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Application of Methyl Cinnamate/ Montmorillonite as Ultraviolet Radiation Shelters

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ABSTRACT

The interaction of methyl cinnamate/montmorillonite samples prepared by melting the former onto the second or by joint grinding, has been studied by x-ray diffraction, differential thermal analysis, thermogravimetric analysis and Fourier–transform infrared spectroscopy. Formation of an interlayer compound has been observed, leading to an increase of 4.15 or 3.42 Å (samples obtained by melting or grinding, respectively) in the basal spacing of the clay. Formation of such a complex leads to a displacement of molecular water from the interlayer space, as concluded from the thermal studies. No chemical change is observed in the methyl cinnamate molecule, as confirmed by infrared spectroscopy. The systems prepared improve the shelter properties of the clay and the drug separately, mainly in the C zone of the ultraviolet spectrum (290–190 nm).

INTRODUCTION

The increasing demand for products to be used as shelters against ultraviolet "C" radiation, due to the increasing problems of skin cancer, has led to studies and development of drugs to solve this problem. Many chemicals known as absorbers for ultraviolet radiation are currently studied in order to fulfill the requirements that would accomplish these aims. In many cases, such compounds are used dispersed on a suitable support, although in such a case, the question is whether the protecting properties are enhanced (or canceled) in the supported form, if compared to those exhibited by the same compound when used in the bulk.

Methyl cinnamate is currently one of the most common components of solar filters. In the present work,

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we have studied whether adsorption/dispersion of this drug onto the surface of an inert clay, such as montmorillonite, leads to an improvement of the protecting ability of the drug against solar radiation. Many papers deal with the interaction of clays and drugs (1–3); however, preparation of the drug/clay compounds is most often achieved by adsorption from liquid (usually aqueous) solutions, and only in very few cases have alternative preparation methods been used (4,5). However, this method cannot be followed for this drug, as it is insoluble in water. So, alternative methods, such as intimate grinding of drug/clay mixtures, or melting of the drug onto the clay surface, should be followed in this case (6).

METHODS AND PROCEDURES

Montmorillonite was commercial K-10 from Fluka (Germany, ref. 69866). Fraction with a grain size lower than 2 μm was used and saturated with sodium (sample M). Methyl cinnamate was also from Fluka (ref. 96410). It is a white solid, with melting point of 34°–36°C, insoluble in water, but soluble in diethyl ether, acetone, or benzene (7).

The clay was characterized by chemical analysis and its exchange capacity was also measured. The x-ray diffraction (XRD) diagrams were recorded in a Philips PW1700 instrument, using CuKα radiation. The Fourier-transform infrared spectra (FT-IR) were recorded in a Perkin–Elmer FT-1730 instrument, connected to a Perkin–Elmer 3700 data station, following the KBr disk technique, averaging 100 spectra with a nominal resolution of 4 cm^{-1}. The differential thermal analysis (DTA) and thermogravimetric analysis (TG) were performed on Perkin–Elmer DTA-1700 and TGS-2 apparatuses, respectively, connected to a Perkin–Elmer 3600 data station, using calcined alumina in the first case as reference material, and with a heating rate of 5°C/min. The specific surface area was calculated following the BET method (Brunauer–Emmett–Teller, Ref. 8) by nitrogen adsorption at −196°C in a conventional high-vacuum apparatus. The absorbing ability for visible–ultraviolet (Vis–UV) radiation was measured by Vis-UV spectroscopy following the diffuse reflectance technique (Vis-UV/DR) in a Shimadzu UV-240 spectrophotometer, using a 5-nm slit and MgO as reference. Most of these techniques were also used to characterize the drug and the drug/clay systems, when applicable.

The samples were prepared by intimately mixing the required amounts of drug and clay to obtain samples containing 1, 2, 3, 5, 10, 25, 50, 75, or 90 g drug/100 g clay. The mixture was ground at room temperature for 10 min, as it was previously established that this was the optimum grinding time (6). These samples are labeled samples "MC-G." Samples were prepared also by heating, for 24 hr at room temperature, the mixtures at the melting point of methyl cinnamate (35 ± 1°C); these samples are labeled "MC-M."

As one of the aims of the present work is to provide insight in the protecting properties of the drug/clay systems, we have also studied the desorption of the drug from the clay system, when submitted to aqueous suspension with characteristics close to those of human sweat (4). For these studies, 100 mg of the drug/clay system were suspended in 50 ml of an aqueous solution prepared by dissolving 2.925 g NaCl and 0.745 g KCl in 1 liter of water, at pH = 5.5. The suspension was placed in a water bath at 40°C and was continuously stirred during 15 min. After centrifugation, one half of the liquid was removed, and an equal volume of solution was added. The process was repeated 6 times. Although usually the amount of drug desorbed is determined from the absorbance of the liquid, in this case, as the drug is insoluble in water, the amount of drug desorbed was calculated from the spectra of the solids before and after the desorption process.

In the following, only data obtained for the samples containing the maximum amounts of drug are reported.

RESULTS AND DISCUSSION

The Vis–UV/DR spectra of the samples containing the minimum and maximum amounts of methyl cinnamate are shown in Fig. 1. A broad band is recorded at 272 nm, with a shoulder at 220 nm. The spectra of the pure drug and clay are also included in the same figure. As can be concluded from this figure, the spectra of the drug/clay systems are not merely the addition of the spectrum of the drug and that of the clay.

Both preparation methods (melting and grinding) seem to be adequate to obtain drug/clay systems with enhanced ability for solar protection, specially in the 290–190 nm range, that is, the range corresponding to the most dangerous "C" radiation.

The XRD diagrams in Fig. 2 indicate formation of interlayer compounds, following both preparation methods. Basal spacing for montmorillonite is increased from 14.24 to 18.34 Å upon formation of the compound following the melting route (sample MC-M/M), while for the sample prepared by grinding the basal spacing for

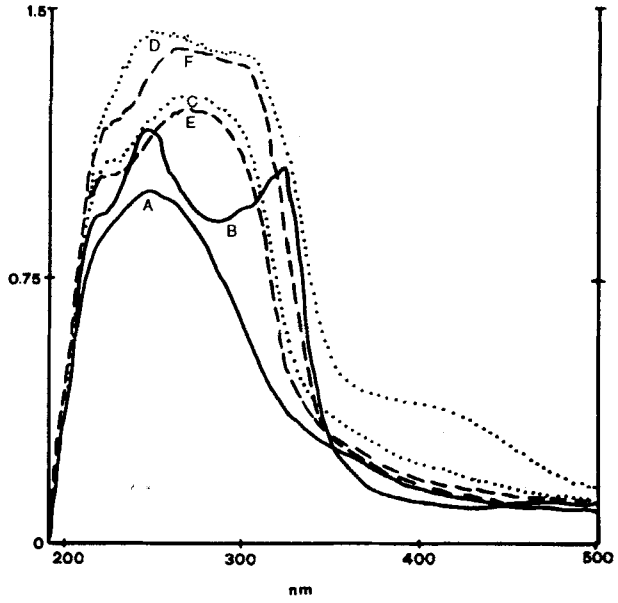

Figure 1. Vis–UV spectra of samples: (A) montmorillonite; (B) methyl cinnamate; (C) MC-MM/20; (D) MC-MM/90; (E) MC-MG/20; (F) MC-MG/90.

the sample is 17.66 Å, that is, the increases are 4.10 and 3.42 Å, respectively. Two peaks, recorded at 9.81 and 7.13 Å, are due to illite and kaolinite, existing as impurities in the original montmorillonite.

The DTA curve for Na-exchanged montmorillonite is shown in Fig. 3(a). The first, intense, endothermic peak at 134°C is due to removal of loosely held molecular water, while the broad feature at 485°C is due to removal of structural water in kaolinite, existing as an impurity in this natural montmorillonite sample, already detected by x-ray diffraction. The broad, ill-defined, endothermic effect at 609°C is probably due to removal of structural hydroxyl groups from montmorillonite.

The DTA curve recorded for montmorillonite after being submitted to 10 min grinding is shown in Fig. 3(b). The first endothermic peak is now recorded at 109°C, while the second one is much weaker, and extends along a very wide temperature range (200°–550°C), with the minimum at 426°C. Most probably, this second endothermic effect covers the two effects previously distinguished in the DTA curve of the original, unground montmorillonite in Fig. 3(a).

The curve for the pure drug is shown in Fig. 3(c). Two endothermic effects are recorded, but their shapes are rather uncommon. The first one, at 43°C, corresponds to melting of the drug, while the second one, at 256°C, is clearly asymmetric, and corresponds with total weight loss recorded in the TG analysis (vide infra); nevertheless, the extreme sharpness of the peak and its asymmetry suggest that the liquid is removed before burning, as, in this last case, an exothermic effect would be recorded.

The curve recorded for sample MC-M/M is shown in Fig. 3(d). The sharp, endothermic effect at 49°C should be ascribed to melting of the dispersed drug. No endothermic peak is recorded close to 100°C (i.e., due to removal of water molecules), thus suggesting that most of interlayer water existing in the original montmorillonite has been replaced by drug molecules. Probably, it is not a mere "molecular exchange" process, but it should be undoubtedly favored by the hydrophobic nature of the organic drug. The broad, weak, endothermic effect close to 256°C can be attributed to volatilization of the drug, but it is immediately followed by a very broad and intense effect, with maximum at 442°C, that should be ascribed to burning of the dispersed drug.

Finally, the DTA curve recorded for sample MC-M/G is shown in Fig. 3(e). The shape of the curve is very similar to that for sample MC-M/M, with the minimum of 49°C due to melting of the drug, the absence of any endothermic effect close to 100°–110°C (thus indicating that in this case interlayer water has been also replaced), and the endothermic shoulder at 220°C, just before the intense exothermic effect centered at 443°C.

The TG curves for these five samples are shown in Fig. 4. The conclusions reached from this study are in all cases coincident with those just given from the DTA study. The curve for Na-montmorillonite is shown in Fig. 4(a). A first weight loss, corresponding to 7% of the initial sample weight, is recorded between 41° and 119°C. Its position almost coincides with the endothermic effect at 134°C in the DTA curve of this same sample, Fig. 4(a). The second weight loss, 6%, extends over a very wide temperature range (119°–713°C) and covers the two endothermic effects recorded at 485° and 609°C.

The curve recorded for ground montmorillonite is qualitatively identical, Fig. 4(b). The first weight loss, recorded in the same temperature range (41°–119°C), is 5% of the initial sample weight, a value slightly lower than that recorded for the unground sample. The second weight loss is also weaker (3%) and extends over a wide temperature range, but starts at a higher temperature than for the unground sample (422°–686°C).

The TG curve for methyl cinnamate, Fig. 4(c), shows a single weight loss starting at 256°C, which

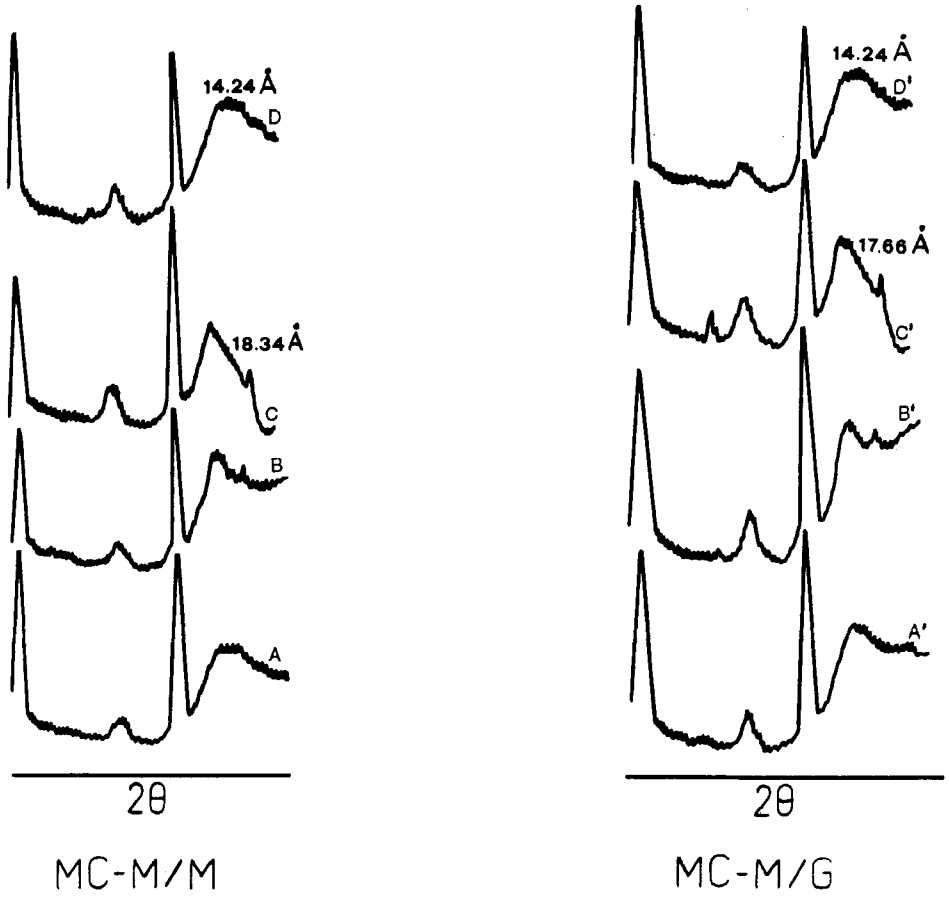

Figure 2. X-ray diffraction diagrams of sample: (A) MC-MM/1; (B) MC-MM/25; (C) MC-MM/90; (D) original montmorillonite; (A') MC-MG/1; (B') MC-MG/25; (C') MC-MG/90; (D') ground montmorillonite.

position coincides with the second endothermic effect [Fig. 3(c)] recorded in the DTA curve for this sample.

The curves for the drug-containing samples are rather different from the pure clays, Fig. 4(d). So, for sample MC-M/M the first weight loss, ascribed to molecular weight removal from the interlayer space (41°–119°C) has been canceled, thus again confirming molecular exchange by the drug molecules in the interlayer space. The first weight loss, between 103° and 216°C, corresponds to 32% of the initial sample weight and should be ascribed to a partial decomposition of the drug. The remaining weight loss (only 5%) between 431° and 739°C, should correspond to removal of hydroxyl groups from the clay structure, as its value is rather similar to that recorded for unchanged montmorillonite.

Finally, the curve in Fig. 4(e) corresponds to sample MC-M/G. Again, no weight loss is recorded below ca. 85°C, thus confirming total water/drug exchange also in this sample. The main weight loss (35%) is recorded between 85° and 216°C, and should correspond to removal of the drug. Again, and as observed for the previous sample, a weight loss close to 4% is recorded between 413° and 642°C, and should be ascribed to removal of hydroxyl groups from the clay network.

The results of the FT-IR study of this series of samples have been summarized in Fig. 5, where the spectra of the clays, the drug, and the drug/clay systems have been included.

The spectrum for Na-montmorillonite is included in Fig. 5(a). The broad band at 3436 cm^{-1} is due to stretch-

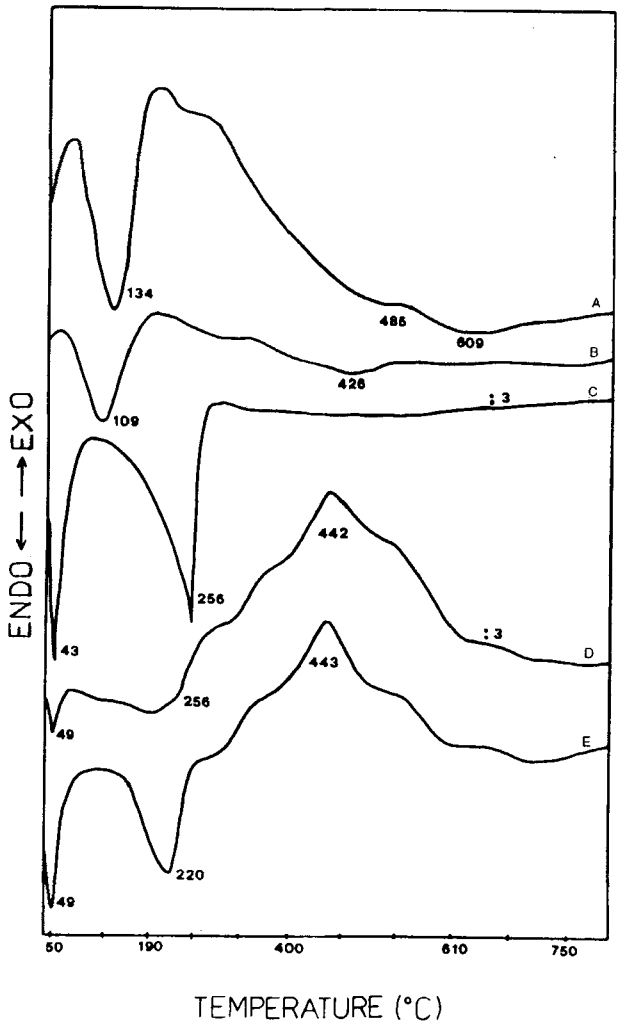

Figure 3. Differential thermal analysis curves of samples: (A) montmorillonite; (B) ground montmorillonite; (C) methyl cinnamate; (D) MC-MM/90; (E) MC-MG/90.

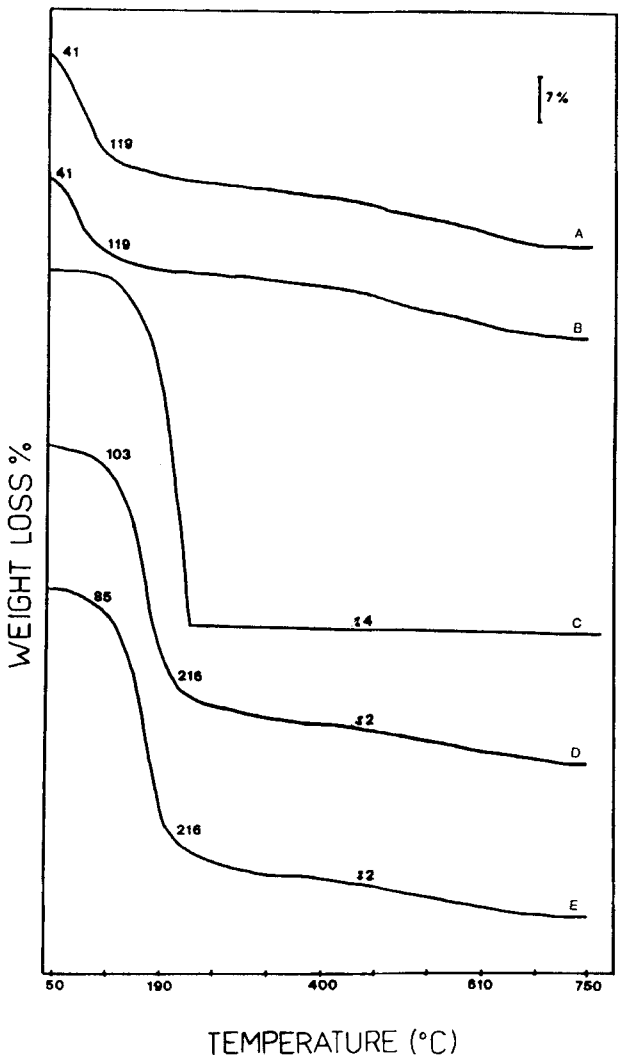

Figure 4. Thermogravimetric analysis curves for samples: (A) montmorillonite; (B) ground montmorillonite; (C) methyl cinnamate; (D) MC-MM/90; (E) MC-MG/90.

ing mode of hydroxyl groups (9). The broadness of the band is caused by the existence of hydrogen bonding between the structural hydroxyl groups and the water molecules in the interlayer. The deformation mode of molecular water is evidenced by the absorption at 1639 cm^{-1}. The broad feature close to 1000 cm^{-1} is due to lattice vibrations of the clay network (10). Only minor changes develop in the spectrum when the sample is submitted to grinding for 10 min, Fig. 5(b).

The spectrum of pure methyl cinnamate is included in Fig. 5(c). The most intense band, at 1719 cm^{-1}, is due to stretching mode of the carboxylic C=O moiety, while the C-O mode of the ester group is responsible for the band at 1172 cm^{-1}, although also the band at 1279 cm^{-1} could be ascribed to this mode. The medium-intensity band at 1636 cm^{-1} is due to the C=C stretching mode, and there is a conjugation between this double bond with the delocalized system in the phenyl ring, and with the carbonyl group. The series of weak bands slightly below 3000 cm^{-1} is due to CH stretching modes, while deformation of these bonds accounts for the absorption at 1477 cm^{-1}. Finally, several very weak peaks are also recorded between 3100 and 3000 cm^{-1},

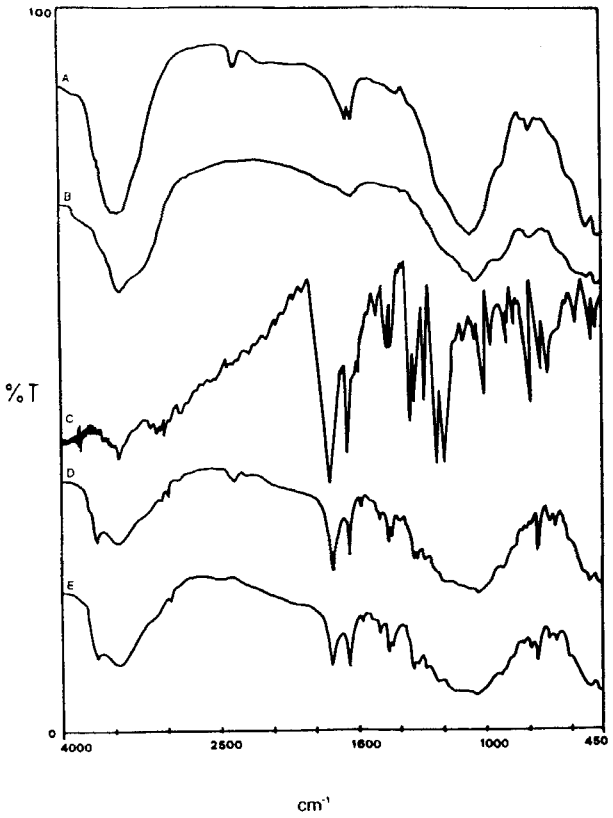

Figure 5. FT-IR spectra of sample: (A) montmorillonite; (B) ground montmorillonite; (C) methyl cinnamate; (D) MC-MM/90; (E) MC-MG/90.

and are due to C–H stretching modes of the phenyl group.

When the drug is adsorbed on the clay, following the methods above described, the spectra recorded for the samples thus obtained consist of the bands of the drug and the bands of the clay. So, the spectrum for sample MC-M/M shows a band at 3627 cm^{-1} due to the stretching mode of structural hydroxyl groups. Even the weak bands close to 3000 cm^{-1} and due to C–H stretching modes (both aliphatic and aromatic) are still recorded. The sharp, medium-intense bands at 1718 and 1638 cm^{-1} are due to C=O stretching mode of α,β-unsaturated ester and conjugation of the aromatic ring with the double bond of the molecule. The differences between the positions of these bands for the pure drug and when supported on montmorillonte in sample MC-M/M are very small, thus indicating that there is no decomposition of the drug because of its dispersion on the clay surface.

A similar conclusion can be reached from the FT-IR spectrum of sample MC-M/G, Fig. 5(e). The C=O mode of the ester group gives rise to the sharp band at 1718 cm^{-1}. The band at 3622 cm^{-1} is also clearly recorded.

The FT-IR study indicates that both for sample MC-M/M and MC-M/G, the drug substitutes the water molecules originally existing in the interlayer space. The band due to O–H stretching mode of free hydroxyl groups is clearly recorded for these samples, where hydrogen bonding has been diminished because of the drug/water substitution. If results for samples with lower drug loadings are compared, it can be observed that substitution takes place steadily, as it is the change in the relative intensities of the FT-IR bands that is recorded. Also, it should be noticed that the positions of the drug bands are not changed because of melting or grinding, thus indicating that it remains stable and undecomposed on the montmorillonite surface.

Finally, it should be taken into account that studies on the desorption of the drug from the clay surface indicated that only 4% and 6% of the drug was desorbed, respectively, from samples MC-M/M and MC-M/G. These values are extremely low, thus indicating that the protective properties of the drug/clay system should be prevented.

CONCLUSIONS

The adsorption systems obtained following the melting method show an appreciable increase in the protective properties of methyl cinnamate against UV radiation, especially in the high-energy range ("C" radiations, 290–190 nm). Desorption when treated in vitro with a physiological solution similar to the human sweat is very low, thus indicating the suitability of these systems as sunlight protectors.

Results from the FT-IR and TG/DTA studies have shown that substitution of water molecules by drug molecules in the interlayer space takes place steadily as the amount of drug is increased. X-ray diffraction diagrams show an increase in the basal spacing.

REFERENCES

1. K. S. E. Su and T. J. Carstensen, J. Pharm. Sci., 61, 420 (1972).
2. J. W. MacGinity and J. L. Lach, J. Pharm. Sci., 65, 896 (1976).

3. J. S. Porubcan, C. J. Serna, J. L. White, and S. L. Hem, J. Pharm. Sci., 67, 1081 (1978).
4. M. A. Vicente, M. Sánchez-Camazano, M. J. Sánchez-Martín, M. del Arco, C. Martín, and V. Rives, Clays and Clay Min., 37, 157 (1989).
5. C. del Hoyo, V. Rives, and M. A. Vicente, Appl. Clay Sci., 8, 37 (1993).
6. C. del Hoyo, Ph.D. thesis, University of Salamanca, Spain (1995).
7. *The Merck Index*, 11th Edition, Centennial Edition, Merck and Co., Rahway, NJ, 1989.
8. S. Brunauer, P. M. Emmett, and G. Teller, J. Am. Chem. Soc., 60, 309 (1938).
9. V. C. Farmer, *The Infrared Spectra of Minerals*, Mineralogical Society, London, 1974.
10. B. Cicel and Z. G. Kranz, Clay Min., 16, 151 (1981).