

Ketoprofen-LDH Nanohybrid for Transdermal Drug Delivery System

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Two dimensional inorganic matrix have attracted a great attention due to their medical applications in storage, delivery, and controlled-release of drug, gene and cosmeceuticals.¹⁻³ Among inorganic layered materials, layered double hydroxides (LDHs) have been systematically studied to design bio-inorganic nanohybrids, since the biocompatible LDHs are considered as efficient nano-reservoir for stabilizing fragile bio and organic molecules as well as nano-carrier with controlled release of intercalated pharmaceutical, nutritional and cosmetic molecules.^{4,5} On the other hand, ketoprofen (KP, $C_{16}H_{14}O_3$), a water-poorly soluble non-steroidal anti-inflammatory drug (NSAIDs), has been widely used due to its pharmaceutical therapeutic functions for the treatment of rheumatoid arthritis, osteoarthritis and other inflammatory musculoskeletal disorders, and also for traumatic pain with acute low back injury or soft-tissue injury.⁶ As with other NSAIDs, however, oral or intrarectal administration of the KP drug accompanies adverse side effects on the gastrointestinal tract.⁷ For this reason, transdermal delivery system of the KP drug were reported such as nano-emulsion, gel formulation, or patch system for topical treatment to minimize side effects associated with use of oral anti-inflammatories.⁸⁻¹⁰ The aim of this study was, therefore, subjected to the intercalation of KP drug into LDH to induce the controlled release property, and the structural and chemical characterizations of the KP-LDH nanohybrid. And at the same time, an attempt was made to figure out the *in-vitro* release behavior of the KP-LDH and its transdermal delivery efficacy in topical application on the bases of mouse-skin permeability experiment.

As shown in Figure 1(A), the powder XRD patterns of the KP-LDH nanohybrid with ideal chemical composition of $[Zn_2Al(OH)_6][KP] \cdot nH_2O$ exhibited well-ordered (00l) X-ray reflections attributable to the corresponding layered structure. The basal spacing was drastically expanded from 8.4 Å for the pristine NO_3 -LDH to 23.1 Å for the KP-LDH upon KP intercalation. Considering the thickness of LDH (4.8 Å) and the size of KP molecule (15.6 Å), it was estimated that the overlapped bilayer of KP molecules would be present in the LDH layers with the tilting angle of 37° with respect to the c-axis, as shown in Figure 1(b).^{5(b)}

According to the FT-IR spectra of the KP-LDH, the KP molecules are stabilized in the interlayer space of LDH without any noticeable changes in its structure as shown in Figure 1(C). After intercalation of KP into LDH, an asym-

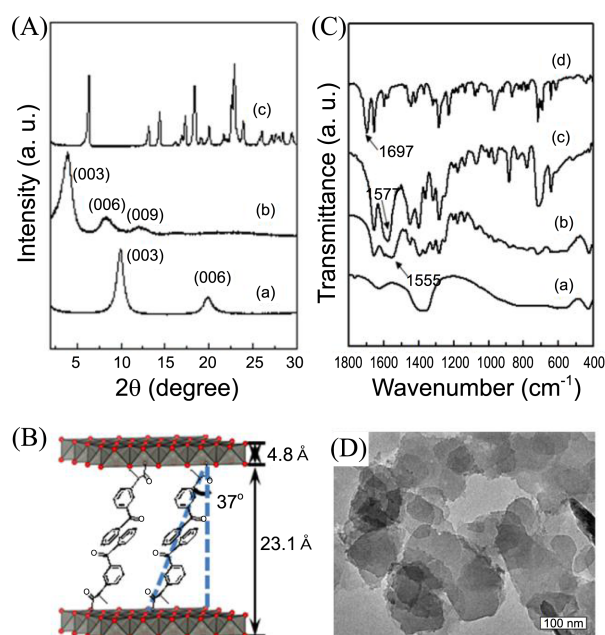


Figure 1. (A) Powder XRD patterns of (a) pristine NO_3 -LDH, (b) KP-LDH, and (c) KP only. (B) Structural model of KP-LDH, (C) FT-IR spectra of (a) pristine NO_3 -LDH, (b) KP-LDH, (c) Na-KP salt, and (d) KP only. (D) TEM image of KP-LDH.

metric stretching band of $-COO^-$ at 1697 cm^{-1} in the protonated KP molecule shifts to 1555 cm^{-1} assigned to one of deprotonated carboxylate ($-COO^-$), which is similar to IR spectrum of Na^+KP^- . And an additional IR band assigned to a symmetric stretching of COO^- is observed at 1400 cm^{-1} , confirming that the KP drug molecules are electrostatically incorporated with its anionic form between ZnAl hydroxide layers. And the other peaks below 800 cm^{-1} are due to the LDH lattice vibrations such as metal-oxygen (M-O and M-O-M) stretching and bending modes. According to the TEM analysis, shown in Figure 1(D), the KP-LDH has a hexagonal plate-like morphology with an average lateral size of 300 nm. The content of KP in the KP-LDH was determined to be 23 wt % by HPLC.

In-vitro release profile and plots for various kinetic equations for release of KP out of the KP-LDH nanohybrid are shown in Figure 2 (A) and Fig. S1; an initial bursting release in the early stage (about 40% released in the initial 30 min) and followed by a sustained release of 82% for 6 hrs.^{5(b)} The partial release of KP in initial stage is mainly due to the

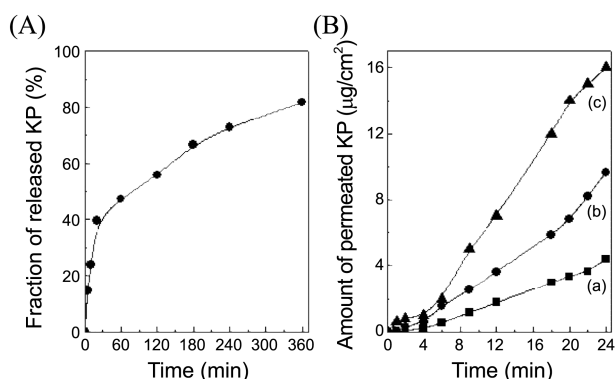


Figure 2. (A) *In-vitro* release profile of the KP-LDH at pH 7.4 PBS mixed with ethanol. (B) *In-vitro* skin permeability profiles of KP from the KP-LDH permeated across mouse-skin in PBS mixed with ethanol at (a) pH 7.4, (b) pH 6.8, and (c) pH 5.5.

release of KP molecules adsorbed outer surface of LDH and those intercalated close to the edges of LDH. On the other hand, sustained release of KP in the later stage is mainly due to the slow ion-exchange reaction of interlayered KP with phosphate anions in the phosphate buffer solution (PBS, pH 7.4) mixed with ethanol. At the same time, a part of LDH lattice could be much slightly dissolved, therefore, intercalated KP molecules are slowly diffused out of the LDH lattice. To investigate skin permeation behavior, as-prepared suspension of the KP-LDH (at pH 5.5, pH 6.8 and pH 7.4) was applied on the mouse skin. The cumulative amount of the KP from KP-LDH penetrated across the mouse skin was, $4.4 \mu\text{g}\cdot\text{cm}^{-2}$ at pH 7.4, $9.6 \mu\text{g}\cdot\text{cm}^{-2}$ at pH 6.8, and $24.2 \mu\text{g}\cdot\text{cm}^{-2}$ at pH 5.5, respectively, as shown in Figure 2(B). Based on this results, we found that the permeation rate increased from 0.025 to $0.837 \mu\text{g}\cdot\text{cm}^{-2}\cdot\text{h}^{-1}$ as the pH decreased. Such a skin permeation profile of KP-LDH could be explained by the increase of released KP concentration in donor part due to the dissolution of LDH under a slightly acidic condition. Therefore, the present skin permeation

behavior indicates that the pH could influence on the transdermal release rate as well as controlled release property in preparing pharmaceutical formulation of transdermal drug delivery systems containing KP-LDH.

In this study, we have synthesized KP intercalated LDH with controlled release function for transdermal drug delivery system. The KP molecules in the LDH lattice were stabilized with a tilted bilayer orientation. According to the *in-vitro* release study, we found that the release kinetics were initially controlled by the desorption of adsorbed KP molecules and the diffusion of intercalated ones, and then followed by ion exchange reaction. The cumulative amount of the KP permeated on mouse skin from KP-LDH increased as the pH of donor part decreased from pH 7.4 to pH 5.5.

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References

- Choy, J. H.; Kwak, S. Y.; Park, J. S.; Jeong, J. Y.; Portier, J. *J. Am. Chem. Soc.* **1999**, *121*, 1399.
- Oh, J. M.; Biswick, T. T.; Choy, J. H. *J. Mater. Chem.* **2009**, *19*, 2553.
- Paek, S. M.; Oh, J. M.; Choy, J. H. *Chem. Asian J.* **2011**, *6*, 324.
- Hwang, S. H.; Han, Y. S.; Choy, J. H. *Bull. Korean Chem. Soc.* **2001**, *22*, 1019.
- (a) Choy, J. H.; Son, Y. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 122.
(b) Yang, J. H.; Han, Y. S.; Park, M.; Park, T.; Hwang, S. J.; Choy, J. H. *Chem. Mater.* **2007**, *19*, 2679.
- Kantor, T. G. *Pharmacotherapy* **1986**, *6*, 93.
- Sekiya, I.; Morito, T.; Hara, K.; Yamazaki, J.; Ju, Y. J.; Yagishita, K.; Mochizuki, T.; Tsuji, K.; Muneta, T. *AAPS Pharm. Sci. Tech.* **2010**, *11*, 154.
- Sakeena, M. H. F.; Muthanna, F. A.; Ghassan, Z. A.; Kanakal, M. M.; Elrashid, S. M. *J. Oleo. Sci.* **2010**, *59*, 223.
- Mazières, B. *Drugs R. D.* **2005**, *6*, 337.
- Silion, M.; Hritcu, D.; Jaba, I. M.; Tamba, B.; Ionescu, D.; Mungiu, O. C.; Popa, I. M. *J. Mater. Sci.: Mater. Med.* **2010**, *21*, 3009.