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INTERACTION OF DEXAMETHASONE AND MONTMORILLONITE

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Clay-drug interactions have been widely studied during the last decade. However, the reaction mechanisms responsible of these interactions only have been elucidated in some cases (1,2), most of them when cationic drugs are involved. Neutral molecules are known to interact with clays by physical adsorption (3), and/or by hydrogen bonding (4). Digoxin is adsorbed onto montmorillonite by a reversible adsorption mechanism (5) and degrades by acid-catalyzed hydrolisis. The mechanism of adsorption and degradation of the neutral steroid hydrocortisone by palygorskite and sepiolite has been recently studied (6,7). Two types of ferric iron present in these clays may be responsible for the different degradation rates of hydrocortisone.

Dexamethasone was chosen as the model drug because it is one of the most powerfull antiinflammatory steroid, which is orally or topically administered because of its minimal mineralcorticoid properties. This neutral drug degrades by oxidation and may be coadministered with clay-containing pharmaceuticals.

Montorillonite was used as a model clay because it possesses the highest accesible surface area and exchange capacity of the clays commonly used in pharmacy.

EXPERIMENTAL

All chemicals were either official or reagent grade. An X-ray diffractogram of the clay sample indicated that it was composed of montmorillonite and traces of quartz. A high-pressure liquid chromatographic method useful for the analysis of hydrocortisone and its degradation products (6) was slightly modified for this study. Changes in

the A-ring of dexamethasone were monitored by UV spectrometry at 240 nm.

Kinetic studies were carried out at 25, 35 and 55°C. 100 mg of clay was mixed with 30 ml of an aqueous solution of dexamethasone (50 μg/ml) in 50 ml stoppered centrifuge tubes and aged in a shaker-incubator. At appropriate intervals, aliquots were centrifuged and supernate was filtered and analyzed by HPLC and UV spectrometry. The pH of each suspension was mantained within a range 8.7-9.0.

The sample preparation for the study of adsorption as a function of concentration was carried out according to the method described for the kinetic study, but 5-50 μg/ml dexamethasone concentration and 50 mg of clay were used.

RESULTS AND DISCUSSION

Dexamethasone exhibited a very slow degradation in aqueous solution at pH 6-9 and 25°C (Fig. 1b). In a montmorillonite suspension it was observed that dexamethasone content of the aqueous phase continuously decreased as determined by HPLC analysis (Fig. 1a, D). The degradation profile shown in Fig. 1a suggests that compounds A (acidic product) and N (neutral product) arise directly from dexamethasone. However, the degradation profile (Fig. 1a) was treated as consisting in three different reaction phases (Fig. 1b): a) the initial decrease of dexamethasone concentration from 50 to 9 μm/ml, suggested that the drug is adsorbed by montmorillonite. This effect was also observed by UV spectrometry and is similar but greater than that reported (6) for sepiolite-hydrocortisone interaction; b) a second reaction phase could be consistent with a rapid degradation rate of dexamethasone as shown by HPLC analysis together with dexamethasone adsorption by the clay; c) the third reaction phase suggests a slow degradation rate of dexamethasone as indicated by HPLC and UV analysis.

The d(001) spacing for montmorillonite in the absence of drug under dehydration conditions was 9.6 Å, indicating that no interlayer molecules (i.e., water or drug) were present in the control sample. Adsorption of drug molecules between the layers of montmorillonite increased the d(001) spacing to 14.9 Å. This result indicated that dexamethasone penetrated into the interlayer space of the clay and is in agreement with the first reaction phase of the degradation profile above described.

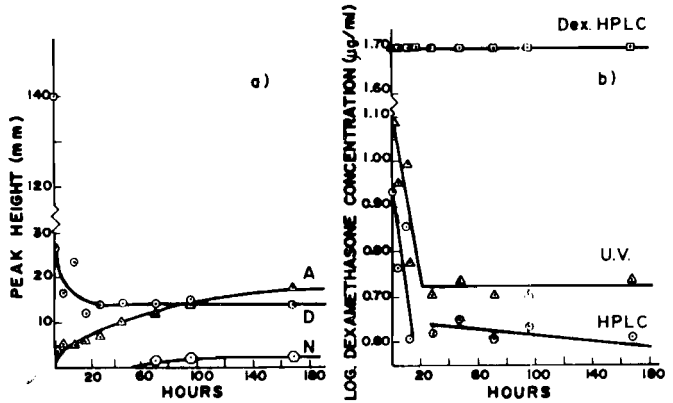

Fig. 1

The IR spectrum of dexamethasone-montmorillonite complex supports weak adsorption mechanism. The carbonyl-stretching vibration of the C-17 dexamethasone side-chain shifted from 1705 to 1690 cm^{-1}. In addition, the carbonyl-stretching vibration of the C-3 dexamethasone A-ring also shifts from 1660 to 1650 cm^{-1}, as a result of the interaction with montmorillonite. This shift to lower frecuency indicates hydrogen bonding as the main adsorption mechanism, although van der Waals' forces also may contribute. Desorption studies confirmed that dexamethasone is weakly adsorbed by montmorillonite since it was easily desorbed by washing with water.

It may be concluded that the montmorillonite-dexamethasone reaction mechanism is consistent with a reversible adsorption process and simultaneous degradation reaction.

REFERENCES

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

(2) Hem,S.L. and White,J.L.(1985),Chemtec.,1,44.

(3) Bradley,W.F. (1945),J. Am. Chem. Soc.,67,975.

(4) MacEwan,D.M.C.(1948),44,349.

(5) Porubcan,L.S.,Born,G.S.,White,J.L. and Hem,S.L.(1979),J. Pharm. Sci. 68,358.

(6) Cornejo,J.,Hermosín,M.C.,White,J.L.,Peck,G.E. and Hem,S.L.(1980),J. Pharm. Sci.,69,945.

(7) Hermosín,M.C.,Cornejo,J.,White,J.L. and Hem,S.L.(1981),J. Pharm. Sci. 70,189.