Chem. Pharm. Bull.
34(11)4760—4766(1986)

Interactions between Crystalline Medicinals and Porous Clay

YOSHINOBU NAKAI,* KEIJI YAMAMOTO, KATSUHIDE TERADA,
TOSHIO OGUCHI and SATOSHI IZUMIKAWA

Faculty of Pharmaceutical Sciences, Chiba University,
1-33 Yayoicho, Chiba 260, Japan

(Received May 15, 1986)

The physicochemical properties of drug molecules in a mixture with montmorillonite or pillar interlayer montmorillonite (PILM) were studied by using differential scanning calorimetry (DSC), powder X-ray diffraction and infrared (IR) spectroscopy. The DSC and IR data indicated that benzoic acid was converted to ionic species by heating to 400 K in PILM200 and PILM400 mixtures, whereas benzoic acid molecules partially existed in an amorphous state in both montmorillonite and PILM600 mixtures.

The decomposition rate of aspirin in the montmorillonite mixtures was studied at 40 °C and 0, 31.3 and 79% relative humidities (RH). Aspirin was decomposed rapidly at 0% RH as compared with 79% RH in the PILM mixtures. This result indicates that the aspirin did not react with the bulk water but with active water adsorbed on the internal pore surfaces of PILM.

Keywords——pillar interlayered montmorillonite; sodium montmorillonite; differential scanning calorimetry; powder X-ray diffraction; infrared spectroscopy; adsorption; benzoic acid; aspirin; alumina; aluminum hydroxide

Introduction

Most clays have a cation-exchange capacity and a large surface area. In particular, montmorillonite has a high cation-exchange capacity of 0.8—1.5 meq/g, and a large surface area of 600—800 m^2/g because of the extensive internal surface area.[1] However, powdered montmorillonite has a relative small surface area of 30—70 m^2/g, as the aluminosilicate layers are close to each other. Many researchers have reported on the interactions between montmorillonite and drugs.[2] McGinity and Lach reported that amphetamine sulfate–montmorillonite complex showed a sustained release pattern compared with the drug alone.[2b] Porubcan *et al.* reported that in single layers of montmorillonite, clindamycin was oriented parallel to the montmorillonite surface while tetracycline showed a in slightly tilted orientation.[2c] Montmorillonite aluminosilicate layer consists of two tetrahedral layers of silica and one octahedral layer of aluminum sandwiched by the two tetrahedral layers. In the octahedral layer, some Al^{3+} ions are randomly substituted with Fe^{3+} or Mg^{2+} ions, and any deficiency of lattice charge can be balanced with exchangeable cations, especially Na^+.

Recently, pillar interlayered montmorillonite (PILM)[3] was obtained by substitution of the exchangeable Na^+ ion by $[Al_{13}O_4(OH)_{24+x}(OH_2)_{12-x}]^{7-x}$ ion, and subsequent calcination of the solid. The polynuclear Al-oligomer cation acted as a pillar substance in PILM. It was reported that PILM has a large number of pores and a large surface area in the powder state owing to the formation of pillars between the interlayers.[4] The aim of the present work was to examine the physicochemical properties of medicinals in physical mixtures with PILM by using differential scanning calorimetry (DSC), X-ray diffraction and infrared (IR) spectroscopy. In addition, a physical mixture of aspirin and PILM was used for studying the effects of dispersion on the stability of aspirin. The possible usefulness of solid dispersions of drugs and

PILM is discussed.

Experimental

Materials——Benzoic acid (Koso Chemical Co., Ltd.), aspirin (Iwaki Pharmaceutical Co., Ltd.), and bentonite (Wako Pure Chemical Industries Ltd.) were used as received from the suppliers. Other reagents were of analytical reagent grade.

Preparation of Sodium Montmorillonite——The source clay was bentonite. Bentonite larger than 2 μm in diameter was used after sedimentation from the aqueous suspension. Fine bentonite (2 g) was suspended in 100 ml of distilled water, about 50 ml of 1 N NaCl aqueous solution was added, and the mixture stirred for 3 h at 25 °C. The supernatant was removed by centrifugation. The cation exchange with 1 N NaCl aqueous solution was repeated three times. The excess salt was removed by washing with double-distilled water until the supernatant became negative for chloride by the silver nitrate test. Then the sediment was dried in an oven at 120 °C for 24 h.

Preparation of (PILM)——An aqueous solution of $AlCl_3$ (0.3 M, 180 ml) was vigorously stirred, and 1.0 M NaOH (about 130 ml) was added dropwise until the OH/Al ratio became 2.37[3]; the polynuclear cation $[Al_{13}O_4(OH)_{24}(OH_2)_{12}]^{7+}$ was thus formed.[4a] This Al-hydroxide oligomer solution was added to sodium montmorillonite aqueous solution (3%) in an amount of up to five times the cation-exchange capacity (*ca.*1 meq/g) of sodium montmorillonite. The solid was washed with double-distilled water in the same manner as described for the sodium montmorillonite preparation. Then the sediment was dried in an oven at 120 °C for 24 h and calcined in air at 200, 400, or 600 °C. The products were designated as PILM200, PILM400, PILM600, respectively. These PILMs were kept in a desiccator over diphosphorus pentaoxide *in vacuo*.

Preparation of the Mixtures——The mixtures of a crystalline drug and either a PILM or sodium montmorillonite were prepared with mortar and pestle in various mixing ratios.

DSC——Accurately weighed samples of mixtures were sealed into liquid sample pans and measurements were made on a Perkin-Elmer DSC-1B instrument. The heating rate was 4 K/min under a nitrogen atmosphere. The temperature was raised from 323 to 395 K then allowed to fall to 323 K, and the test was repeated. The first test was named the 1st run, and the second, the 2nd run.

Nitrogen Gas Adsorption——The adsorption apparatus was made in this laboratory following the specifications of the technical bulletin of Mellon Institute of Industrial Research. Dead space was measured by using helium gas.

Powder X-Ray Diffraction——Powder X-ray diffraction patterns were measured using a Rigaku Denki 2027 diffractometer with Ni-filtered Cu-K_α radiation. The scanning speed was 2°/min.

IR Spectroscopy——IR spectra were obtained with a Hitachi model 270 spectrometer by the KBr disk method.

Measurement of Decomposition Rate of Aspirin——The samples used were aspirin and physical mixtures of 5% aspirin and 95% PILM or sodium montmorillonite. The powder samples were kept at 0%, 31.3%, or 79% relative humidity (RH), which were obtained by using P_2O_5, and saturated solutions of $MgCl_2 \cdot 6H_2O$ and KBr respectively. The samples were kept in an air bath at 40 °C. At regular intervals, samples were removed for analysis. To determine the percentage of remaining aspirin in the stored samples, concentrations of aspirin and salicylic acid were analyzed spectrophotometrically at 275 and 303 nm[5] on a Shimadzu UV 200S double-beam spectrophotometer.

Results and Discussion

Figure 1 shows the powder X-ray diffraction patterns of sodium montmorillonite, PILM200, PILM400, PILM600, respectively. Differences among the patterns were observed in the range of $2\theta < 10°$. Low-angle peaks in the patterns showed the layered structure of montmorillonite. The montmorillonite aluminosilicate layer is 9.6 Å in thickness.[4] Sodium montmorillonite showed a diffraction peak at $2\theta = 7.0°$ and the calculated interplanar spacing is 12 Å, which is in good agreement with that of hydrated sodium montmorillonite.[6] The PILMs showed *ca.* 20 Å interplanar spacing, which is considered to be the sum of the aluminosilicate layer (9.6 Å) and the interporous layer (about 10 Å).[3]

The values of specific surface area of sodium montmorillonite and PILMs were determined by the nitrogen gas adsorption method (Table I). The specific surface areas of PILMs were approximately 4 times larger than that of sodium montmorillonite. Increases in the interplanar spacing and the specific surface area confirmed the production of PILM.

Figure 2 shows the DSC curves of the physical mixture of 40% benzoic acid and either 60% sodium montmorillonite or 60% PILM. A broad endothermic peak was observed on the curve of the mixture at lower temperature than the melting point of the crystalline drug (392

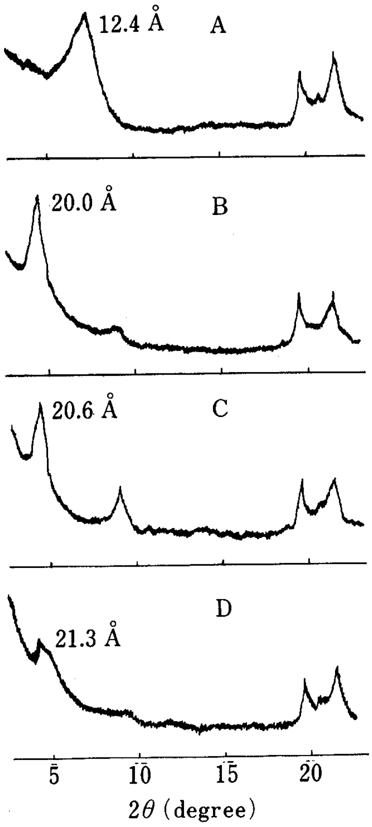

Fig. 1. Powder X-Ray Diffraction Patterns of Sodium Montmorillonite and PILMs

(A), sodium montmorillonite; (B), PILM200; (C), PILM400; (D), PILM600. The numbers on the diffractograms indicate interlayer distances (Å) calculated from Bragg's equation.

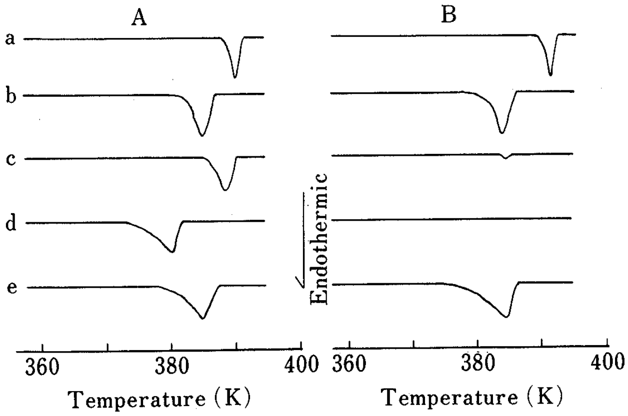

Fig. 2. DSC Curves of the Physical Mixtures of 40% Benzoic Acid and Either 60% Sodium Montmorillonite or 60% PILMs

(A), 1st run; (B), 2nd run. (a), benzoic acid alone; (b), montmorillonite–benzoic acid; (c), PILM200–benzoic acid; (d), PILM400–benzoic acid; (e), PILM-600–benzoic acid. Heating rate, 4 K/min.

K). The mixture of sodium montmorillonite and benzoic acid showed no significant difference between the 1st run and the 2nd run. In the mixture of benzoic acid and either PILM200 or PILM400, on the other hand, the endothermic peak became very small in the 2nd run. In the DSC curves of the drug and PILM600 mixture, the broad endothermic peak was observed in both the 1st run and the 2nd run, though the peak temperature in the 2nd run was lower than that in the 1st run.

Figure 3 shows the IR spectrum of the physical mixture of 40% benzoic acid and 60% PILM400, and the IR spectra of the mixtures of benzoic acid with sodium montmorillonite, PILM400 and PILM600 before and after DSC measurement. The IR spectra of the physical mixtures of 40% benzoic acid and either 60% sodium montmorillonite or 60% PILM600 were the same as that of PILM400 physical mixture, as shown in curve A in Fig. 3. In the cases of sodium montmorillonite or PILM600 mixtures, the IR spectra before and after DSC measurements were identical. However, the mixture with PILM400 showed a quite different IR pattern after DSC measurement. In the IR spectrum of PILM400 physical mixture, the carbonyl stretching absorption of benzoic acid was observed at 1700 cm^{-1}. However, after DSC measurement, the band at 1700 cm^{-1} had disappeared, and new absorption bands appeared at 1604, 1564 and 1435 cm^{-1}, as shown in curve C. Disappearance of the carbonyl absorption band at 1700 cm^{-1} was also observed in PILM200 mixture. Generally, the carbonyl anion has weak symmetric stretching vibrations near 1400 cm^{-1} and strong asymmetric vibrations in the vicinity of 1610—1550 cm^{-1}.[7)] From the IR spectra of the heated

Table I. Specific Surface Area of Sodium Montmorillonite and Various PILMs Measured by the N_2 Gas Adsorption Method

	Specific surface area (m^2/g)
Sodium montmorillonite	46.1
PILM200	179.6
PILM400	144.8
PILM600	191.2

Table II. Enthalpy Change (ΔH) in Mixtures of 40% Benzoic Acid and Either 60% Sodium Montmorillonite or 60% PILMs

	ΔH (J/g)	
	1st run	2nd run
Calculated	56.7	56.7
Sodium montmorillonite	41.5	40.2
PILM200	37.5	1.0
PILM400	25.2	0
PILM600	36.6	35.1

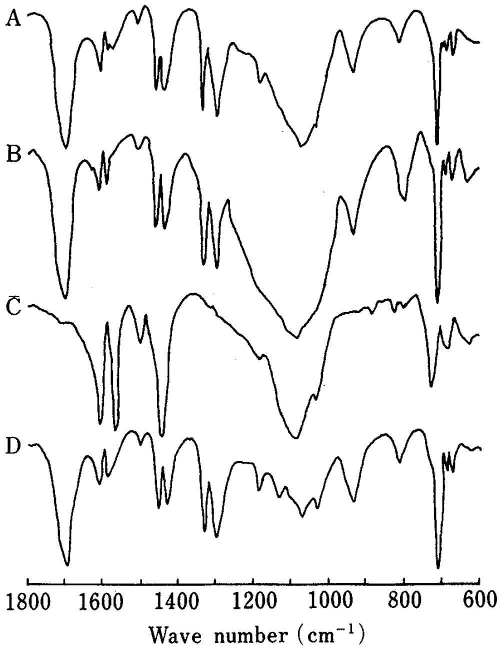

Fig. 3. IR Spectra

(A), freshly prepared physical mixture of 40% benzoic acid and 60% PILM400; (B), after DSC measurement of the physical mixture of 40% benzoic acid and 60% sodium montmorillonite; (C), after DSC measurement of sample (A); (D), after DSC mesurement of 40% benzoic acid and 60% PILM600. All spectra were taken in KBr disks.

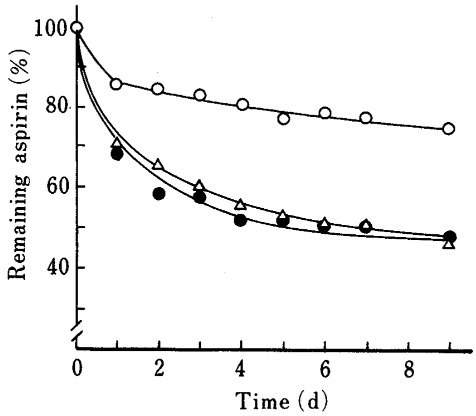

Fig. 4. Decomposition Kinetics of Aspirin in the Mixture of 5% Aspirin and 95% Sodium Montmorillonite at 40 °C

(○), RH 0%; (△), RH 31.3%; (●), RH 79%.

PILM400 mixture, benzoic acid was considered to be present in the ionic form in the PILM400 mixture. In the case of PILM200 mixture, benzoic acid also changed into the ionic form during DSC measurement, while no IR spectral changes were observed in the PILM600 mixture after DSC measurement.

The heats of fusion were calculated from the DSC peak areas. When 1 g of the mixture contains 0.4 g benzoic acid, the heat of fusion can be calculated as 56.7 J/(g mixture), from the enthalpy value of benzoic acid of 141.8 J/(g benzoic acid). The heats of fusion of all mixtures, however, were found to be lower than 56.7 J/(g mixture) as shown in Table II. In the case of sodium montmorillonite mixture, it was found that about a 27% decrease in enthalpy occurred in the 1st DSC run as compared with the calculated value of 56.7 J/g. It was considered that the decrease of enthalpy was attributable to the adsorption of drug molecules on the surface of sodium montmorillonite, and to the penetration of drugs into the porous aluminosilicate layer. The greater decrease of the enthalpy in the PILM600 mixture was due to the greater surface area and the presence of pore structure. When the PILM200 or PILM400 mixture was heated in DSC pans, benzoic acid molecules were converted to the ionic form simultaneously with melting, and in the 2nd run the value of enthalpy abruptly became smaller than that of the 1st run. This result is compatible with the changes in the IR spectra shown in Fig. 3. Nakai *et al.* reported that a chemical reaction occurred between carboxylic acid and oxide during heating of the mixture.[8] In this case, the species produced predominantly was considered to be an aluminium benzoate. In the case of PILM600, the concentration of reactive Al anion might be decreased significantly by the calcination at 600 °C.

Decomposition rate of aspirin—Figure 4 shows the remaining aspirin (percent) in 5% aspirin and 95% sodium montmorillonite physical mixtures stored at 40 °C and various levels of RH. In the case of RH 0%, aspirin decomposed relatively quickly in the initial period, but thereafter the period the rate of decomposition decreased. This result could be related to the amount of water adsorbed on the sodium montmorillonite surface. The reaction may cause a

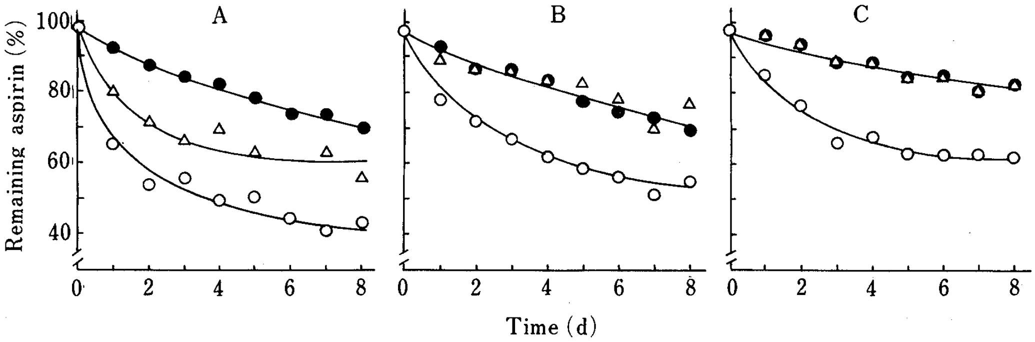

Fig. 5. Decomposition Kinetics of Aspirin in the Mixture of 5% Aspirin and 95% PILMs at 40 °C

(A), PILM200–aspirin; (B), PILM400–aspirin; (C), PILM600–aspirin. (○), RH 0%; (△), RH 31.3%; (●), RH 79%.

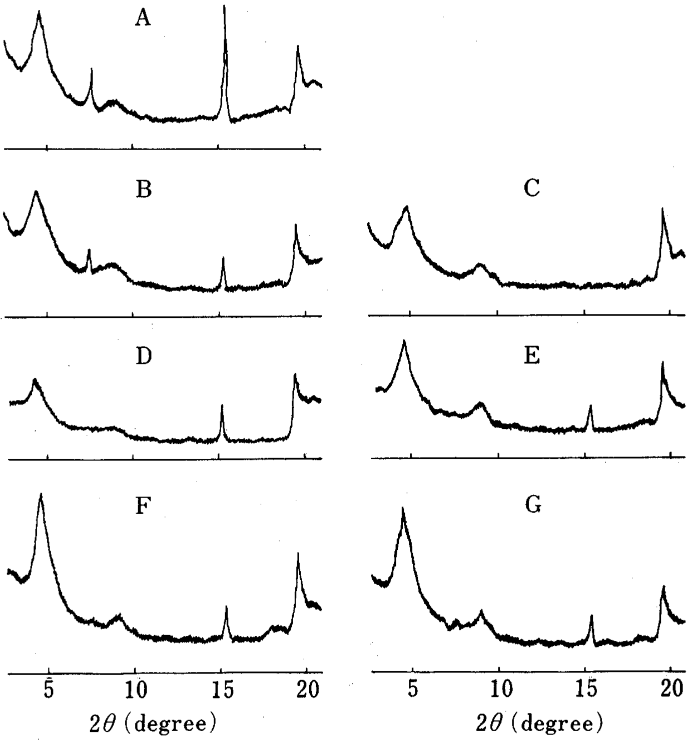

Fig. 6. Powder X-Ray Diffraction Patterns of the Mixture of 5% Aspirin and 95% PILM200 at 40 °C

(A), immediately after mixing; (B), after the storage for 3 d at RH 0%; (C), 10 d at RH 0%; (D), 3 d at RH 31.3%; (E), 10 d at RH 31.3%; (F), 3 d at RH 79%; (G), 10 d at RH 79%.

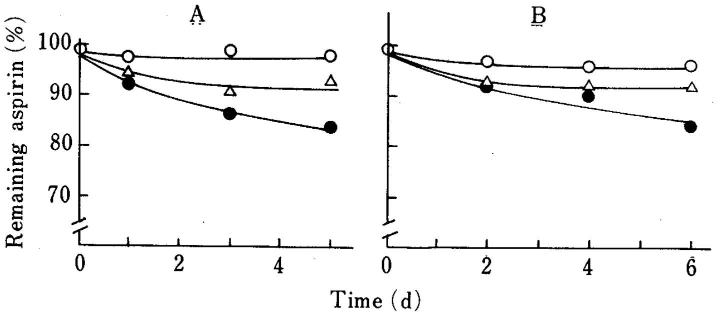

Fig. 7. Decomposition Kinetics of Aspirin in the Mixture of 5% Aspirin and Either 95% Al_2O_3 or 95% $Al(OH)_3$ at 40 °C

(A), Al_2O_3–aspirin; (B), $Al(OH)_3$–aspirin; (○), RH 0%; (△), RH 31.3%; (●), RH 79%.

desorption of water from sodium montmorillonite at 0% RH. When these samples were stored at 31.3% and 79% RHs, water was adsorbed and penetrated into the aluminosilicate layer of sodium montmorillonite. Penetration of water would induce expansion of the montmorillonite layers. This was confirmed by the change of the X-ray diffraction peak of sodium montmorillonite, that is, the peak shifted to a lower diffraction angle about $2\theta = 4°$ (the interplanar spacing was calculated as 22 Å) with increase in the water content. Higher decomposition rates of aspirin were observed at 31.3% and 79% RH, and these were considered to be due to increases of the surface area and the amount of adsorbed water.

Figure 5 illustrates the time course of remaining aspirin (percent) for aspirin–PILMs mixtures stored at 40 °C and 0%, 31.3% and 79% RH. In all PILM mixtures, the maximum decomposition rate was observed at 0% RH, in contrast to the sodium montmorillonite system. The faster decomposition of aspirin at 0% RH can be attributed to the existence of porous structure in PILM and to the migration of aspirin molecules into the structure through the gas phase. On the other hand, in the case of 31.3% and 79% RH, it was assumed that the migration of aspirin was hindered, since water vapor adsorption at the pore sites would compete with the migration of aspirin. Figure 6 shows the X-ray diffraction patterns of aspirin–PILM200 mixture stored at 0%, 31.3% and 79% RH for various time intervals. In the fresh mixture, the diffraction peaks of aspirin crystals were observed at $2\theta = 8.0°$ and 15.5°. The intensities of these peaks decreased significantly after storage of the mixture for 3 d. After storage for 10 d at 0% RH, aspirin crystal diffraction peaks disappeared, while at 31.3% and 79% RH these peaks were still observed. The changes in the X-ray diffraction patterns appeared to be closely related to the decomposition patterns shown in Fig. 5. The X-Ray diffraction peaks due to crystalline salicylic acid formed by decomposition of aspirin were not observed. Therefore, it seems reasonable to assume that salicylic acid and aspirin molecules existed in the pores of the PILM interlayer. We also studied the aspirin decomposition in a mixture of aspirin with either Al_2O_3 or Al $(OH)_3$ (components of the PILM). Figure 7 shows the remaining aspirin (percent) under the same conditions as for the aspirin–montmorillonite mixture or aspirin–PILM mixtures. It is clear that the decomposition patterns of aspirin are very similar to that in the sodium montmorillonite system. Consequently, the RH dependence of aspirin decomposition observed in the PILM mixtures was not related to the component substances, but to the presence of pores in PILM. In the montmorillonite aluminosilicate layer, water exists in three states, *i. e.*, free water, cation hydrated water and water intercalated with the silicate surface.[9] In the case of PILM mixtures, it can be suggested that the decomposition of aspirin was accelerated by the water included in the pillar structure, and that the free bulk water had little effect.

The PILM mixtures showed quite different behavior from conventional montmorillonite complex in which medicinals are intercalated into the montmorillonite aluminosilicate layers.

When components having these pore structures are used, special care is necessary concerning the conditions of storage because the physicochemical properties of the medicinals in the mixture may change.

Acknowledgment The authors are grateful to Miss Sonoko Nakano for skillful technical assistance.

References and Notes

1) J. L. White and S. L. Hem, *Ind. Eng. Chem. Prod. Res. Dev.*, **22**, 665 (1983).

2) *a*) J. W. McGinity and J. L. Lach, *J. Pharm. Sci.*, **65**, 896 (1976); *b*) *Idem, ibid.*, **66**, 63 (1977); *c*) L. S. Porubcan, C. J. Serna, J. L. White and S. L. Hem, *ibid.*, **67**, 1081 (1978); *d*) L. S. Porubcan, G. S. Born, J. L. White and S. L. Hem, *ibid.*, **68**, 358 (1979); *e*) M. S. Camazano, M. J. Sanchez, M. T. Vicente and A. Dominiguez-Gill, *ibid.*, **69**, 1442 (1980); *f*) M. S. Stul, D. P. Vliers and J. B. Uytterhoven, *ibid.*, **73**, 1372 (1984).

3) N. Lahav, U. Shani and J. Shabtai, *Clays Clay Miner.*, **26**, 107 (1978).

4) *a*) M. Matsumoto, S. Shinoda, H. Takahashi and Y. Saito, *Bull. Chem. Soc. Jpn.*, **57**, 1795 (1984); *b*) M. Matsumoto, M. Suzuki, H. Takahashi and Y. Saito, *ibid.*, **58**, 1 (1985).

5) R. B. Tinker and A. J. McBay, *J. Am. Pharm. Ass. Sci. Ed.*, **43**, 315 (1954).

6) U. D. Pennio, E. Mazzega, S. Valeri, A. Alietti, M. F. Brigatti and L. Poppi, *J. Colloid Interface Sci.*, **84**, 301 (1981).

7) K. Nakanishi, "IR Absorption Spectroscopy: Practical," Nankodo, Tokyo, 1960, p. 49.

8) Y. Nakai, K. Yamamoto, K. Terada and Y. Matsuoka, *Yakuzaigaku*, **40**, 219 (1980).

9) M. P. Atkins, D. J. H. Smith and D. J. Westlake, *Clay Miner.*, **18**, 423 (1983).