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Thermal studies of pharmaceutical clay systems. Part II. Sepiolite-based systems

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Abstract

Pharmaceutical–clay systems, used as solar radiation shields, obtained by interaction of natural sepiolite and several pharmaceuticals using two methods of preparation (melting the drug onto the clay or by intimate mixing and grinding of both), have been studied. The shielding ability against solar radiation is improved by using these preparation methods. Differential thermal analysis and thermogravimetric analysis confirm displacement of water molecules adsorbed onto the clay surface by the pharmaceutical molecules. The grinding method seems to facilitate adsorption and dispersion of the drug onto the clay surface.

Keywords: Clay; Drug–clay complex; DTA; Pharmaceutical; Sepiolite; Solar radiation shield; TG

1. Introduction

The method most commonly used to adsorb pharmaceutical molecules onto the surface of clays consists in adsorption from aqueous or organic solutions, specially by using layered silicates [1–4]. However, the use of non-layered clays has also been investigated; in a previous paper [5] we reported the adsorption of the methyl sulphate of *N*-methyl-8-hydroxy quinoline (MSMHQ), a solar shielding agent, on sepiolite using this method, and also an alternative method consisting in manually grinding intimate mixtures of both solids (the drug and the clay). We have also reported that these samples improve the light absorption ability of the drug–clay complexes [6].

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A systematic study on the thermal properties of several organic molecules present in several sun-protecting creams, with montmorillonite, has been reported [7]; in that paper, samples had been prepared by alternative methods (grinding drug–clay mixtures, or melting the former onto the surface of the later), and it was found [8] that the light-absorbing properties had been improved. The preparation method is rather new, and it has rarely been reported in the literature [9]. We here describe a parallel, systematic study, on the thermal properties of drug–sepiolite systems, prepared by grinding and melting. In all cases, and as expected from the previous studies described above, the light-absorption properties are improved.

2. Experimental

2.1. Materials

Natural sepiolite from Tolsa S.A. (Madrid, Spain), commercial name Pangel S-9, was used after selection of the <2 μm fraction (sample S). Pharmaceuticals tested were phenyl salicylate (ϕS), methyl cinnamate (MC), ethyl cinnamate (EC) and *p*-aminobenzoic acid (AB), all from Fluka, and the methyl sulphate of *N*-methyl-8-hydroxyquinoline (MSMHQ), synthetized by the method by Faller and Phillips [10]. The formulae of these molecules are given in Fig. 1.

2.2. Apparatus

Sepiolite was characterized by chemical analysis, exchange capacity and several physicochemical techniques. Powder X-ray diffraction (PXRD) profiles were recorded in a Philips PW-1710 diffractometer, using CuK_α radiation, equipped with a Ni filter. The FTIR spectra were recorded in a Perkin–Elmer FT-1730 spectrometer, using the KBr pellet technique. Specific surface area and porosity assessment were carried out by nitrogen adsorption at -196°C in a conventional high-vacuum system. Finally, the light absorption ability of the drug–clay systems was studied by Vis–UV spectroscopy, following the diffuse reflectance technique (V–UVDR) in a Shimadzu UV-240 apparatus, using MgO as reference and 5 nm slits. Thermal analysis was carried out in a Perkin–Elmer DTA-1700 differential thermal analyzer using α-Al_2O_3 as reference; thermogravimetric analysis (TG) was performed in a Perkin–Elmer TGS-2 apparatus; both systems were connected to a Perkin–Elmer 3600 data station. Analysis was carried out in air, using a heating rate of 12°C min^{-1}. Characterization of the drugs was carried out by FTIR DTA and TG; chemical analysis also was used for MSMHQ.

2.3. Preparation of the samples

Samples were prepared by melting (M) or mixing and grinding (G) 1, 2, 3, 5, 10, 25, 50, 75, and 90 g drug per 100 g clay. The mixture was gently hand ground for 10 min, as it had previously been checked that longer grinding times did not improve the light absorption ability of the systems [11, 12]. This was measured in the

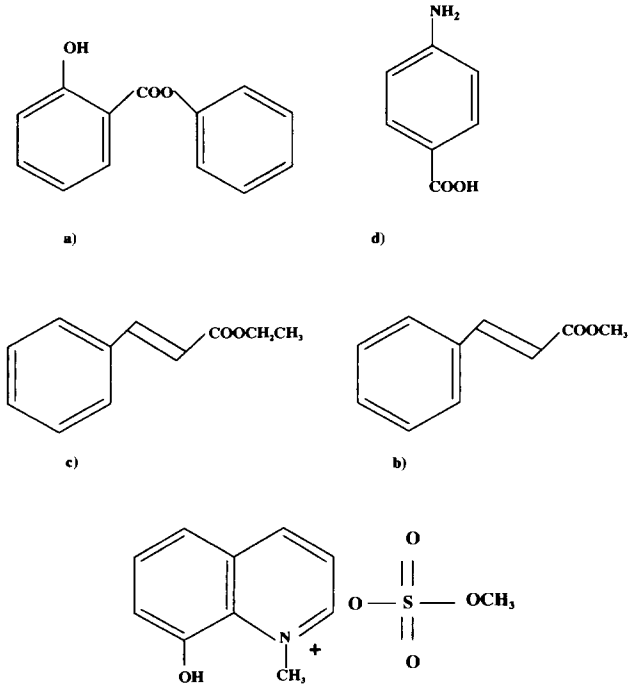

Fig. 1. Molecular structures of the drugs for which adsorption has been studied in the present work: (a) phenyl salicylate, ϕS; (b) methyl cinnamate, MC; (c) ethyl cinnamate, EC; (d) *p*-aminobenzoic acid, AB; (e) methyl sulphate of *N*-methyl-8-hydroxyquinoline, MSMHQ.

500–190 nm range. As ethyl cinnamate is liquid at room temperature, the method followed was the so-called "wet grinding", by adding the corresponding amounts of drug to sepiolite and gently mixing with a spatula. For comparison, a fraction of sepiolite was also submitted to the same grinding treatment, without adding any pharmaceutical.

Except for *p*-aminobenzoic acid, which melts at 188°C, all other pharmaceuticals melt at temperatures below that needed to dehydrate sepiolite; no irreversible change in the structure of the clay was, therefore, expected during the melting process used to obtain samples (M). The same relative amounts of drug and clay were used to prepare samples (G).

For the sake of clarity, only data for systems containing the maximum amounts of drug are given below.

3. Results and discussion

A summary of the results obtained is given in Table 1. Thermal properties of the bulk pharmaceuticals have been described previously [7].

Table 1
Summary of DTA and TG features of the samples studied

Sample	DTA		TG	
	Endo	Exo	ΔT/°C	Weight loss%
Sepiolite	120		41–128	7
	325		128–236	1
			236–340	2
	815		650–800	16
		830		
Ground sepiolite	120		41–125	8
	325		213–318	3
			428–672	3
	815		803–876	1
		830		
ϕS–S(G)	53[a]			
	255		177–266	40
		422	280–340	3
ϕS–S(M)	53[a]			
	97			
	241		115–199	40
		435	205–740	11
MC–S(G)	45[a]			
	233		99–201	38
		430	279–353	3
MC–S(M)	53[a]			
	108		110–199	43
	240		330–740	11
		442		
EC–S(G)	94		108–239	29
	247		298–362	3
		421		
AB–S(G)	101		42–110	2
	266		228–770	29
		506		
AB–S(M)	196[a]		175–252	34
	238		265–740	22
	337			
		502		
MSMHQ–S(G)	114		41–119	3
	208		254–385	18
	260		458–535	15
		511		
MSMHQ–S(M)	100		42–106	3
	169		165–210	3
			251–353	11
		511	421–618	22

[a] Melting.

3.1. Sepiolite

The DTA profile for natural sepiolite is given in Fig. 2(a). It shows a sharp endothermic effect noticeable from 70°C upwards, and with a minimum at 120°C. Such an effect is due to removal of water molecules from the external surface of the fibres constituting this fibrous clay, or from the channels [11]. A second endothermic effect is recorded between 240 and 360°C, rather broad, and less pronounced with a minimum at ca. 325°C, due to removal of rather strongly held water molecules. Finally, a weak endothermic effect is recorded at 815°C, immediately followed by an exothermic effect at 830°C; the first is due to dehydroxylation of the sepiolite structure, while the exothermic effect is due to crystallization of clinoenstatite, in agreement with previous results reported elsewhere [12]. The profile for the sample ground for 10 min, Fig. 2(b), shows no apparent difference from the DTA curve of the original sample, so it can be

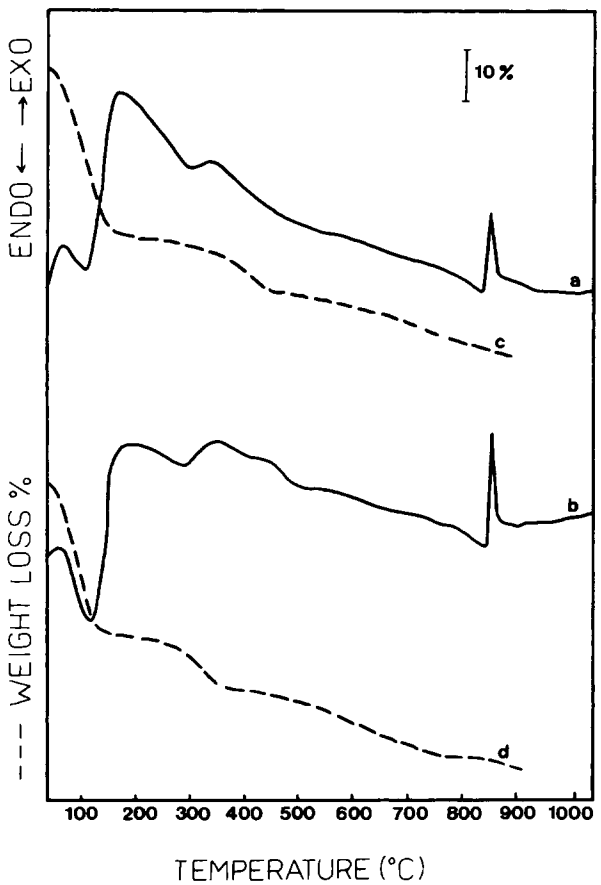

Fig. 2. Differential thermal analysis curves of (a) sepiolite, and (b) ground sepiolite, sample S. Thermogravimetric analysis curves of (c) sepiolite, and (d) ground sepiolite.

concluded that no important changes in the thermal properties of sepiolite are induced by grinding [13].

The corresponding TG curves are also shown in Fig. 2. For original sepiolite a sharp weight loss is recorded up to 128°C (representing 7% of the initial weight loss), followed by a second, steady weight loss up to ca. 236°C, representing only 1% of the initial weight loss. Above this temperature, a sharp change in the slope of the curve is observed and 2% of the initial sample weight loss is recorded up to 340°C. Weight loss up to 800°C corresponds to 16% of the initial weight loss, and can be envisaged as two consecutive steps; the first corresponds to the first ill-defined DTA endothermic peak at 325°C, while the weight loss between 340 and 800°C does not give rise to any defined DTA peak, as it extends along a wide temperature range and it is not very intense.

The TG profile corresponding to the ground sample is shown in Fig. 2(d), where four different weight losses are recorded. The first, in the 41–125°C range, corresponds to 8% of the initial weight loss, and can be ascribed to the same physicochemical process responsible for the DTA minimum at 120°C, i.e., removal of rather free water molecules on the external surface of the structural channels. The second weight loss (213–318°C, 3%), corresponds to removal of bonded water, while dehydroxylation would account for the third weight loss (428–672°C, 3%), the fourth weight loss, corresponding to 1%, is recorded between 803 and 876°C.

3.2. *Phenyl salicylate–sepiolite systems*

The DTA curve for system ϕS–S(M) is shown in Fig. 3(a). The first endothermic effect is recorded at 53°C, and is due to melting of the drug. The endothermic effect due to removal of "free" water is not recorded in this case (if the profile is compared to that of pure sepiolite), probably because of substitution of the water by the drug. The following endothermic effect, due to "bonded" water, at 325°C for pure sepiolite, is not recorded either. The pronounced endothermic effect at 255°C is due to partial decomposition of phenyl salicylate, as concluded from comparison with the curve for bulk drug [7]. The exothermic effect at 422°C should be due to burning of residual drug.

The DTA curve for sample ϕS–S(G), Fig. 3(b), is very similar to that recorded for the sample prepared by melting. The only noticeable difference is the endothermic effect, with a minimum at 97°C, due to removal of "free" water. Nevertheless, the intensity of this effect is very low, and so it should be concluded that water–drug substitution should be almost complete. Burning of the drug gives rise to the intense exothermic effect at 435°C.

The TG curves for these samples confirm the conclusions reached from the DTA study. So, the lack of any weight loss at low temperatures for sample ϕS–S(M), Fig. 3(c), confirms the substitution of the drug for the "free" and, probably, also the "bonded" water molecules; in this case weight loss starts at 177°C, while for pure sepiolite, Fig. 2(a), "free" water is removed between 41 and 128°C. "Bonded" water is removed in sample ϕS–S(M) between 280 and 340°C, and amounts to 3% of the initial sample weight.

The TG curve in Fig. 3(d) corresponds to sample ϕS–S(G). The first weight loss (40%) is recorded between 115 and 199°C and although removal of residual "free"

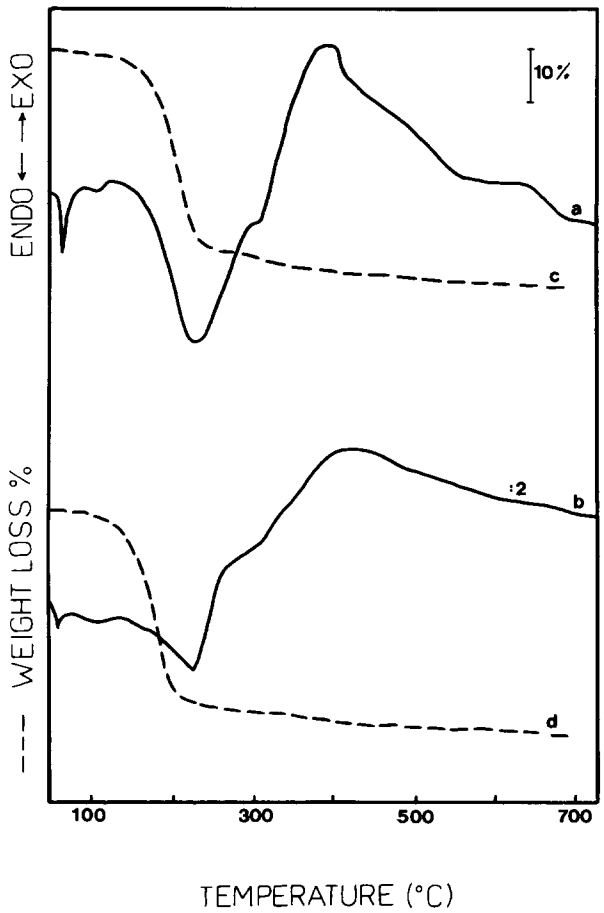

Fig. 3. Differential thermal analysis curves of (a) ϕS–S(M); (b) ϕS–S(G). Thermogravimetric analysis curves of (c) ϕS–S(M); (d) ϕS–S(G).

water cannot be ignored (as substitution is not complete for samples prepared by grinding), the main origin of such a weight loss is elimination of the drug. Removal of structural water between 205 and 740°C gives rise to a weight loss of 11%, together with total combustion of the remaining drug residues.

3.3. *Methyl cinnamate–sepiolite systems*

The DTA profile for sample MC–S(M) is shown in Fig. 4(a). The endothermic effect at 45°C is due to melting of the drug, as there is no weight loss in this temperature range (see below). The sharp, intense endothermic peak at 233°C is due to partial decomposition of methyl cinnamate and removal of residual bonded water. The broad, ill-defined exothermic effect at 430°C is due to burning of the drug.

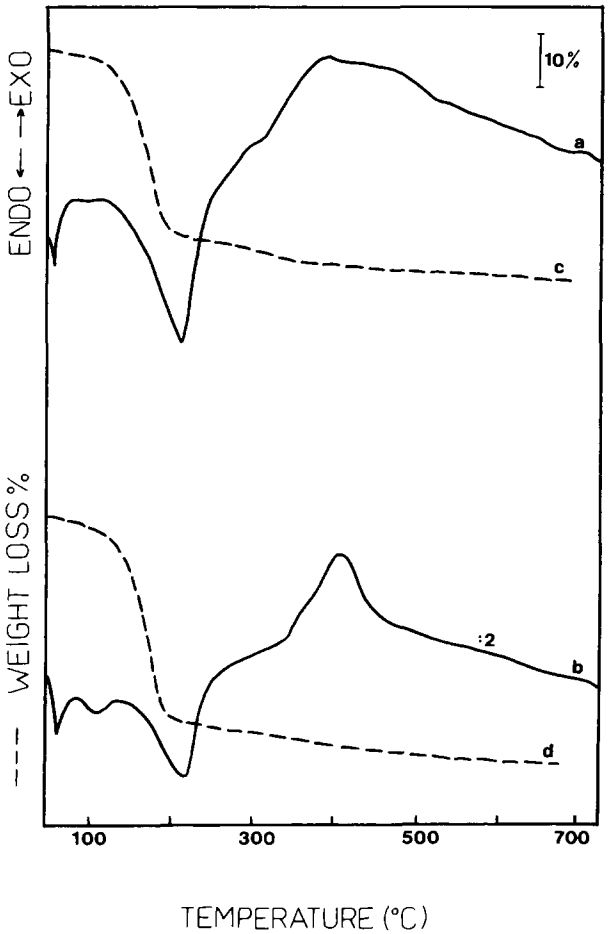

Fig. 4. Differential thermal analysis curves of (a) MC–S(M); (b) MC–S(G). Thermogravimetric analysis curves of (c) MC–S(M); (d) MC–S(G).

The DTA curve for sample MC–S(G) is shown in Fig. 4(b). Again, melting of the supported drug gives rise to an endothermic effect at 53°C. The weak minimum at 108°C corresponds to removal of residual "free" water, while the last endothermic effect, with minimum at 240°C, is due to partial decomposition of the drug and removal of bonded water molecules. Combustion of the drug accounts for the exothermic effect centered at 442°C.

The TG curve for sample MC–S(M) is shown in Fig. 4(c). Drug–free water substitution should be complete, as weight loss starts above 100°C, and this type of water molecule is removed between 41 and 128°C, according to the TG curve recorded for sepiolite, Fig. 2(c). Removal of the drug between 99 and 201°C gives rise to a weight loss of 38% The weak weight loss recorded between 279 and 353°C, merely 3% of the initial sample weight, is due to removal of residual bonded water molecules.

Finally, the TG curve in Fig. 4(d) corresponds to sample MC–S(G). The first weight loss (43%) between 110 and 199°C originates removal of residual free water molecules and, mainly, partial decomposition of methyl cinnamate. The remaining weight loss (11%) between 330 and 740°C, is due to combustion of drug not decomposed in the first decomposition stage.

3.4. *Ethyl cinnamate–sepiolite systems*

As ethyl cinnamate (EC) is liquid at room temperature, adsorption of this drug on sepiolite was carried out by the "wet grinding" method only. The DTA curve, shown in Fig. 5(a), has been recorded using alumina impregnated with the drug. The first endothermic effect, at 94°C is rather weak, and the free water content should be low. The endothermic effect sharpens, reaching a minimum at 247°C, a position coincident

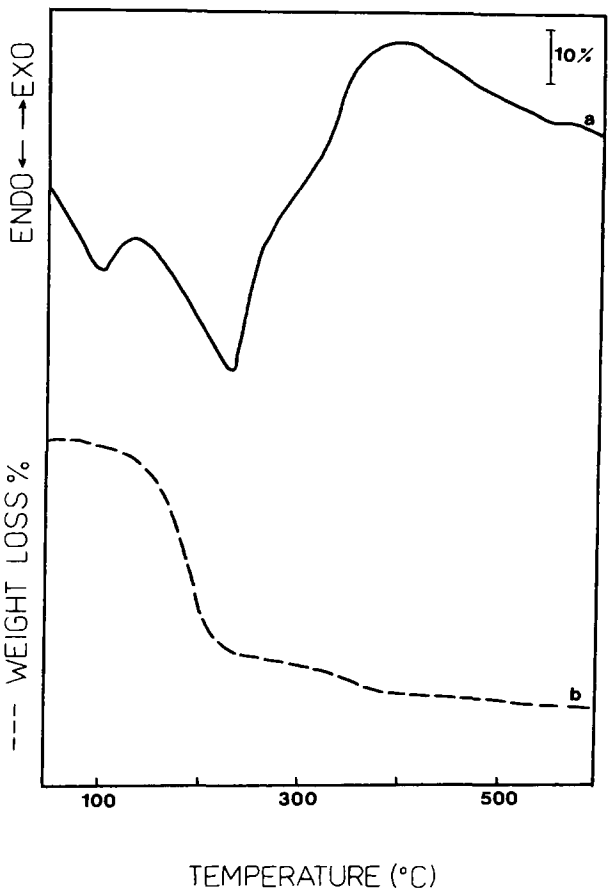

Fig. 5. Differential thermal analysis curves of (a) EC–S(G). Thermogravimetric analysis curves of (b) EC–S(G).

with that recorded for the pure drug [7] and should thus be originating as a result of its partial decomposition. Again, the amount of bonded water remaining on the sample should be very low, the endothermic peak corresponding to its removal being recorded at 325°C for ground sepiolite, Fig. 2(b). The sharp maximum (exothermic) at 421°C originates as a result of combustion of remaining drug.

The TG curve recorded in air for sample EC–S(G) is shown in Fig. 5(b). The lack of any endothermic effect at low temperature confirms total drug–free water substitution. The first weight loss starts at 108°C, and extends up to 239°C; it corresponds to decomposition of the drug, and represents a weight loss of 29%. The second weight loss is rather weak (3% of the initial sample weight), and extends between 298 and 362°C. From comparison with the profile recorded for sepiolite, this weight loss should correspound to removal of bonded water.

3.5. *Aminobenzoic acid–sepiolite systems*

The endothermic effect recorded with a minimum at 101°C in the DTA profile of sample BA–S(M), Fig. 6(a), originates as a result of removal of free water, similarly to the process recorded for the pure support, Fig. 2(a). The endothermic effect at 266°C could be due to melting and partial decomposition of the supported drug [7]. A broad exothermic effect, without any well-defined maximum, recorded at ca.506°C, can be adscribed to combustion of remaining drug.

The corresponding DTA curve recorded for sample AB–S(G) is shown in Fig. 6(b). Melting of the drug is clearly shown by the endothermic effect at 196°C, the second endothermic effect at 238°C being due to the first stages of decomposition of the drug. The weak endothermic feature at 337°C originates from removal of bonded water on the sepiolite surface. Finally, combustion of the drug gives rise to an exothermic effect centered at 502°C.

TG analysis, the curves of which are shown in Figs. 6(c) and 6(d) for samples AB–S(M) and AB–S(G), respectively, confirms the conclusions reached from the DTA study. So, for sample AB–S(M), a weak weight loss (2%) is recorded between 42 and 110°C, due to removal of free water. The main weight loss (29%) is recorded in the 228–770°C range, and is due to removal of surface hydroxyl groups of sepiolite and combustion of the drug.

Total substitution of free water has been attained in sample AB–S(G), as weight loss starts at 175°C, extending up to 252°C (34% of the initial sample weight), and, from comparison with the profiles for the drug and for sepiolite, originates from removal of remaining bonded water and, mainly, decomposition of the drug. The last weight loss is also rather strong, 22%, and is due to combustion of remaining drug fragments, and structural hydroxyl groups from the support.

3.6. *Methyl sulphate of N-methyl-8-hydroxyquinoline–sepiolite systems*

Fig. 7 summarizes the results obtained for these systems. The curve for sample MSMHQ–S(M), Fig. 7(a), shows a weak endothermic effect at 114°C. Its position and intensity suggest that it is due to removal of small amounts of free water. The first stages

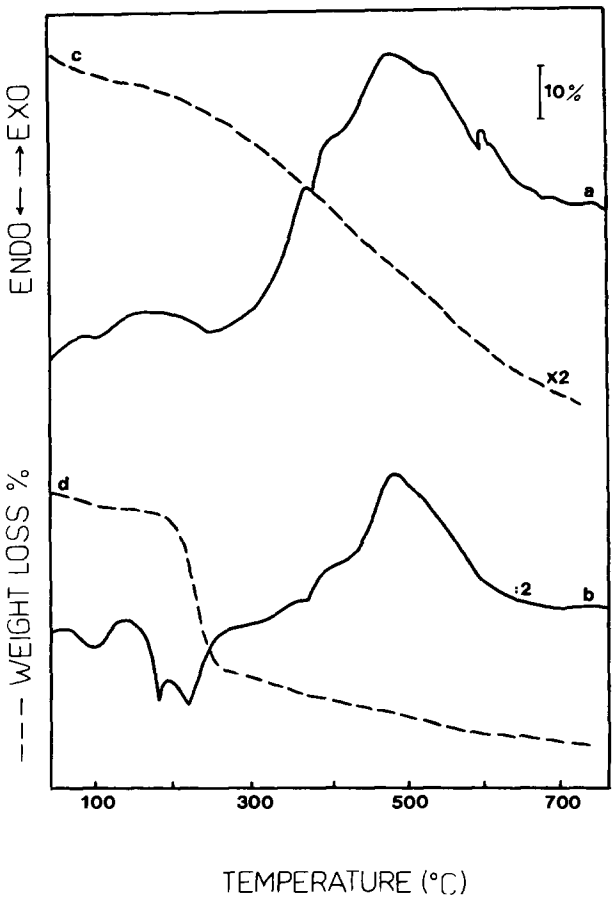

Fig. 6. Differential thermal analysis curves of (a) AB–S(M); (b) AB–S(G). Thermogravimetric analysis curves of (c) AB–S(M); (d) AB–S(G).

of decomposition of the drug give rise to a second endothermic effect at 208°C, as well as a third effect at 260°C, very close to that recorded for the pure drug at 265°C [7]. Combustion of remaining drug residues causes the exothermic effect at 511°C.

The profile for sample MSMHQ–S(G), Fig. 7(b), shows some small differences. The endothermic effect at 100°C due to removal of free water is very weak (almost absent), indicative of almost complete substitution. Decomposition of the drug gives rise to the endothermic effect at 169°C, while removal of water bonded to sepiolite extends between 236 and 340°C and overlaps an exothermic effect with a maximum at 511°C due to combustion of the drug.

The TG curve in Fig. 7(c), corresponding to sample MSMHQ–S(M), shows a first weight loss between 41 and 119°C corresponding to 3% of the initial sample weight,

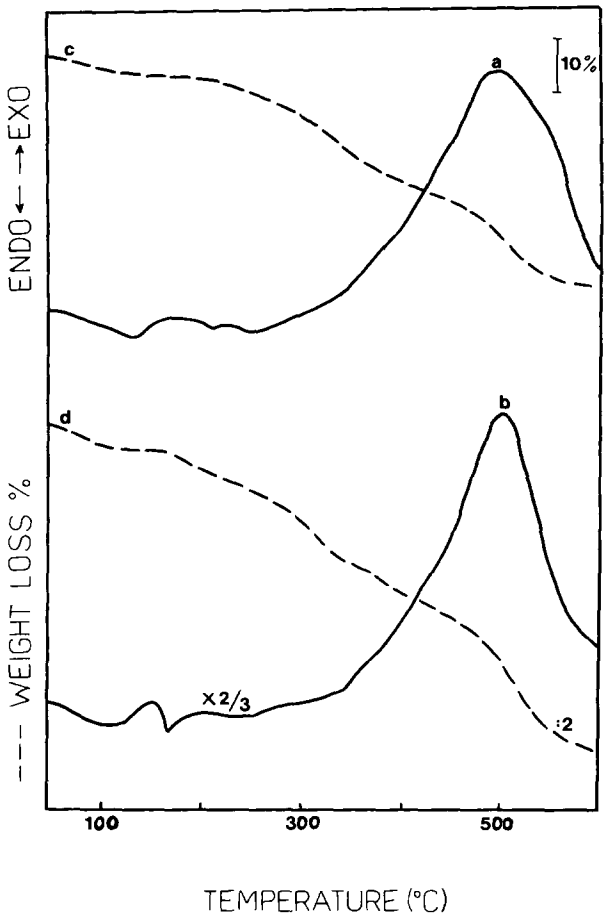

Fig. 7. Differential thermal analysis curves of (a) MSMHQ–S(M); (b) MSMHQ–S(G). Thermogravimetric analysis curves of (c) MSMHQ–S(M); (d) MSMHQ–S(G).

and is due to removal of the small amount of free water existing after incorporation of the drug. Decomposition of this accounts for the second, more important, weight loss (18%) between 254 and 385°C, while combustion of the drug residues on the support surface gives rise to a weight loss of 15% between 458 and 535°C.

Finally, the TG profile for sample MSMHQ–S(G) is shown in Fig. 7(d). The first weight loss, 3%, is recorded between 42 and 106°C, and is due to removal of free water. Decomposition of the drug is recorded as a series of consecutive weight losses: a small weight loss (3%) between 165 and 210°C, originates from partial decomposition of the drug, followed by a third weight loss (11%). Finally, a 22% weight loss is recorded between 421 and 618°C, and corresponds to two overlapping processes: combustion of residual drug and removal of structural hydroxyl groups.

4. Conclusions

The results obtained in this study indicate that incorporation of the different drugs on the sepiolite surface takes place with almost complete substitution of free water, although, due to the fibrous character of the mineral, such a process does not give rise to any change in the XRD diagrams [8]. Substitution of bonded water is also achieved in some cases.

Grinding of the drug–sepiolite mixtures seems to be more effective at achieving good dispersion than melting of the former onto the surface of the latter, comprising a result contrary to those found for systems comprising the same drugs, but supported on montmorillonite [7]. It is probable that the surface tension of the melted drug on the sepiolite surface, together with the narrower diameter of the sepiolite pores compared with those of montmorillonite) could account for such a difference.

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