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Thermal studies of pharmaceutical–clay systems Part I. Montmorillonite-based systems

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Abstract

Pharmaceutical–clay systems, used as solar radiation shields, obtained by interaction of Na montmorillonite and several pharmaceuticals using two methods of preparation, have been studied. Samples have been prepared by melting the drug onto the clay or by intimate mixing and grinding of both. The shielding ability against solar radiation is improved by use of these preparation methods. Differential thermal analysis and thermogravimetric analysis confirm the steady substitution of water molecules from the interlayer space of the clay by drug molecules, as the amount of the latter is increased. The melting method seems to facilitate access of the drug into the interlayer space of the clay.

Keywords: DTA; Pharmaceutical; Powder X-ray diffraction (PXRD); Sodium montmorillonite clay; Solar radiation shield; TG

1. Introduction

Preparation of drug–clay systems by melting the former onto the later, or by intimate mixing and grinding of both in the solid state are alternative methods to that most widely currently used, adsorption from solutions [1–4]; moreover, these two methods give yields larger than that of the adsorption method. Adsorption through intimate mixing and grinding has previously been used by Vicente et al [5] and Ogawa and

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cowerkers [6–8]. Adsorption by melting has been reported in the literature [9] solely for the preparation of octadecylamine on montmorillonite; if the mixture is overheated, however, decomposition of the organic molecule is observed at 75°C.

In the present paper, we report several drug–montmorillonite systems, prepared both by melting and by mixing and grinding, in order to assess the dispersion of the organic molecule and its interaction with the clay substrate.

2. Experimental

2.1. Materials

Montmorillonite was K-10 from Fluka; after selection of the $< 2\ \mu m$ fraction, it was saturated with Na^+ (sample M). Pharmaceuticals tested were phenyl salicylate (ϕS), methyl cinnamate (MC), ethyl cinnamate (EC) and *p*-aminobenzoic acid (AB), all also from Fluka, and the methyl sulphate of N-methyl-8-hydroxyquinoline (MSMHQ), synthesized by following the method of Faller and Phillips [10]. The formulae of these molecules are given in Fig. 1.

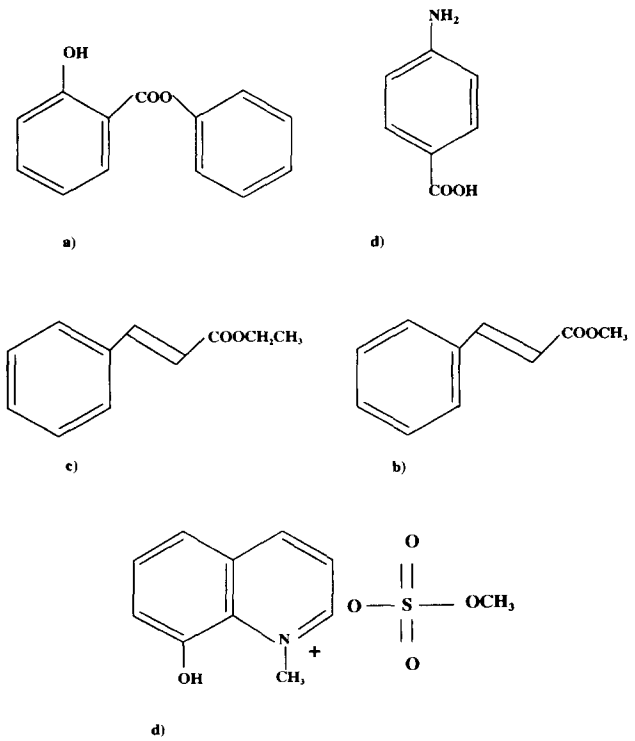

Fig. 1. Molecular structures of the drugs the adsorption of which has been studied in the present work: (a) phenyl salicylate, ϕS; (b) methyl cinnamate, MC; (c) ethyl cinnamate, EC; (d) *p*-aminobenzoic acid, AB; (e) methyl sulphate of N-methyl-8-hydroxyquinoline, MSMHQ.

2.2. Apparatus

Montmorillonite was characterized by chemical analysis, exchange capacity and several physicochemical techniques. Powder X-ray diffraction (PXRD) profiles were recorded in a PW-1710 Philips diffractometer, using CuK_α radiation, equipped with a Ni filter. The FTIR spectra were recorded in a Perkin–Elmer FT1-1730 spectrometer, using the KBr pellet technique. Specific surface area and porosity assessment were determined 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–UV/DR) 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. Analyses were carried out in air, using a heating rate of 12°C min^{-1}. Characterization of the drugs and MSMHQ was carried out by FTIR, DTA and TG, and chemical analysis.

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 500–190 nm range. As ethyl cinnamate is liquid at room temperature, the method followed was the so-called "wet grinding"—appropriate amounts of drug were added to montmorillonite and gently mixed with a spatula. For comparison, a fraction of montmorillonite was also submitted to the same grinding treatment, without addition of any pharmaceutical.

Except for *p*-aminobenzoic acid, which melts at 188°C, all other pharmaceuticals melt at temperatures below that needed to dehydrate montmorillonite, so no irreversible change in the structure of the clay was expected as a result of 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.

3.1. Montmorillonite

DTA profiles for Na-saturated montmorillonite and for the same sample after grinding for 10 min are given in Figs. 2(a) and 2(b) respectively. For the original sample,

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

Sample	DTA		TG	
	Endo	Exo	ΔT/°C	Weight loss/%
Na-Montmorillonite	134		41–119	7
	485		119–713	6
	609			
Ground Na-Montmorillonite	109		41–119	5
	426		422–686	3
ϕS	59[a]			
	285		160–290	88
		415	330–540	12
		524		
ϕS-M(M)	55[a]			
	253		156–278	37
		443	278–739	14
ϕS–M(G)	55[a]			
	236		139–252	37
		429	255–731	15
		584		
MC	43[a]			
	256		230–740	90
MC–M(M)	51[a]			
	190		103–216	32
		443	431–739	5
MC–M(G)	49[a]			
	220		85–216	35
		443	413–642	4
EC	77			
	183		Continuous	
	248			
EC–M(G)	100			
		275	121–234	37
		455	360–722	13
AB	198[a]			
	256		190–260	86
		597	500–675	14
AB–M(M)	110		41–101	1
		489	400–750	15
AB–M(G)	188[a]			
	216		174–243	38
		457	400–700	18
MSMHQ	167			
	265		< 300	13
	319		307–359	38
		518	470–680	49
MSMHQ–M(M)	124			
	238		70–250	6
	332		298–380	16
		453	410–450	14

Table 1 (*Continued*)

Sample	DTA		TG	
	Endo	Exo	ΔT/°C	Weight loss/%
MSMHQ-M(G)	154			
	234		70–250	6
	319		298–380	16
		447	410–450	14

[a] melting.

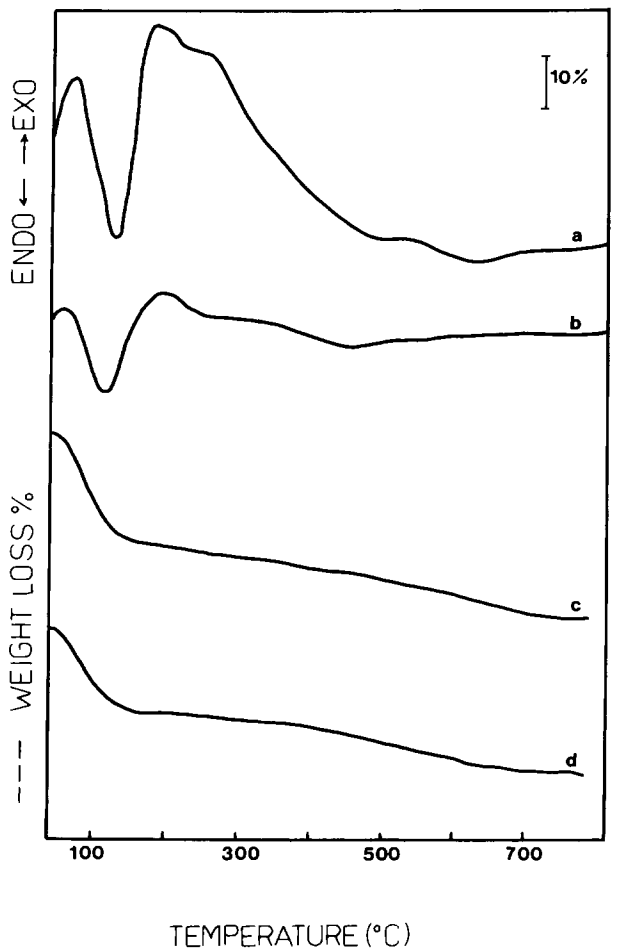

Fig. 2. Differential thermal analysis curves of (a) Na-montmorillonite, and (b) ground montmorillonite, sample M. Thermogravimetric Analysis curves of (c) Na-montmorillonite, and (d) ground montmorillonite.

a first endothermic effect is recorded at 134°C, due to dehydration, followed by two weak, ill-defined endothermic peaks at 485 and 609°C due to removal of structural water. The profile for the ground sample shows two minima at 109 and 426°C, the second seems to overlap the two distinct peaks recorded for the unground sample at 485 and 609°C.

The corresponding TG curves are shown in Figs. 2(c) and 2(d). For the original montmorillonite two weight losses are recorded. The first, between 41 and 119°C, corresponds to a weight loss of 7%, and is due to dehydration (the temperature range coincides with the strong minimum in the DTA profile for this sample). The second weight loss, extending from 119 to 713°C, amounts to only 6%. For the ground sample, the weight losses in approximately the same temperature ranges, were 5 and 3%, respectively; however, the second weight loss starts at a slightly higher temperature than for unground montmorillonite, and less amount of water is lost, thus suggesting that a partial removal of structural water is achieved during grinding.

3.2. *Phenyl salicylate and phenyl salicylate–montmorillonite systems*

DTA and TG curves for bulk phenyl salicylate (ϕS) and ϕS–M systems obtained by melting (M) and mixing and grinding (G) are shown in Fig. 3. The sharp minimum at 59°C for bulk ϕS is due to melting, and is followed by a broad endothermic effect at 285°C due to partial decomposition. Several weak and medium exothermic peaks at 415 and 524°C are due to combustion of the organic material. Weight loss starts above 150°C, confirming ascription of the peak at 59°C to a melting process. The large weight loss (88%) occurs between 160–290°C; combustion of residual fragments leads to a weight loss of 12% between 330 and 540°C, Fig. 3(d).

The DTA curve for system ϕS–M(M), Fig. 3(b), shows three effects: an endothermic effect at 55°C, most probably due to melting of the drug; the minimum at 253°C corresponds to decomposition of ϕS, and is followed by a maximum (combustion) at 443°C. From comparison of this curve with that of the unloaded montmorillonite, Fig. 2(a), it can be concluded that the endothermic effect due to removal of molecular water is absent for system ϕS–M(M), probably because water molecules have been displaced from the interlamellar space by pharmaceutical molecules. Also, the two well defined exothermic effects recorded in the profile of the drug at 415 and 524°C are substituted by a broad effect at 443°C.

The DTA curve for system ϕS–M(G), Fig. 3(c), is similar to that shown by the sample prepared by melting, but in this case the same two exothermic effects recorded in the DTA profile of bulk drug, see Fig. 3(a), are here recorded, although shifted towards higher temperatures; it seems that spreading and adsorption of the drug onto the clay surface in some sort of way hinders its combustion.

Data reported by the TG curves in all cases confirm the conclusions reached from the DTA study. The curve corresponding to sample ϕS–M(M), Fig. 3(e) shows a two-step weight loss. The first weight loss, between 156 and 278°C, corresponds to 37% of the initial weight and should be ascribed to partial decomposition of the drug, coinciding with the endothermic effect in the DTA profile at 253°C, Fig. 3(b). The second weight loss, between 278 and 739°C, corresponds to only 14% of the initial weight, could

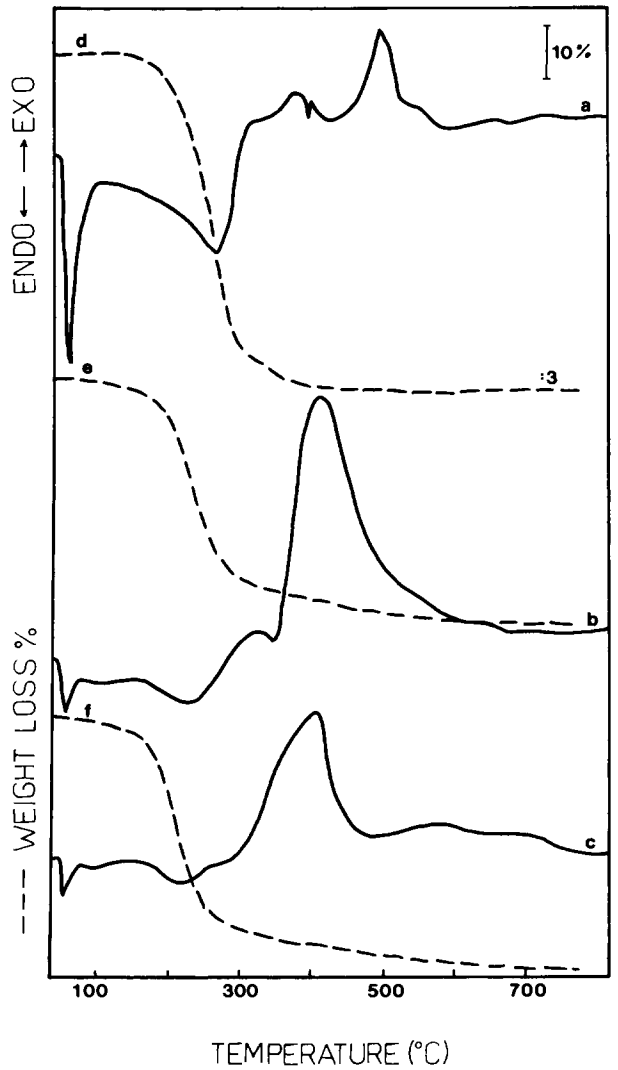

Fig. 3. Differential thermal analysis curves of (a) ϕS; (b) ϕS–M(M); (c) ϕS–M(G). Thermogravimetric analysis curves of (d) ϕS; (e) ϕS–M(M); (f) ϕS–M(G).

originate from combustion of phenyl salicylate (responsible also for the exothermic effect at 443°C in the DTA profile) together with removal of structural water from montmorillonite.

The TG curve for sample ϕS–M(G), Fig. 3(f), is rather similar to that recorded for sample ϕS–M(M); the first weight loss, 37% between 139 and 252°C, is due to partial decomposition of the drug, and that between 255 and 731°C (15%) is due to combustion of remaining drug and removal of structural water. Total weight loss is 51% for

sample ϕS–M(M) and 52% for sample ϕS–M(G). Taking into account that in this sample, the weight percentage of drug is 47%, the difference between the drug content and the total weight loss (as all products arising from drug combustion are volatile) should correspond to the percentage of water removed during TG analysis. That value was 4% for sample ϕS–M(M) and 5% for sample ϕS–M(G). These values are in both cases lower than that recorded for the pure montmorillonite, indicating that adsorption (although weak) of the drug onto the surface of the clay has given rise to a partial displacement of water molecules.

3.3. *Methyl cinnamate and methyl cinnamate–montmorillonite systems*

The DTA profile of this drug is given in Fig. 4(a). Two endothermic peaks are recorded, but their shapes are rather peculiar. If the positions of these minima are compared to the weight losses recorded in the TG curve, Fig. 4(d), it can be concluded that the first endothermic effect, at 43°C, does not correspond to any weight loss, and should correspond to melting of the drug (m.p reported in the literature: 40°C). The position of the second endothermic peak coincides with the weight loss, and its asymmetry and the sharp ending of the TG curve around 256°C indicates that volatilization of the drug is occurring.

The system prepared by melting, MC–M(M), shows a DTA profile, Fig. 4(b), with a weak, endothermic peak at 51°C, which position coincides with that expected for melting of the drug. A broader, weak, endothermic effect is recorded at ca. 190°C; this is probably due to partial decomposition of methyl cinnamate. However, the main feature of this decomposition profile is the, strong, broad, complex exothermic peak with a maximum at 443°C, that can be unambiguously related to combustion of the supported drug. It should be noted that this effect starts at just the same temperature as the second minimum in the DTA curve corresponding to the pure drug, Fig. 4(a), but in this case the shape of the endothermic peak was rather peculiar, asymmetric, indicating some volatilization of the drug. However, in the present case, dispersion and anchoring of the drug onto the clay surface retains it, avoiding its volatilization, and enables recording of its thermal decomposition along a very wide temperature range.

The curve is rather similar for sample MC–M(G), with the minimum corresponding to melting of the drug, now being recorded at 49°C, and the same broad, structured, intense exothermic peak, due to combustion of the drug, with a maximum at 443°C. It should be noted that the endothermic peak due to partial decomposition of the drug, coincident with the endothermic peak of the pure drug, recorded at 220°C, is now more clearly defined, Fig. 4(c).

The TG curves provide some confirmation of the conclusions reached from the DTA study. So, for both samples MC–M(M), Fig. 4(e), and MC–M(G), Fig. 4(f), the main weight loss is recorded from 95 ± 10°C to 216°C. This weight loss starts well above the first weight loss for the original montmorillonite (41°C, see Fig. 2(c)), indicating that the methyl cinnamate molecules have substituted the water molecules responsible for the very first weight loss recorded for the original clay. This weight loss represents 32 and 35%, respectively, for samples MC–M(M) and MC–M(G). The curves run almost parallel to the x-axis from 216°C up to 420 ± 10°C, where a second, weak, weight loss

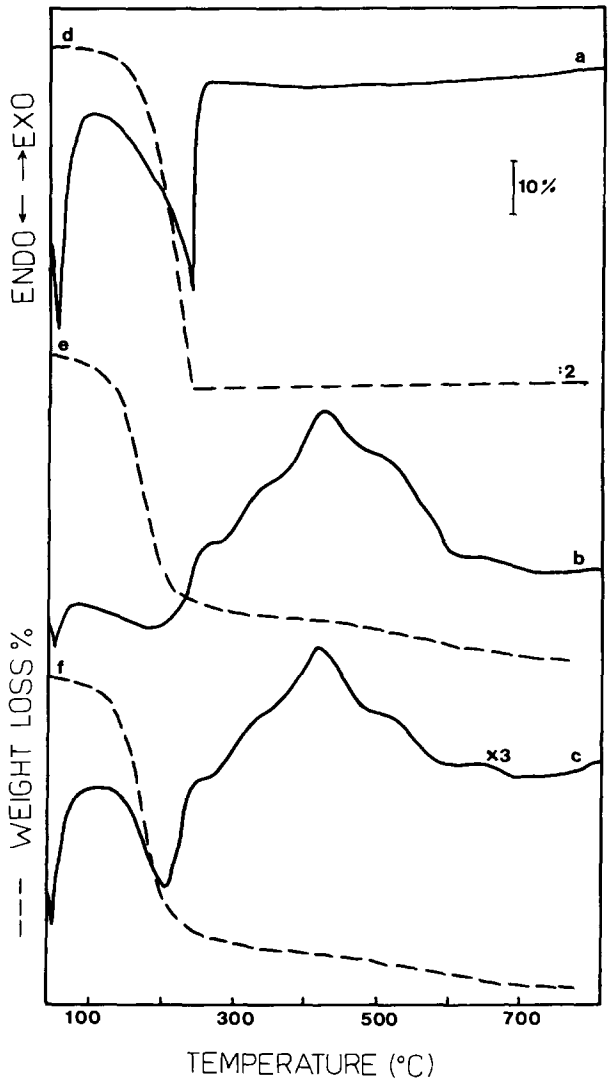

Fig. 4. Differential thermal analysis curves of (a) MC; (b) MC–M(M); (c) MC–M(G). Thermogravimetric analysis curves of (d) MC; (e) MC–M(M); (f) MC–M(G).

starts, extending up to 740°C. It should be noted that this weight loss is very weak and extends along a wide temperature range, and so it is not detected at all in the corresponding TG derivative curves. From the integral TG curve, weight loss in this temperature range corresponds to 5 and 4%, respectively, for samples MC–M(M) and MC–M(G), and is due to removal of structural hydroxyl groups and combustion of methyl cinnamate residues.

3.4. Ethyl cinnamate and ethyl cinnamate–montmorillonite systems

As ethyl cinnamate (EC) is liquid at room temperature, adsorption of this drug on montmorillonite was carried out solely by the "wet grinding" method.

The DTA curve of EC was recorded after impregnation on α-Al_2O_3 previously calcined in air at 1200°C. There is a strong endothermic effect at 248°C, Fig. 5(a), with a shoulder at 260°C, preceded by a broad, ill-defined minimum at 77°C and a sharp shoulder at 183°C. The TG curve, Fig. 5(c), shows a sharp weight loss in this same temperature range, although, as observed previously for other drugs here studied, recovery of the horizontal line is not smooth, thus suggesting some volatilization of the

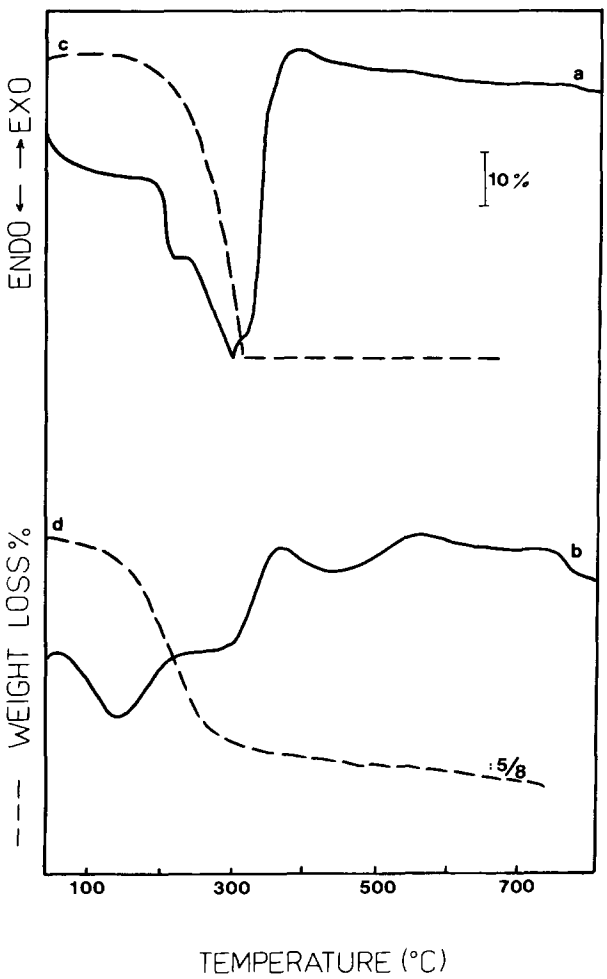

Fig. 5. Differential thermal analysis curves of (a) EC; (b) EC–M(G). Thermogravimetric analysis curves of (c) EC; (d) EC–M(G).

sample after thermal decomposition. However, in contrast with the other drugs studied, the remaining weight is not zero, but amounts to ca. 30% of the original weight, indicating that the residue cannot be completely volatilized.

The DTA curve for system EC–M(G) is shown in Fig. 5(b). After an endothermic, broad peak slightly above 100°C, the curve shows several features with a maximum at 275°C, followed by another at 455°C. The presence of these two maxima suggests, as for the other drugs studied above, that anchoring of these molecules onto the clay surface in some sort of way stabilizes them, thus retarding their decomposition. Most probably, the adsorption of the drug onto differently reactive sites of the clay surface would account for the presence of several shoulders in this DTA curve.

The TG curve, Fig. 5(d), suggests that incorporation of the drug has taken place with the simultaneous removal of weakly bonded water molecules, as no weight loss is recorded below 120°C. The main weight loss, amounting to 37% of the initial sample weight, ends at 234°C, with a second, small weight loss (13%) extending above 450°C, probably due to removal of hydroxyl groups.

3.5. *Aminobenzoic acid and aminobenzoic acid–montmorillonite systems*

The DTA curve recorded in air for *p*-aminobenzoic acid (AB) is shown in Fig. 6 (a). The sharp endothermic peak at 198°C corresponds to melting of the drug (reported m.p. 188°C), as no weight loss is recorded at this temperature in the TG curve, Fig. 6(d). The position of the main weight loss between 190 and 260°C (86% of the initial sample weight) coincides with the medium intense endothermic peak at 256°C, that should be ascribed to partial decomposition of the *p*-aminobenzoic acid molecule and, most probably, formation of carbonaceous residues. At higher temperatures (500–675°C) a broad, structured, exothermic peak is recorded, in the same temperature range as where a weight loss of 14% takes place; that corresponds to combustion of the residue.

The DTA profiles for samples AB–M(M) and AB–M(G) are rather different. Although both show, Figs. 6(b) and 6(c), a strong exothermic feature between 400 and 600°C, due to combustion of the carbonaceous residues formed after partial decomposition of AB; it should be noted that the curve for sample AB–M(M) does not show the expected endothermic doublet recorded around 200°C for the pure drug, and which is also present in the profile of sample AB–M(G), Fig. 6(b). In addition, a weak, medium broad endothermic peak is recorded at ca. 100°C, that can be ascribed to removal of water molecules. The TG curve for sample AB–M(M), Fig. 6(e), is rather different from those recorded for other drug–montmorillonite systems described above, as a small weight loss (1%) is recorded at around 110°C, thus coinciding with the weak endothermic effect just mentioned in the DTA curve, and the main weight loss is recorded in the 400–750°C range, that is, coinciding with the exothermic effect due to combustion of the residue. In contrast, the TG profile for sample AB–M(G), Fig. 6(f), corresponds to that expected, with no weight loss below 174°C, i.e., the *p*-aminobenzoic acid molecules have displaced weakly bonded water molecules, while the main weight loss (ca. 38%) is recorded in the 174–243°C range, i.e., coinciding with the endothermic effect recorded at 216°C and ascribed, from the DTA profile of the pure drug, to its partial decomposi-

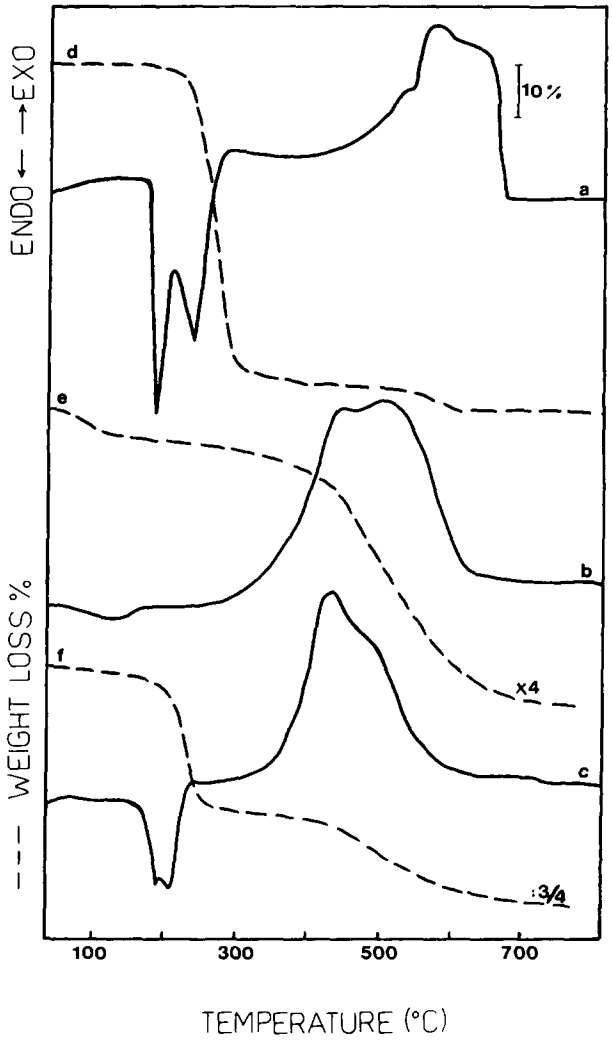

Fig. 6. Differential thermal analysis curves of (a) AB; (b) AB–M(M); (c) AB–M(G). Thermogravimetric analysis curves of (d) AB; (e) AB–M(M); (f) AB–M(G).

tion; also, the sharp, endothermic peak due to melting of the drug, is recorded for sample AB–M(G), but is absent from the profile of sample AB–M(M). Finally, it should be mentioned that total weight loss for sample AB–M(G) is ca. 56%, while for sample AB–M(M) such a value is only 16%.

Summarizing the data for these two samples, we can conclude that melting of *p*-aminobenzoic acid on the surface of montmorillonite should lead to its partial decomposition, while dispersion via grinding leads to a well dispersed system, where

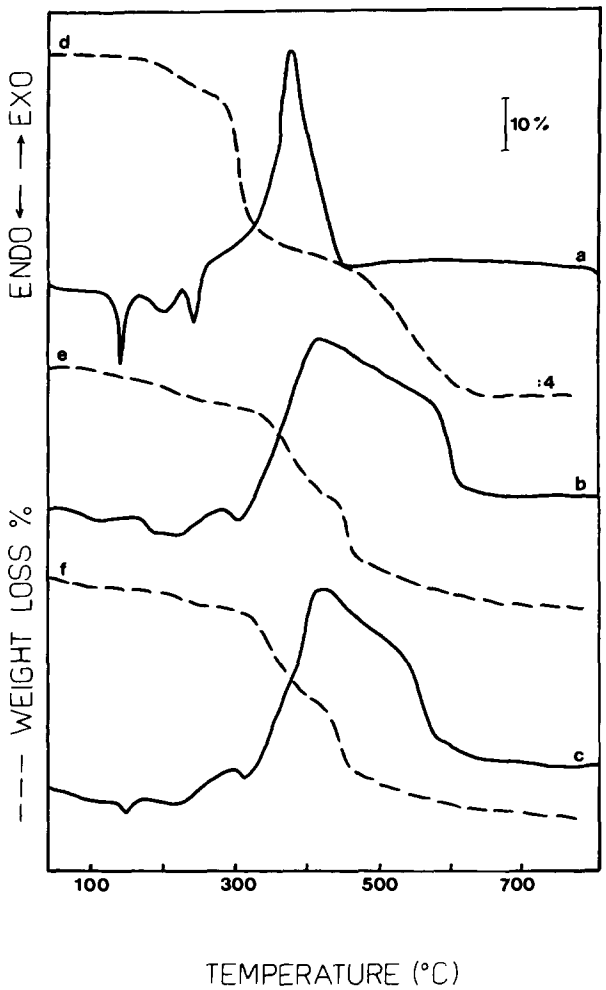

Fig. 7. Differential thermal analysis curves of (a) MSMHQ; (b) MSMHQ–M(M); (c) MSMHQ–MG. Thermogravimetric analysis curves of (d) MSMHQ–M(M); (f) MSMHQ–M(G).

the overall thermal behaviour of the drug does not differ significantly from that observed for other drug–montmorillonite systems here studied. As a result, some weakly bonded water molecules should remain on the montmorillonite surface, and its removal accounts for the small weight loss and the endothermic peak close to 110–120°C for sample AB–M(M), but that is absent in the corresponding DTA and TG profiles of sample AB–M(G). The weight loss between 174 and 243°C is very much larger for sample AB–M(G) than for sample AB–M(M), and, most importantly, the characteristic endothermic peak close to 250°C due to partial decomposition of the drug, is not recorded for sample AB–M(M).

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

The DTA profile of drug MSMHQ is shown in Fig. 7(a). Three endothermic effects are recorded, with minima at 167, 265, and 319°C, followed, by an intense exothermic effect with a maximum at 518°C. The corresponding TG curve is shown in Fig. 7(d). Weight loss starts at temperatures close to 260°C, and so the first minimum in the DTA curve at 167°C, could be ascribed to melting of the product. The inflexion points of the three weight losses recorded can be easily determined from the derivative TG curve (not shown in the figure) at 260, 330 and 540°C, i.e., all of them coinciding with the DTA effects, except for the first at 167°C, due to melting of the drug. Weight loss was 100% at the end of the run, indicating total combustion. As the weight losses are fairly well separated, some insights on the decomposition path can be attained from analysis of the weight losses. So, the first weight loss, centered at 260°C, corresponds to 13% of the initial sample weight, this value matching the weight loss expected for removal of the methyl group bonded to the nitrogen atom. The main weight loss, between 307 and 359°C, corresponds to 38%, a value very close to that expected (37%) for removal of the methyl sulphate moiety.

The DTA curve for sample MSMHQ–M(M) is shown in Fig. 7(b). The weak, broad endothermic effect close to 124°C can be tentatively ascribed to removal of small amounts of molecular water existing on the sample, not displaced by the drug molecules. The other two endothermic effects are recorded in positions very close to those for the pure drug, and so should be ascribed to the same chemical processes. The shape of the exothermic peak is, however, rather different and broader than for the pure drug, indicating that dispersion on the montmorillonite surface modifies the way the drug is thermally decomposed.

A similar DTA curve is obtained for sample MSMHQ–M(G), Fig. 7(c), with minima at 154, 234 and 319°C, followed by the exothermic effect. The shape of this effect is now intermediate between that of the drug, Fig. 7(a), and that recorded when spread onto the montmorillonite surface by melting, Fig. 7(b), suggesting that spreading is not as effective by grinding as melting.

Finally, the TG curves are almost coincident for both samples Figs. 7(e) and 7(f), with a small weight loss below 300°C, followed by the main weight loss in the 300–450°C range.

4. Conclusions

As a general conclusion, it can be stated that the drug is in all cases, thermally stabilized upon interaction with the surface of montmorillonite, but *p*-aminobenzoic acid is partially decomposed during melting. Generally speaking, melting leads to better dispersed systems than those obtained by grinding.

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