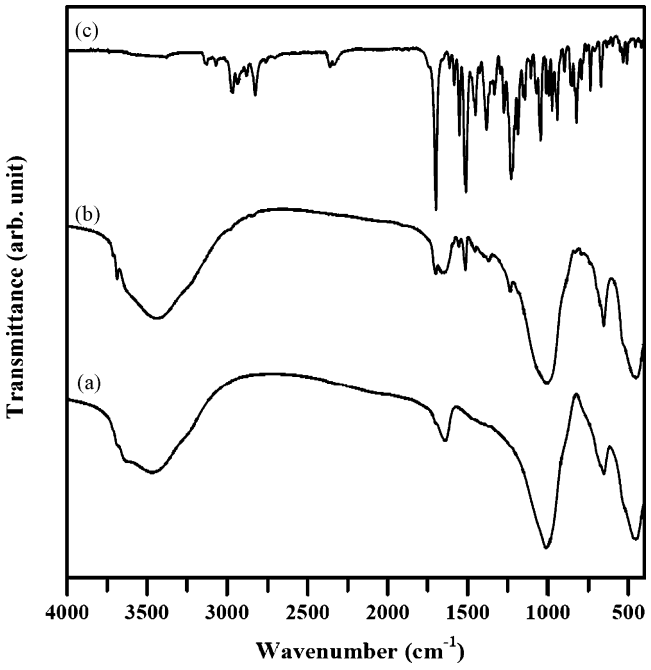


Fig. 3. Fourier transform infrared spectra of (a) pure Na-laponite, (b) ITA-laponite hybrid, and (c) ITA.

3.3. FT-IR analysis

FT-IR spectra were examined to prove further evidence for the intercalation of ITA into the laponite interlayer. Fig. 3 shows the FT-IR spectra of the laponite, hybrid, and ITA. For laponite, the absorption bands of $\nu_{S(O–H)}$ and $\nu_{S(Si–O)}$ modes were observed at 3675 and 1011 cm^{-1}, respectively. The characteristic peaks of ITA were seen at 3381, 3127, 3066, 1698, 1614, and 1425 cm^{-1}. The band located at 3381 cm^{-1} was assigned to the stretching vibration (ν_s) of free NH_2 group in ITA molecule and those at 3127 and 3066 cm^{-1} resulted from ν_s of the amino-group. A sharp band at 1698 cm^{-1} is due to C=O, and the bands at 1614 and 1425 cm^{-1} are assigned to $\nu_{S(C=N)}$ and $\nu_{S(C–N)}$ bonds, respectively (Nesseem, 2001). It should be noted that all the characteristic bands of ITA were also detected in the spectrum of the hybrid, which suggests that the ITA is intercalated within the interlayer of clay maintaining their functionalities.

Compared with pure ITA, the intercalated form exhibited slight up-shifts of the absorption bands from 1510 to1513 cm^{-1} and from 1451 to 1455 cm^{-1}, which suggests that ITA was stabilized in its amorphous form. In this study, the intercalation was performed at pH 4, where half of the ITA molecules were protonated. Since only the protonated molecules could be intercalated, it could be reasonably said that the molecules in the interlayer space existed in an ionized form.

3.4. Thermal analysis

The TG–DTA curves of laponite, hybrid, and pure ITA powder are shown in Fig. 4. For laponite, the first weight loss

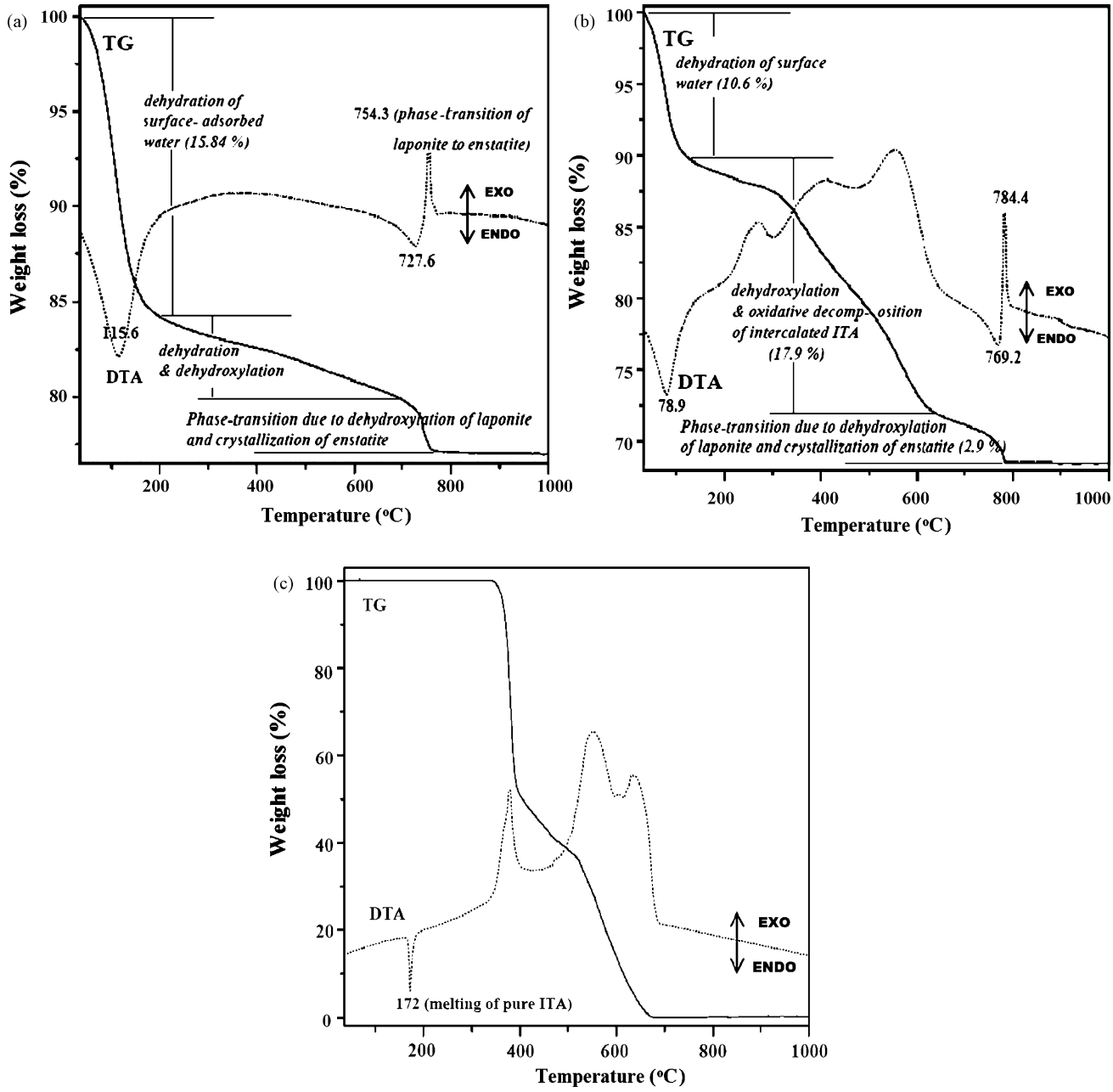


Fig. 4. TG and DTA curves of (a) pure Na-laponite, (b) ITA-laponite hybrid, and (c) ITA.

accompanied with a large endothermic response up to 200 °C was due to the dehydration of interlayer water. Weak endothermic followed by exothermic responses at around 728 and 754 °C resulted from dehydroxylation and phase transition of laponite, respectively (Luyer et al., 2001). On the other hand, the TG–DTA curves of ITA-laponite hybrid shows the thermal evolution with three consecutive stages due to the dehydration, decomposition, and dehydroxylation. The first weight loss (ca. 10.6%) by dehydration was smaller than the pure laponite (ca. 15.84%) because of the presence of intercalated hydrophobic ITA. The second one was associated with an exothermic reaction in the range from 200 to 676 °C resulted from the oxidative decomposition of intercalated ITA (ca. 13.09%). The content of ITA in the hybrid measured by CHNS elemental analysis was 12.43 ± 0.3 wt.%, which was slightly lower than the one estimated by thermal analysis because the latter was overestimated by concurrent dehydration and dehydroxylation of silicate layer at 200–676 °C.

In the DTA curve for pure ITA, a sharp endothermic peak at 172 °C was observed without any weight loss in TG (Fig. 4c), which corresponded to the melting point of ITA (Kapsi and Ayres, 2001). However, possibly due to the absence of recrystallized ITA, such characteristic peak was not seen in the hybrid. In addition, the intercalated ITA was thermally decomposed at lower temperature at 200–676 °C than the pure ITA at 342–690 °C. The result could be due to the amorphous nature

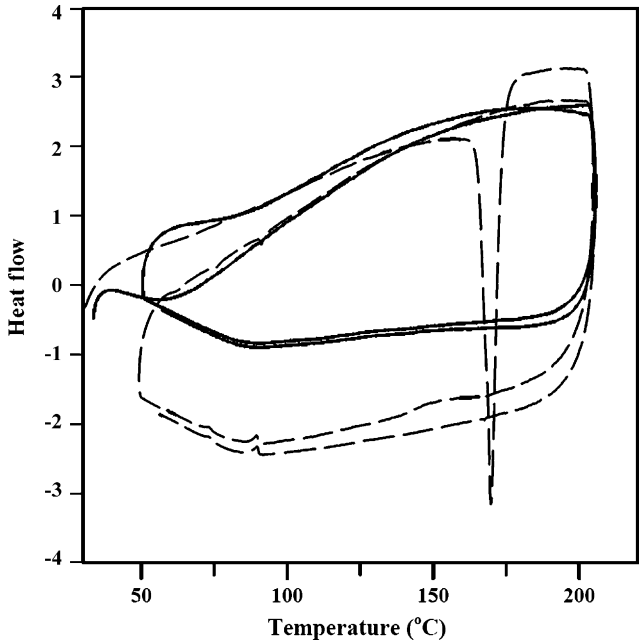


Fig. 5. Cycled DTA profile of ITA (dashed line) and ITA-laponite hybrid (solid line) from 30 to 200 °C.

of ITA upon intercalation, which would possibly lead to the enhancement of ITA solubility.

Cycled DTA profiles from 30 to 200 °C of pure ITA and hybrid are shown in Fig. 5. ITA showed a clear endothermic peak near at 172 °C due to the melting of pure ITA but not with the ITA-laponite hybrid. This result suggests that ITA molecules are stabilized between the interlayer of laponite as a molecular level, which could diminish the intermolecular interaction between ITA molecules.

3.5. Field emission scanning electron microscopy (FE-SEM)

Fig. 6 shows SEM images of laponite, pure ITA, and laponite-ITA hybrid. Laponite showed the plate-like and uniform morphology with some aggregates. Its primary particle size was estimated as 25 nm in diameter. ITA had rod-like morphology with approximately 2–4 °C in length. The ITA-laponite hybrid showed severely curled or crumpled edges and irregular plate-like aggregated form as shown in Fig. 5b (Choy et al., 1998; Lee and Kim, 2002). The crystal morphology of laponite changed dramatically due to the flocculation and restacking immediately after ITA was added to the laponite suspension.

3.6. In vitro drug release studies

Intercalated species in interlayer space of smectite is typically released by ion exchange reaction with other cations. However, bulky and hydrophobic organic cations in interlayer space cannot be easily deintercalated by ion exchange reaction with the simple cations such as Na^+, Ca^{2+}, etc. Deintercalation of ionized ITA could be facilitated by other organic ones with similar or larger molecular size and charge (Jain and Sehgal, 2001; Zhang et al., 1993). Fig. 7 shows that only 18% of intercalated ITA was released during the first 24 h when treated with a 0.034 M NaCl solution. The amount released was minimal afterwards probably due to the hydrophobicity of hybrid and difficulty in ion exchange reaction with smaller sized sodium ion. The ion exchange reaction occurred first at the edge of laponite and con-

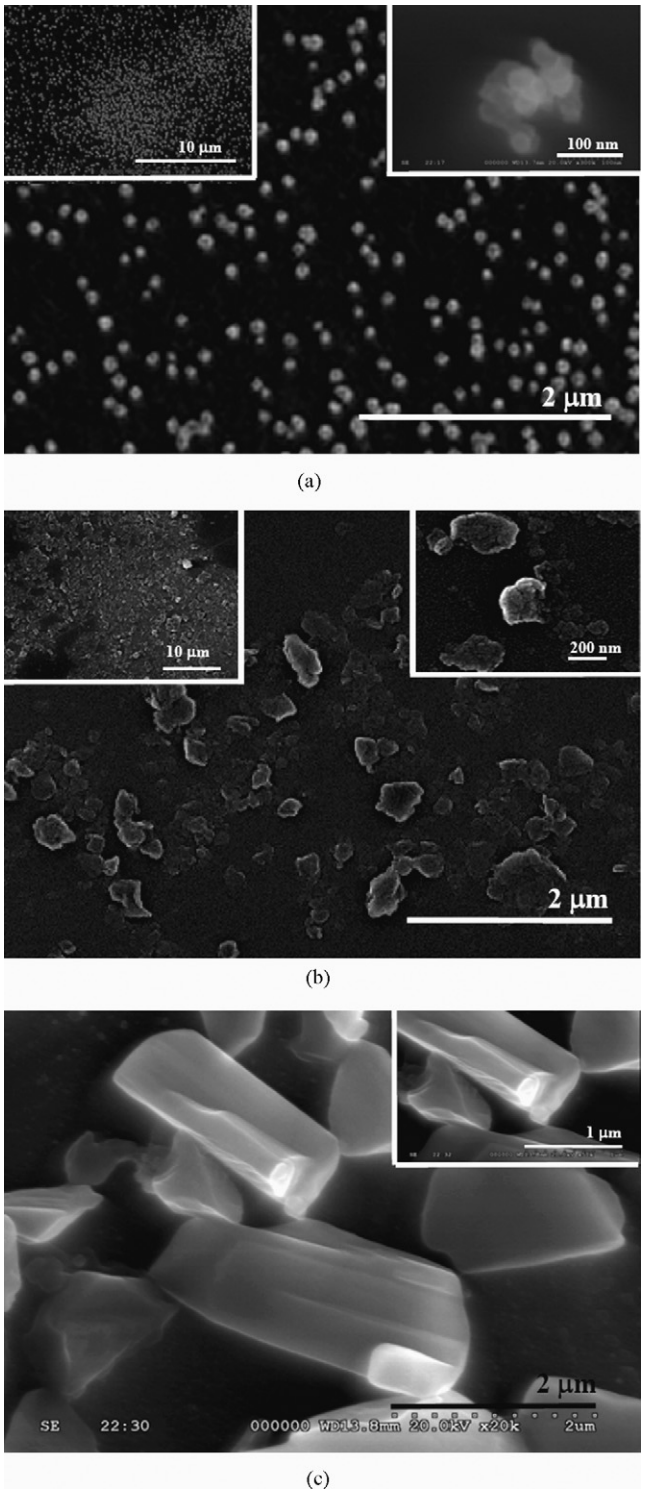


Fig. 6. Scanning electron microscopic images of (a) pure Na-laponite; (b) ITA-laponite hybrid, and (c) ITA.

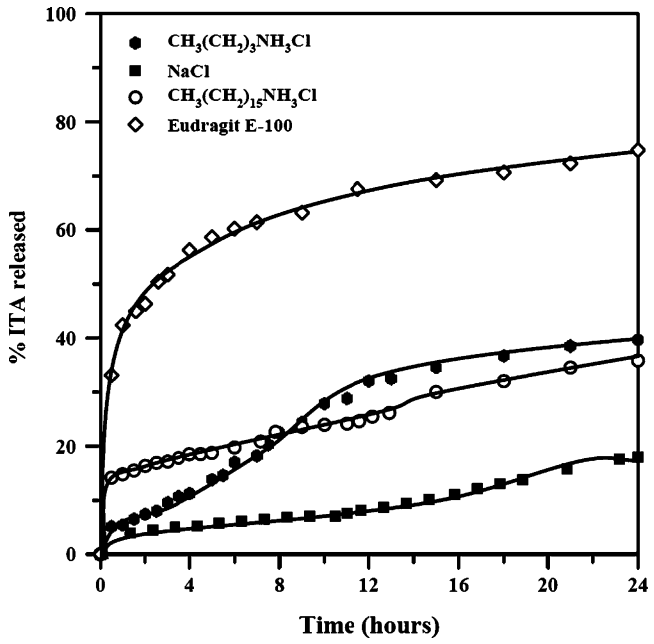


Fig. 7. Cumulative ITA release profiles.

tracted the interlayer distance. Thus, the drug release through the edge was retarded, giving rise not only to decrease the rate of drug release but also to make continuous release very difficult.

Fig. 8 shows the release profiles of ITA without an additive. In an acidic solution, ITA was released by substitution of H^+ in the solution. The erosion of laponite, which was caused by the reaction with H^+, was also a critical factor in the release of ITA. The total ITA release content was about 29%, which was higher than that (23%) in a solution containing NaCl, which meant that ITA release in a solution containing Na^+ was lower than that in a solution with H^+ alone. The presence of Na^+ disordered the interlayer space since the release of intercalated ITA became more difficult than that with H^+ alone. Therefore, the addition of NaCl caused the drug release kinetics to be different from that in an acidic solution. Each of the agents at 0.034 mol was dissolved in 1-l of the dissolution media. The putative ion exchange mechanism and surfactant solubilization could be separated by comparing the cations without surfactant action, such as NaCl or HCl. These cations have only the ion exchange property, and one could assume that the release of ITA would be caused only by ion exchange effects.

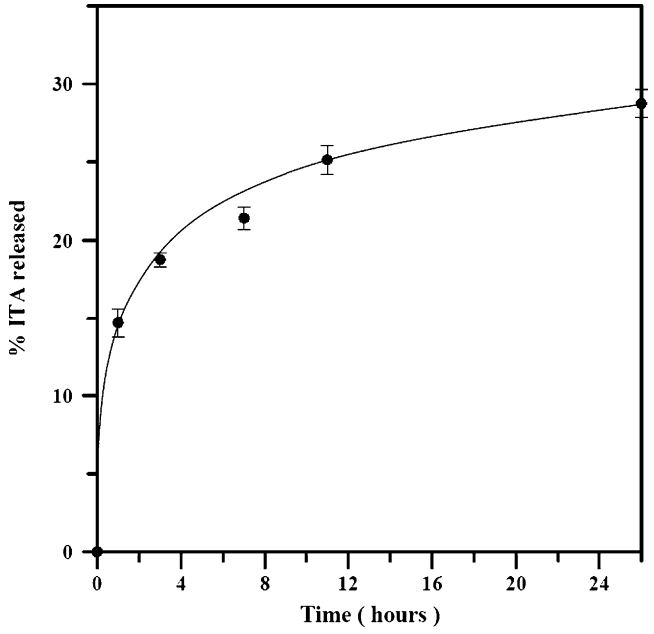


Fig. 8. Profiles of cumulative ITA release in a pH 1.2 solution without any salts.

In order to enhance the release rate of ITA, three different organic compounds containing longer chain length and manifesting higher hydrophobicity, $CH_3(CH_2)_3NH_3Cl$, $CH_3(CH_2)_{15}NH_3Cl$, and Eudragit® E-100 (copolymer with M_w 120,000 g/mol) were employed as an ion exchange reaction agent. As shown in Fig. 6, the total amount of release increased markedly from 18% in a NaCl solution to 40 and 36% in the presence of $CH_3(CH_2)_3NH_3Cl$ and $CH_3(CH_2)_{15}NH_3Cl$, respectively. The ionic surfactants used in this study are cationic surfactants. Thus, the increase in release rate could be explained by the decrease in chemical potential of the drug in a solution due to micelle formation. In the case of Eudragit® E-100, the largest amount of ITA release (75%) was observed. Eudragit® E-100 is a large polymer with $M_w = 120{,}000$ g/mol with many cationic sites in the polymer, which could diffuse into the interlayer space of laponite and replace the intercalated ITA molecules more effectively, resulting in facilitated drug release. Moreover, many hydrophilic side chains in Eudragit® E-100 could enhance the wettability of the hybrid. Thus, both the ion exchange reaction and partial dissolution of laponite under the acidic condition (pH 1.2) (Komadel et al., 1996; Rompaey et al., 2002) would be improved, which in turn influenced the drug release.

4. Conclusion

ITA, an antifungal drug molecule, could be intercalated into interlayer space of laponite and deintercalated in the ionized form. Based on the ease of intercalation and deintercalation, clay could be a good candidate as a drug delivery carrier for pharmaceutical applications. Clay could play a role as solubility controller, since the intercalation of drug molecules into interlayer space would enhance the dissolution rate of the drug like ITA secondary to surface area, wettability or solubility effects. According to the in vitro release test, we found that the amount of drug release from ITA-laponite hybrid could be controlled, ranging from 18 to 75% depending on the kinds of ion exchange agents in different sizes. It is, therefore, concluded that the drug-clay hybridization route could provide a new way of preparing nano drug delivery devices with controlled release and solubility functions.

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