Interaction of Dexamethasone and Montmorillonite – Adsorption-Degradation Process

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(Received February 1, 1988; accepted after revision August 8, 1988)

ABSTRACT

Forteza, M., Galán, E. and Cornejo, J., 1989. Interaction of dexamethasone and montmorillonite - adsorption-degradation process. Appl. Clay Sci., 4: 437–448.

The degradation of dexamethasone in an aqueous suspension of montmorillonite seems to be the result of two apparent first order reactions. The dexamethasone content, as determined by high-pressure liquid chromatography (HPLC), rapidly decreases from 50 to 4.7 μg/ml after 24 h, and then remains almost constant during 168 h. The first stage of the decomposition is mainly consistent with an adsorption process, while the second one is characterized by a slow degradation of dexamethasone remaining in solution.

X-ray diffraction (XRD) and infrared (IR) studies showed the presence of dexamethasone molecules adsorbed in the interlayer space of montmorillonite, with the basal spacing being consistent with an orientation of the plane of the rings parallel to that of the silicate sheets. Desorption studies showed a slow release of the dexamethasone from the interlayer space of montmorillonite.

INTRODUCTION

The swelling capacity of montmorillonite, as well as its adsorption, suspension-forming and gel-forming properties, makes it suitable as an excipient in pharmaceutical uses. The incorporation of various grades of montmorillonite in the matrix of solid forms of dosage such as disintegrants, binders and lubricants was studied by Wai et al. (1966). Other reports dealing with the use of montmorillonite as a "disintegrating" agent were performed by Gross and Becker (1952) and Firouzabadian and Huyck (1954).

Recently, the ability of montmorillonite to form interlayer complexes with organic molecules of pharmaceutical interest has been widely studied. McGinity and Lach (1977) and Sánchez-Camazano et al. (1980a,b and 1987)

have suggested that montmorillonite could be used in designing sustained-release formulations as a result of drug–montmorillonite interaction.

Nevertheless, most investigations in this field have been mainly carried out on cationic drugs, as well as on weak bases (Porubcan et al., 1978; Browne et al., 1980a,b), while minor attention has been paid to the interaction of neutral or polar drugs with clays (Porubcan et al., 1979; Cornejo et al., 1980; Hermosín et al., 1981). Such interactions can result in complex adsorption-degradation processes.

The aim of this paper is to investigate if the interaction of montmorillonite with dexamethasone could lead to changes in the bioavailability of this drug. Dexamethasone is one of the most powerful anti-inflammatory drugs which is orally or topically administered because of its minimal mineral-corticoid properties. This neutral drug is known to degrade by an oxidation mechanism that produces elimination or transformation of the C-17 dihydroxiacetone side chain (Cohen, 1973). For the above-mentioned purpose, adsorption-desorption and the profile of the degradation of the drug in presence of montmorillonite were investigated in an attempt to elucidate the mechanism responsible for these processes.

EXPERIMENTAL

Materials

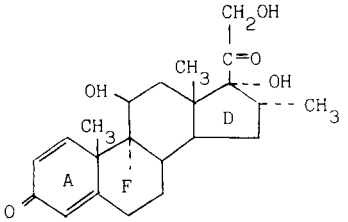
All chemicals were high-purity or reagent grade. The sodium montmorillonite (SW_y-1) from Clay Mineral Repository, was used as received. An X-ray diffractogram indicated that montmorillonite was the major mineral present although small amounts of quartz, calcite and feldspar were found. The dexamethasone used was obtained from Sigma Chemical Co.

Dexamethasone assay

The dexamethasone concentration was determined by high-pressure liquid chromatography (HPLC). The method was slightly modified from that used by Cornejo et al. (1980) for the analysis of hydrocortisone and its degradation products. The liquid chromatograph was an ALC 501 from Waters Associates, equipped with an ultraviolet (UV) detector operating at 240 nm and an universal injector. A microparticulate reversed-phase column (Nova-Pak C_{18}) was used with acetonitrile:water (40:60) as the mobile phase. The operating parameters were: flow rate 1 ml/min; pressure 2000–2200 psi; room temperature; injection volume 10 μl and UV attenuator 0.2 aufs.

Changes in the A-ring, mainly due to photolitic degradation, were monitored by UV spectrometry at 240 nm in a Pye-Unicam model SP 1800 spectrophotometer.

The structural formula of dexamethasone is:



Kinetic studies

The montmorillonite concentration was selected as representative of the range usually used for clays in pharmaceuticals; the dexamethasone concentration was below the solubility limit, 10 mg/100 ml at 23°C (Cohen, 1973), to ensure complete solubility during kinetic studies. Thus, 100 mg of montmorillonite were mixed with 30 ml of an aqueous solution of dexamethasone (50 μg/ml) in a 50-ml stoppered centrifuge tube. The samples were aged in a shaker-incubator at 23, 35 and 55°C. At appropriate intervals, aliquots were centrifuged at 14,000 rpm and the supernatant liquid was filtered and analyzed by HPLC and UV. The pH of each suspension was measured and found to be 8.7 at whatever the sampling interval.

Aqueous solutions of dexamethasone (50 μg/ml) were made up at pH 6.0. Some were adjusted to pH 8.7 with sodium hydroxide. The solutions were aged along with the clay–drug suspensions and served as controls.

Adsorption–desorption isotherm

Dexamethasone–montmorillonite suspensions were prepared as described, but dexamethasone concentrations of 1–50 μg/ml and 25 mg of sodium montmorillonite were used. The suspensions were equilibrated in the shaker-incubator at constant temperature (23°C) for 24 h. The pH of each suspension was the same as for kinetic studies.

Desorption studies were performed by recovering the equilibrated clay from adsorption study and resuspending the clay in sufficient water at pH 8.7 to achieve the original concentration. This procedure was repeated six times.

The amount of dexamethasone adsorbed or desorbed was calculated from the change in dexamethasone concentration of the supernatant after equilibration.

In order to study the pH influence on adsorption, dexamethasone–montmorillonite suspensions at pH 2.4, 4.3, 6.2, 8.7 and 10.0 were prepared as for the adsorption isotherm, with a dexamethasone concentration of 50 μg/ml.

Each suspension was adjusted to the desired pH with hydrochloric acid or sodium hydroxide, respectively.

X-ray diffraction

For X-ray diffraction studies, oriented aggregates of sodium montmorillonite and of the unwashed drug–montmorillonite complex were used. The oriented aggregate was prepared by drying an appropriate volume of suspension on a glass slide. Diffractograms were run at room temperature and after heating at 110 °C on a Siemens D-500 Kristalloflex apparatus, using Cu K_α radiation.

IR analysis

Self-supporting films were prepared by pipetting appropriate volumes of either montmorillonite or montmorillonite–dexamethasone suspensions onto a sheet of polyethylene terephthalate (Mylar) and air-drying at room temperature (Porubcan et al., 1978).

Dexamethasone was prepared for IR analysis as potassium bromide pellets. The spectra were recorded on a Nicolet 5DXE spectrophotometer.

RESULTS AND DISCUSSION

Dexamethasone exhibited a very slow degradation in aqueous solution at pH 6.0 which is consistent with previously reported stability results (Hansen and Bundgaard, 1980). Dexamethasone degradation increases with both pH or temperature (Table I). The dexamethasone content of an aqueous solution at pH 8.7 and 23 °C, as determined by HPLC, decreased from 50 to 47.6 μg/ml after aging for 168 h (Fig. 1b), while no appreciable degradation was observed by UV analysis. These data, as well as the peaks present in the high-pressure

TABLE I

Stability of dexamethasone in presence of montmorillonite

Temp.	Aqueous sol. at pH 6.0; k, h^{-1}	r^{*1}	Montmorillonite susp. at pH 8.7			
			k_1, h^{-1}	r^{*1}	k_2, h^{-1}	r^{*1}
23 °C	$1.66 \cdot 10^{-5}$	0.9993	$53.48 \cdot 10^{-3}$	0.9995	$6.15 \cdot 10^{-4}$	0.9965
35 °C	$6.05 \cdot 10^{-5}$	0.9973	$27.00 \cdot 10^{-3}$	0.9901	$10.40 \cdot 10^{-4}$	0.9897
55 °C	$3.95 \cdot 10^{-4}$	0.9989	$15.90 \cdot 10^{-3}$	0.9957	$28.20 \cdot 10^{-4}$	0.9899
pH 8.7 and 23 °C	$1.33 \cdot 10^{-4}$	0.9975	–	–	–	–

*1 r = correlation coefficient.

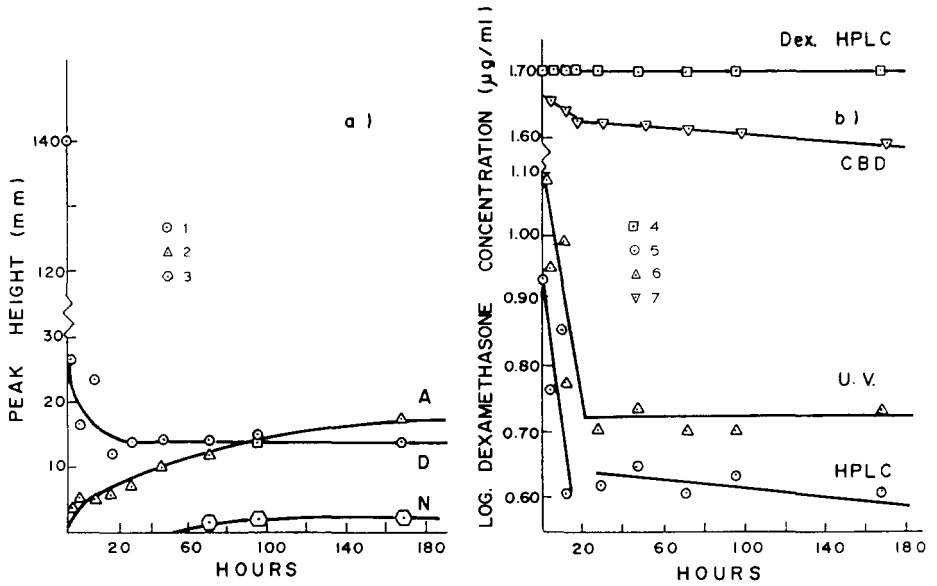


Fig. 1. Stability of dexamethasone in the presence of montmorillonite. a) Relative concentration of dexamethasone and degradation products in a montmorillonite suspension at pH 8.7 during aging at 23 °C: *1* = dexamethasone (*D*); *2* = acid degradation product (*A*); *3* = neutral degradation product (*N*). b) Change in dexamethasone concentration of aqueous phase (theory = 50 μg/ml) at pH 8.7 and 23 °C: *4* = dexamethasone solution by HPLC; *5* = montmorillonite suspension by HPLC; *6* = montmorillonite suspension by UV (degradation products concentration is also measured by UV); *7* = CBD-treated montmorillonite suspension by HPLC.

liquid chromatogram, indicate that dexamethasone degradation is mainly due to oxidation of the C-17 dihydroxyacetone side chain, giving rise to two major degradation products, acidic and neutral in character. A similar degradation pathway of prednisolone was previously described by Guttman and Meister (1958). A plot of the logarithm of dexamethasone concentration versus time gave a straight line indicating that degradation of dexamethasone, at any pH studied, apparently occurs by first-order kinetics (Table I). Hansen and Bundgaard (1980) found similar kinetics for hydrocortisone degradation ($8 < pH < 12$), although an intermediate step is the formation of the corresponding glyoxal.

In a montmorillonite suspension, at pH 8.7 and 23 °C, the dexamethasone content of the aqueous phase decreased from 50 to 4.7 μg/ml during the first 24 h, and very slowing during the next 144 h (Fig. 1b). The HPLC and UV analyses of the dexamethasone–montmorillonite suspension suggested that dexamethasone is adsorbed by montmorillonite, producing an immediate decrease in the dexamethasone concentration. This hypothesis is confirmed by analysis of the peaks appearing in the high-pressure liquid chromatogram. With the HPLC system used, dexamethasone has a retention time of 2.75 min, while

the two initial degradation products have retention times of 0.90 and 2.42 min. The peak height of dexamethasone dropped initially but changed slightly on aging (Fig. 1a). However, the heights of the peaks corresponding to the two initial degradation products, were very low and increased only very little on aging. The initial decrease of dexamethasone concentration, as determined by HPLC and UV analysis (Fig. 1b) seems to be due to adsorption of dexamethasone by montmorillonite rather than to accelerated degradation of dexamethasone.

The relationship between dexamethasone concentration or its logarithm and time, was not linear at any temperature studied. To characterize the dexamethasone degradation rate in the presence of montmorillonite, the degradation profile (Fig. 1b) was treated as consisting of an initial first-order phase, characterized by k_1, which was followed by a slower first-order stage characterized by k_2. Good linear correlations were obtained for both phases (Table I). The first stage could be consistent with a slow degradation of dexamethasone together with a dexamethasone adsorption by the clay, while the second one is thought mainly to be a degradation process.

Similar studies carried out by Cornejo et al. (1980) and Hermosín et al. (1981) for the interaction of hydrocortisone with sepiolite and palygorskite indicated that adsorbed surface iron and/or structural ferric iron was responsible for accelerated degradation of hydrocortisone in the presence of those clays. On the other hand, it has been proved that traces of other metal ions (Cu^{2+}, Fe^{3+} and Ni^{2+}) present as impurities in the buffer reagents could also produce an accelerated degradation of the C-17 dihydroxiacetone side chain of corticosteroids (Hansen and Bundgaard, 1980).

In the present study, k_2 values (Table I) are greater, at any temperature studied, than the corresponding k values obtained for aqueous solution of dexamethasone. It could be hypothesized that accelerated degradation of dexamethasone in presence of montmorillonite could be catalyzed by the surface (0.72 mg/g) and structural (25.6 mg/g) iron of montmorillonite, whose content is similar to that present in palygorskite (Forteza, 1987). To verify this hypothesis, a portion of montmorillonite was treated by the citrate-bicarbonate-dithionate (CBD) method to extract non-structural ferric iron. Dexamethasone was much more stable in a suspension of treated montmorillonite, although the degradation was substantially greater than that occurring in an aqueous dexamethasone solution (Fig. 1b).

To evaluate the amount of dexamethasone adsorbed by montmorillonite the adsorption isotherm at pH 8.7 and 23°C was determined (Fig. 2). The initial slope of the curve suggests an isotherm of "S" type according to the classification of Giles et al. (1960), which is indicative of vertical orientation of surface adsorbed molecules. The second inflection point and the short plateau suggested that formation of a "monolayer" has been reached. The adsorption data above the second inflection point gave a good linear fit when the theoret-

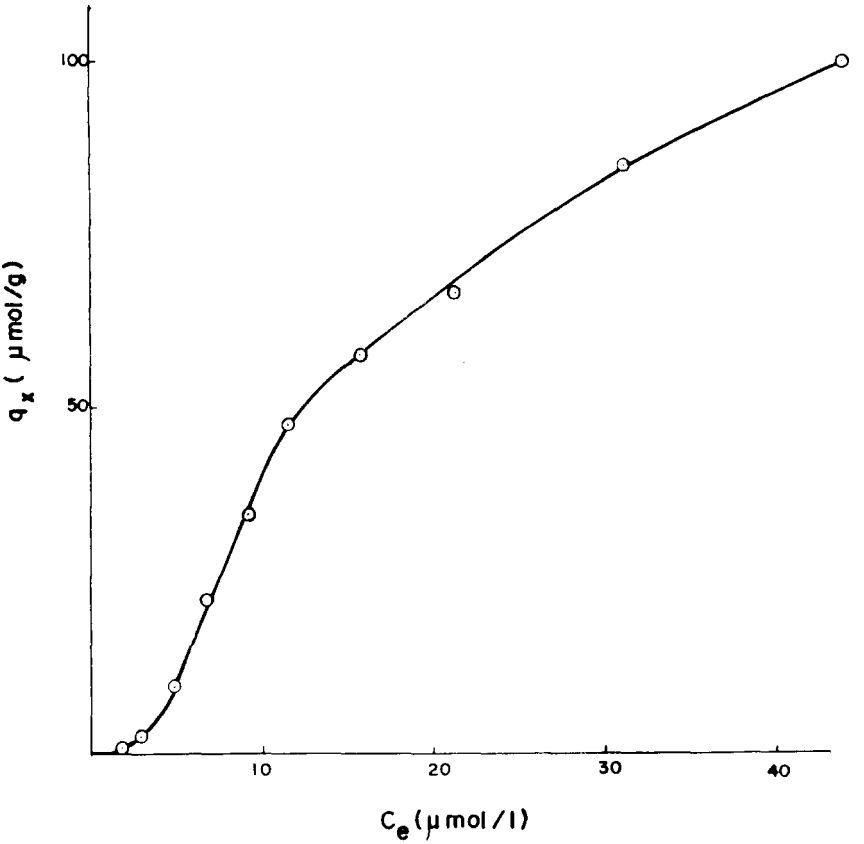


Fig. 2. Adsorption isotherm for dexamethasone by montmorillonite: q_x = amount of dexamethasone adsorbed; C_e = equilibrium concentration.

ical Langmuir equation was applied (r=0.9987). The maximum amount of dexamethasone adsorbed by montmorillonite, as determined by the slope of the Langmuir plot, was 169.1 µmol/g.

The amount of dexamethasone that could be theoretically adsorbed by montmorillonite, calculated on the basis of external (40 m^2/g) and total (748 m^2/g) surface area (Hermosín, 1978), are 92.4 µmol/g and 1.72 mmol/g, respectively. The experimental data obtained from the adsorption isotherm is almost double than that of the external surface. So, it is hypothesized that dexamethasone at low concentrations is weakly surface-sorbed by montmorillonite. As concentration increases, drug molecules are able to penetrate the interlayer space of montmorillonite. In this case, a no completed monolayer could be formed, probably including some water molecules.

Desorption studies (Fig. 3) confirmed the above proposed mechanism. Desorption from samples corresponding to the initial slope of the isotherm was complete after three washings with water at pH 8.7. As the amount of dexa-

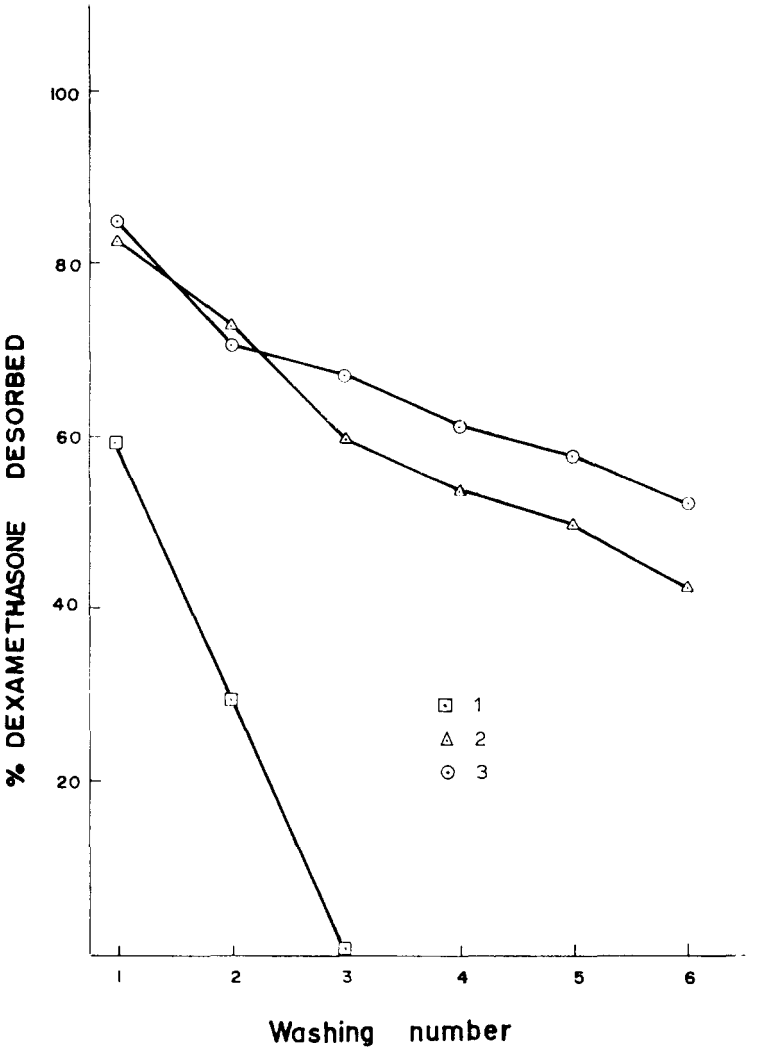


Fig. 3. Percentage of dexamethasone desorbed from equilibrated montmorillonite-dexamethasone complex by water washings: *1* = from $q_x = 9.46$ μmol/g; *2* = from $q_x = 47.41$ μmol/g; *3* = from $q_x = 100.19$ μmol/g (g_x = amount of dexamethasone adsorbed).

methasone adsorbed increased, desorption became slower and incomplete. Only 47% of dexamethasone was recovered after six washings with water. This desorption profile could be explained on the basis of the large size of dexamethasone molecules. These could be trapped in the interlayer space of montmorillonite making desorption difficult due to a steric impediment. No degradation products were found by HPLC analysis during desorption studies.

The adsorption of dexamethasone was examined by X-ray diffraction. The

$d(001)$ spacing of an oriented dexamethasone–montmorillonite aggregate after heating at 110 °C was found to be 13.93 Å (Fig. 4b). This basal spacing is close to the theoretically calculated if 9.7 Å and 4.3 Å are assumed for the basal spacing of completely dehydrated montmorillonite and the height of dexamethasone molecule perpendicular to the plane of the rings, respectively

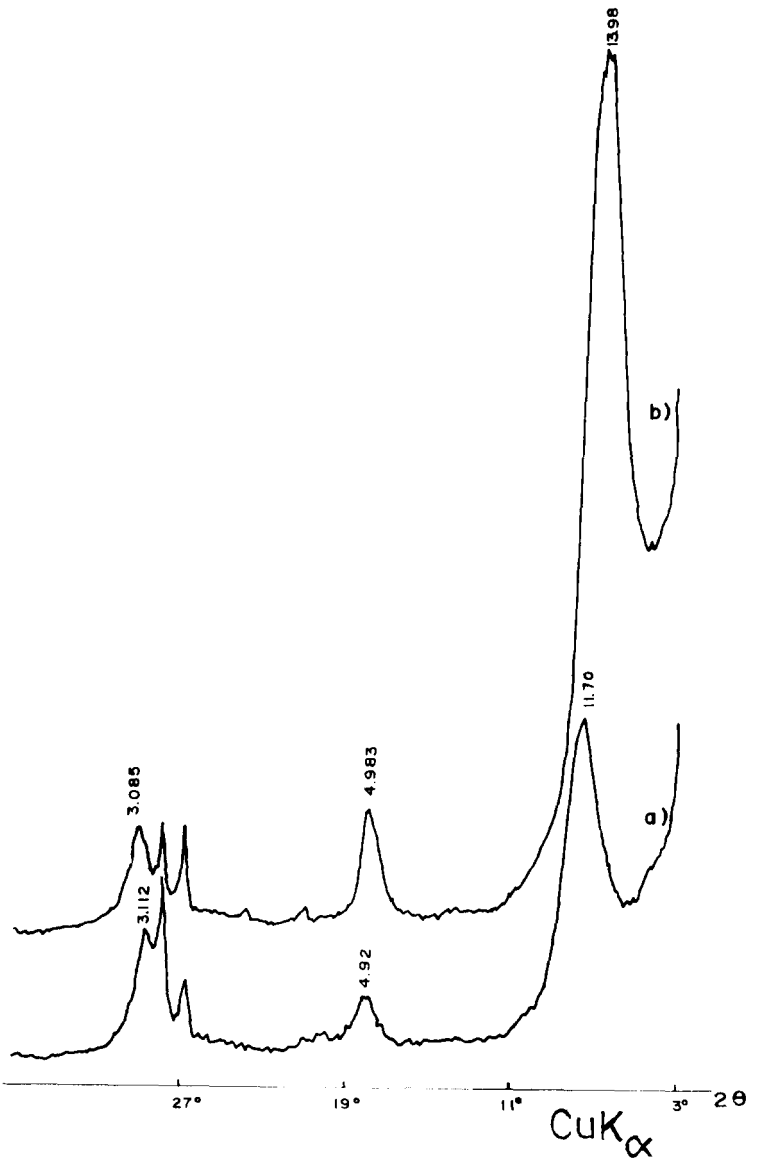


Fig. 4. X-ray diffractogram of oriented aggregates after heating at 110 °C of: a) montmorillonite; and b) an unwashed dexamethasone–montmorillonite complex (Q = quartz; F = feldspar).

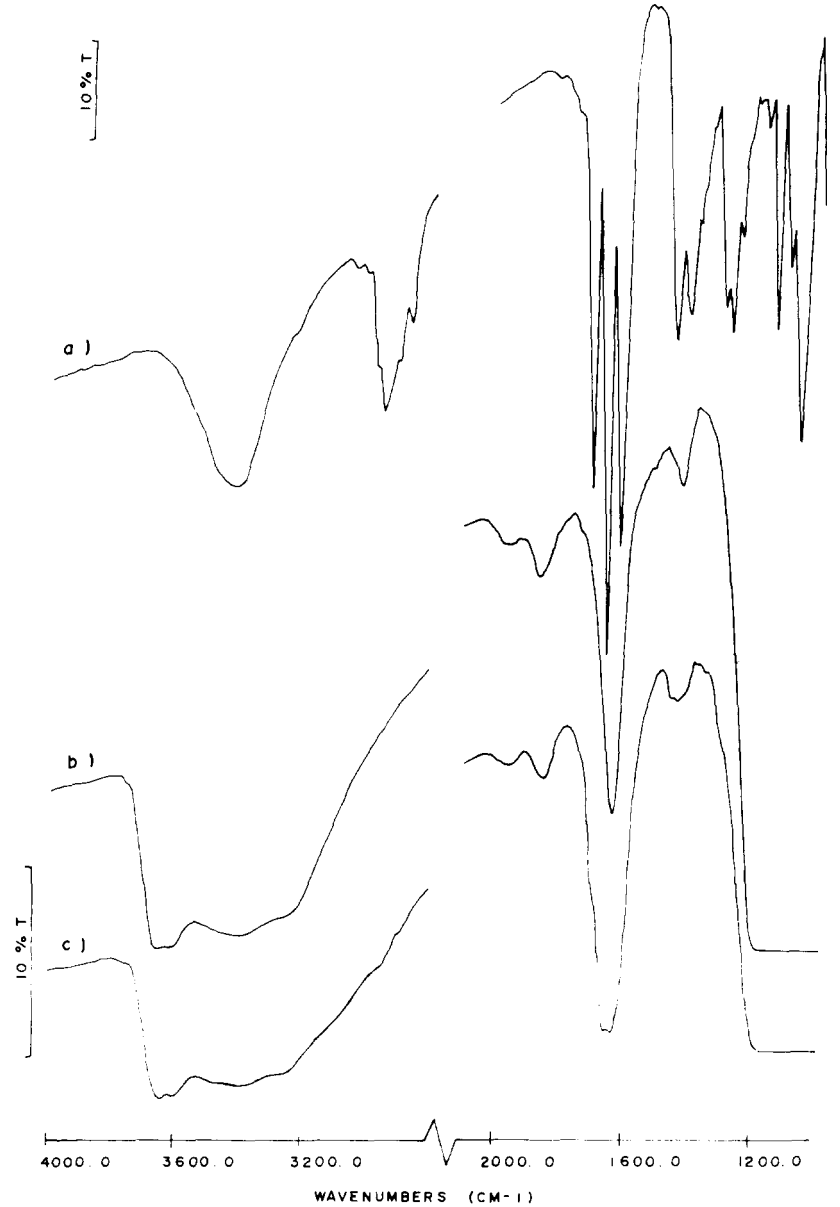


Fig. 5. IR spectra of: a) dexamethasone in a potassium bromide pellet; b) a film of montmorillonite; and c) a film of equilibrated dexamethasone-montmorillonite suspension at pH 8.7.

(Forteza, 1987). These data suggested that dexamethasone molecules penetrate the interlayer space of montmorillonite with a flat orientation, i.e., the mean plane of the steroidal skeleton being parallel to the mineral sheets.

The montmorillonite–dexamethasone complex showed a better ordered diffractogram than that of the untreated sample (Fig. 4). However, the upper orders (3.08 and 4.98 Å) corresponding to the basal reflection were not integral, indicating an irregular distribution of dexamethasone and water molecules around the interlayer cations, throughout different sheets.

An X-ray diffractogram of the dexamethasone–montmorillonite complex after six washings with water at pH 8.7, showed the same basal spacing (13.98 Å) as for unwashed sample. This result, together with those obtained by desorption studies, suggest the presence of dexamethasone molecules in the interlayer space of the clay, indicating a slow desorption profile for this drug.

The IR spectrum of the montmorillonite–dexamethasone system shows relatively weak drug absorption bands (Fig. 5c) and confirms that the drug has been adsorbed by the clay. The 3400 cm^{-1} band of dexamethasone is completely hidden by the OH-stretching band of the interlamellar water (3420 cm^{-1}). However, two small bands at 2962 and 2886 cm^{-1} due to CH-stretching vibrations appear in this spectrum. In addition, a big band composed by a shoulder at 1700 cm^{-1} corresponding to the carbonyl-stretching vibration of the C-17 dihydroxiacetone side chain, and a peak at 1660 cm^{-1} due to the carbonyl-stretching vibration of the C-3 dexamethasone A-ring associated with the 1630 cm^{-1} OH-stretching band of interlamellar water, also are present.

The X-ray diffraction, IR spectroscopy and adsorption–desorption data reveal that the molecules of the drug are adsorbed in both external and internal surface of the clay. Much less than one monolayer of dexamethasone molecules is thought to be associated with interlamellar water molecules into the interlayer space of the clay. These molecules seem to be randomly distributed throughout different clay sheets.

The amount of dexamethasone adsorbed was similar at any pH studied ($2.4 < pH < 10.0$). The maximum dexamethasone adsorbed (160 $\mu g/ml$) was obtained between pH 2 and 4, probably due to a more protonated form of the AlOH and SiOH groups of the crystal borders, favouring hydrogen bonding between dexamethasone carbonyl groups and the clay surface.

CONCLUSIONS

The results of this study suggest that the catalytic influence of surface and structural ferric iron present in montmorillonite (Forteza, 1987), on the degradation pattern of the C-17 dihydroxyacetone side chain of corticosteroids is less than that observed for other clay minerals, such as palygorskite and sepiolite (Cornejo et al., 1980; Hermosín et al., 1981) probably due to a greater amount of drug adsorbed by montmorillonite. In addition, the formation of a dexamethasone–montmorillonite complex results in a reversible process with a slow and extended drug desorption.

In conclusion, montmorillonite should be considered as a good pharmaceut-

ical excipient for designing oral or topical solid forms including relatively polar drugs subject to oxidative degradation. Furthermore, the drug–excipient interaction, between corticosteroids and montmorillonite, could be successfully employed in sustained-release formulations.

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