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The use of thermal analysis and mass spectrometry to study the solid state behavior in pharmaceutical tablet mixtures

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Abstract

The behavior of aspirin in the presence of tablet excipients and in the presence and absence of moisture was investigated. The methods used for investigation were differential thermal analysis (DTA), thermogravimetry (TG), and direct ionization probe mass spectrometry (DIP–MS). In addition, the degradation of aspirin in the absence of moisture was investigated by TG, and the residue after the first decomposition on the TG curve was subjected to DIP–MS. A degradation mechanism for dry aspirin is postulated.

Aspirin in tablet form was shown to be stabilized in the presence of increasing amounts of corn starch. These and related studies on the shelf-life of pharmaceutical products indicate possible interactions between the active ingredient and other ingredients of product formulations.

INTRODUCTION

The objective of this study was to assess the thermal behavior of aspirin, in this case the active ingredient, in pharmaceutical tablet mixtures. The concentration of the inert ingredients, also known as excipients, was varied in order to investigate the effect of these variations on the final tablet mixture. The behavior of aspirin within the tablet mixtures was also studied in the presence and absence of moisture.

It is known that aspirin hydrolyzes in the presence of water to salicylic acid and acetic acid [1,2]. Thus, ordinarily the thermal degradation pattern of aspirin in tablet form might differ before and after exposure to water.

Aspirin by itself is claimed to be a hydrophobic powder, and actually exhibits a hydrophobic field around itself when exposed to water in the liquid state [3]. Water must be present in the condensed form to hydrolyze aspirin. Hydrophilic excipients promote the nucleation and condensation of water around the asipirin thereby facilitating hydrolysis [3,4]. Thus, a hydrophilic excipient such as corn starch, which was used in our study, would be expected to exert this effect.

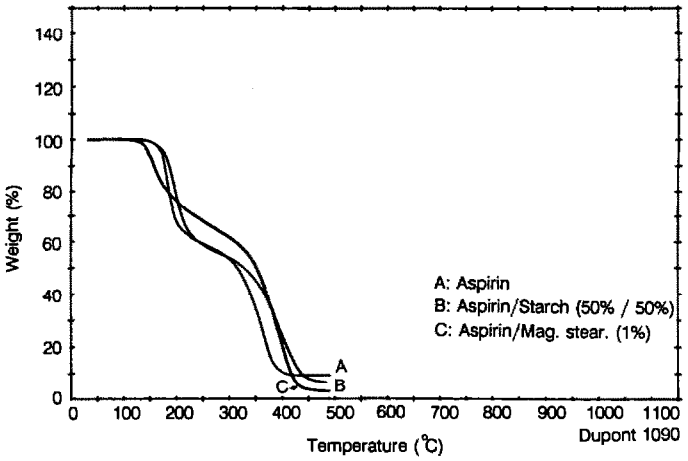


Fig. 1. Comparison of TG curves of aspirin (A), aspirin/corn starch mixture (50%/50%) (B) and aspirin/magnesium stearate (1%) mixture (C).

The decomposition of aspirin has been shown to be accelerated in the presence of stearates [1,5]. However, magnesium stearate itself is hydrophobic, and thus, while accelerating the degradation of aspirin by itself, it could be expected to nullify to some extent the above-mentioned effect exerted by starch.

The behavior of aspirin in tablet mixtures was studied with varying concentrations of starch, both before and after exposure to an aqueous environment.

Aspirin in the absence of water also showed a thermal degradation pattern when subjected to accelerated thermal conditions (5°C min^{-1}, in nitrogen, see Fig. 1). Because aspirin itself is hydrophobic, if there were very little permeation of moisture into the container containing aspirin tablets, hydrolysis would be ruled out. Therefore, a study of the mechanism of degradation of dry aspirin was carried out, and a degradation mechanism is postulated.

EXPERIMENTAL

Materials

Aspirin (Lot 7433) USP and benzoic acid USP (Lot 41623) were purchased form the J.T. Baker Chemical Co., Phillipsburg, NJ. Corn starch USP was purchased from Sigma Chemical Co., St. Louis, MO, Lot 42F-0766. Magnesium stearate USP was purchased from the Ruger Chemical Co., Inc., Irvington, NJ, Lot C-722680. Salicyclic acid USP was purchased from Sherman Research Laboratories, Toledo, OH, Lot WENH. All compounds met the USP XXII specifications.

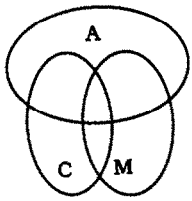


Fig. 2. A schematic diagram of the method of investigation of powder mixtures. A, aspirin; C, corn starch; M, magnesium stearate.

Methods

Conditioning of materials

Powders and powder mixtures. In order to understand the solid state behavior of the tablet as a whole, the behavior of each individual ingredient needs to be investigated. This is followed by assessing mixtures of the individual ingredients using all possible permutations that need to be studied. A schematic diagram of the method of investigation of the powders and powder mixtures pertinent to our study is given in Fig. 2. Thus, the preliminary investigation involved a study of the behavior of aspirin, corn starch and magnesium stearate alone. In addition, three mixtures needed to be studied: those of aspirin and corn starch, aspirin and magnesium stearate, and corn starch and magnesium stearate.

The powders were mixed using a mortar and pestle. The concentrations of the individual powders in the mixtures were representative of the concentrations of these ingredients in the tablets prepared, as described later. The thermal behavior of these samples was assessed both before and after exposure to water for 30 min. This was done to get a better insight into the behavior of the tablet mixtures, because the tablet mixtures were also subjected to identical conditions. Because aspirin is known to degrade to salicyclic acid in the presence of water, the thermal behavior of salicylic acid was also studied before and after exposure to water. The decomposition of benzoic acid was also investigated by TG. With these results, any traces of salicylic acid or benzoic acid behavior could be proportioned in mixtures with aspirin.

The samples studied in this investigation and the methods used to study them are outlined in Table 1.

Tablet mixtures. Aspirin tablets with 1% magnesium stearate alone, and aspirin tablets with corn starch in 5 mg increments with 1% magnesium stearate were prepared.

The powders were weighed and mixed in a Turbula mixer. These powders were then reduced to 80 mesh (particle size 177 micrometers, US standard ASTME 11-61) with an RO-Tap sieve shaker (W.S. Tyler Co.) to

TABLE 1

Preliminary investigation of powders and powder mixtures [a]

Samples studied	Analysis method
Aspirin	DTA, TG
Corn starch	DTA, TG
Magnesium stearate	DTA, TG
Aspirin/corn starch (50%/50%)	DTA, TG
Corn starch/magnesium stearate (80%/20%)	DTA, TG
Salicylic acid	DTA, TG
Benzoic acid	TG

[a] Samples were studied both before and after exposure to water for 30 min.

give a uniform distribution, and then compressed by direct compression with a Korsch single-punch tablet press (Type EK-O).

Sample tablets were disintegrated in a USPXXII disintegration apparatus using water. The tablet fragments that passed through the sieve as well as the intact part of the tablets were collected and dried under vacuum. The duration of the aqueous exposure was 30 min. Table 2 gives an outline of the various tablets made.

Thermal analysis

Tables 1 and 2 give an outline of the samples that were subjected to thermal analysis techniques, both before and after exposure to the aqueous environment.

A Stone 210 differential thermal analyzer was used to obtain the DTA data. The experiments were carried out in flowing nitrogen (20 ml min^{-1}),

TABLE 2

Ingredients of tablet mixtures [a]

Tablet mixture	Analysis method
Aspirin/magnesium stearate (1%)	DTA, TG
Aspirin/magnesium stearate (1%) corn starch (5 mg)	DTA, TG
Aspirin magnesium stearate (1%) corn starch (10 mg)	DTA, TG
Aspirin/magnesium stearate (1%)/corn starch (15 mg)	DTA, TG
Aspirin/magnesium stearate (1%)/corn starch (20 mg)	DTA, TG
Aspirin/magnesium stearate (1%)/corn starch (25 mg)	DTA, TG
Aspirin/magnesium stearate (1%)/corn starch (30 mg)	DTA, TG

[a] Samples were studied both before and after exposure to water for 30 min.

at a heating rate of 10°C min^{-1}. The sensitivity was set at about 50 mV gain which represented 5°C full-scale on the y-axis. The experiments were carried out in platinum crucibles with fired alumina (Al_2O_3) as the reference material. The unit was calibrated using the latent heat of melting for indium.

A Du Pont 1090 TG unit was employed to obtain the TG data. The experiments were carried out in flowing nitrogen (40 ml min^{-1}) at a heating rate of 5°C min^{-1}. The experiments were carried out in aluminum pans.

Gas chromatography and mass spectrometry

It was found that product degradation species could not be eluted on the columns utilized in the gas chromatograph units available. These included a Perkin Elmer 8420 capillary gas chromatograph (50 m fused silica glass capillary column, i.d. 0.25 mm) and a Hewlett Packard 5890 gas chromatograph (5 m silica glass column, i.d. 0.53 mm).

Because the gas chromatographic methods carried out did not yield the required results, direct ionization probe mass spectrometry (DIP–MS) was performed on aspirin, magnesium stearate, corn starch and salicylic acid. These results were correlated with the DTA and TG results to help in assessing the behavior of the tablet mixtures. A Hewlett Packard 5988 mass spectrometer was employed for the samples. A field strength of 70 eV was used in all cases.

RESULTS AND DISCUSSION

Single components

Aspirin

When aspirin in the absence of moisture was subjected to TG at a heating rate of 5°C min^{-1} in nitrogen, degradation was observed (Fig. 1). The residue after the first decomposition, as seen on the TG curve, was subjected to DIP–MS.

A typical DTA plot for aspirin is seen in Fig. 3. Aspirin powder by itself melts at 135 °C, and shows an endothermic peak at 192°C. A further degradation between 300 and 400°C (Fig. 4) also occurs. The first degradation peak on the TG curve corresponds to the melting and first decomposition endotherm on the DTA curve.

For aspirin powder, the heat of the endotherm (ΔH) values for aspirin melting and the first degradation endotherm increased after water treatment (Table 3). These peaks occurred at lower temperatures after water treatment. These results show the instability of aspirin after water treatment.

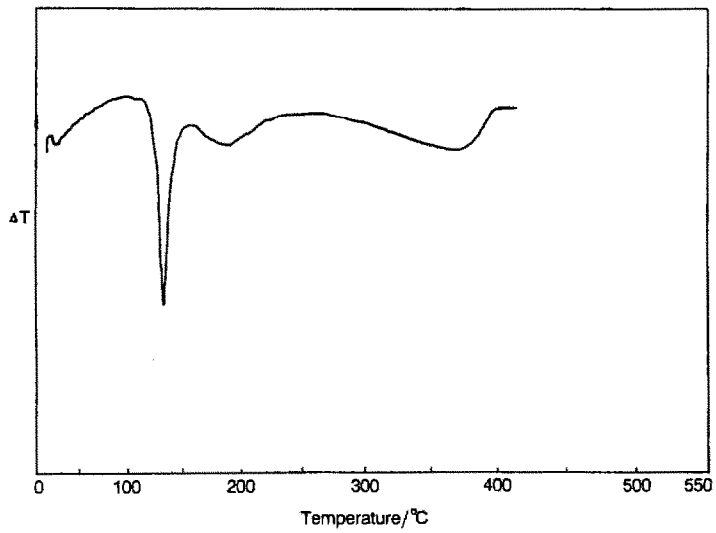


Fig. 3. DTA of aspirin powder, sample weight = 46.2 mg.

Magnesium stearate

The DTA scans on magnesium stearate showed melting at 124°C. This was in agreement with the results of Miller and York [6]. Endothermic activity was seen beyond 350°C. Two mass losses corresponding to 80.14% and 5.08% were seen in this region on the TG plots (Table 4). The TG results for magnesium stearate showed a 2.62% mass loss at 110°C (Table 4) which would be due to loss of moisture.

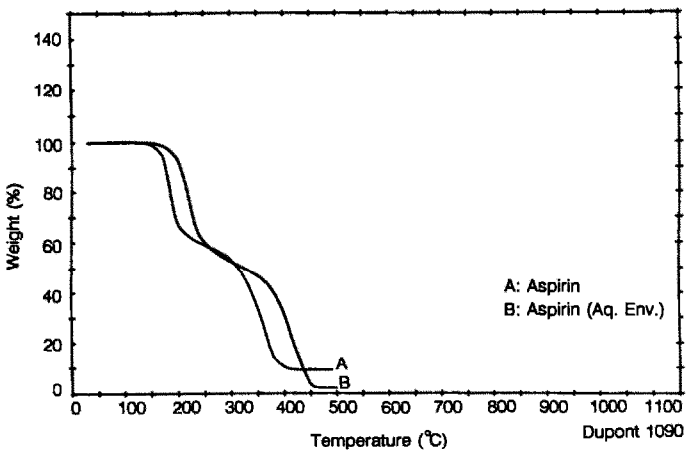


Fig. 4. Comparison of TG curves of aspirin powder (A) and aspirin powder in aqueous environment (B).

TABLE 3

Endotherm observations on aspirin tablets before and after water treatment (heat of endotherm, J g^{-1})

Samples	Asp. melt [a]		First degr. [b]	
	Before	After	Before	After
Aspirin powder	95.0	111.9	20.3	23.4
Asp. tab. plain (asp./mag. stear. (1%))	86.1	87.9	17.6	20.0
Asp. tab. 5 mg starch	86.8	105.3	12.5	21.2
Asp. tab. 10 mg starch	85.2	79.4	17.7	20.1
Asp. tab. 15 mg starch	99.4	88.3	34.1	26.7
Asp. tab. 20 mg starch	98.3	78.3	15.6	24.1
Asp. tab. 25 mg starch	85.5	83.7	21.0	29.7
Asp. tab. 30 mg starch	90.2	99.1	16.1	17.8

[a] Asp. melt. refers to the aspirin melting endotherm.

[b] First degr. refers to the first degradation endotherm.

For the aspirin melting endotherm, the ΔH values reduce after water treatment. For the first degradation endotherm, ΔH values increase throughout. This could possibly indicate degradation by hydrolysis.

Corn starch

There is a controversy in the literature concerning endotherm seen in many starches between 40 and 120°C. Ford and Timmins [7] attribute this peak to a loss of absorbed water, whereas Ager et al. [8] attribute a peak at 40°C to the degradation of starch. From our DTA and TG experiments on corn starch, we have been able to determine that this peak is due to the degradation of starch, especially because it is present in DTA runs of corn starch dried under vacuum. Hence, even if this peak is due to water, it could only be due to water entrapped in the crystal structure of starch, and not due to absorbed water.

Binary mixtures

The thermal behavior of mixtures of two of the tablet ingredients at a time were examined by DTA and DSC. A mixture a corn starch and magnesium stearate showed a 2.20% mass loss at 65°C when subjected to TG. This mass loss was due to the decomposition of starch as explained earlier. A 1.82% mass loss was seen at 100°C owing to loss of moisture. The weight loss corresponding to 70.91% observed at 352°C was due to the decomposition of starch (Table 4).

Superimposition of the TG and DTG curves of aspirin with those of an aspirin/starch or aspirin/magnesium stearate mixture (Fig. 1) showed the following.

(a) The onset and maximum rate of degradation ($d\alpha/dt$) for both the first and second degradations were shifted to higher temperatures for the

TABLE 4

Percent decomposition and residues of tablet ingredients and their mixtures

Sample	First decomp. (%)	Second decomp. (%)	Residue (%)
Individual components			
Aspirin	41.60	49.04	9.15
Aspirin (aq. env.)	48.84	49.16	2.19
Corn starch	4.40	72.47	22.25
Magnesium stearate	2.62	80.14 (1st) 5.08 (2nd)	11.22
Binary mixtures			
Aspirin/starch	44.97	48.05	6.45
Starch/mag. stear.	2.20 (1st) 1.82 (2nd)	70.91	21.00
Asp. tab. plain (asp./mag. stear.)	35.92	60.69	2.94
Asp. tab. plain (aq. env.)	34.67	61.98	3.56
Tertiary mixtures			
Asp. tab. 5 mg starch	35.00	60.45	4.74
Asp. tab. 5 mg starch (aq. env.)	33.04	61.92	4.78
Asp. tab. 10 mg starch	33.60	61.95	4.22
Asp. tab. 10 mg starch (aq. env.)	38.05	59.69	2.33
Asp. tab. 15 mg starch	31.04	63.15	5.61
Asp. tab. 15 mg starch (aq. env.)	38.03	56.28	5.43
Asp. tab. 20 mg starch	31.30	62.16	6.17
Asp. tab. 20 mg starch (aq. env.)	35.10	59.84	4.78
Asp. tab. 25 mg starch	29.27	62.74	7.69
Asp. tab. 25 mg starch (aq. env.)	35.41	58.37	5.70
Asp. tab. 30 mg starch	33.44	58.13	7.85
Asp. tab. 30 mg starch (aq. env.)	36.68	56.73	6.28
Salicylic acid	98.63		1.55

aspirin/starch mixture. This shows stabilization of aspirin in the presence of starch.

(b) the onset and maximum rate of degradation for the first degradation was shifted to lower temperatures, whereas for the second degradation these were shifted to higher temperatures, in the case of the aspirin/magnesium stearate mixture.

Tertiary (tablet) mixtures

Aspirin tablets with 1% magnesium stearate and corn starch in 5 mg increments were subjected to DTA and TG, both before and after exposure to water.

A decrease was shown in the endotherm relating to the melting of aspirin in tablet form and, in general, a further diminution occurred

TABLE 5

Onset and maximum rate of degradation ($d\alpha/dt$) temperatures from DTG curves

Sample	Onset temp. (°C)	Maximum $d\alpha/dt$ temp. (°C)
Aspirin	115 (1st)	180 (1st)
	260 (2nd) [a]	362.5 (2nd
Asp. tab. 5 mg starch	100 (1st)	155 (1st)
	287.5 (2nd	395 (2nd)
Asp. tab. 30 mg starch	122.5 (1st)	192.5 (1st)
	287.5 (2nd)	412 (2nd)

[a] The onset temperatures for the second stage of decomposition may be unreliable because, as can be seen from the TG curves, the end of the first degradation step and the beginning of the second degradation step are almost simultaneous.

following water treatment. This might be due to a decreasing surface area effect upon compaction and to a dissolution effect, also causing a diminished surface area upon water treatment.

It was observed in the results with binary mixtures that there were changes in the degradation pattern of aspirin when corn starch and magnesium stearate were added. In tertiary mixtures, this pattern can be observed as changes in mass loss. The most obvious change could be caused by the liberation of water from the excipient, which then reacts with the aspirin component.

When the TG and DTG curves of the tertiary mixture samples in Table 4 were superimposed the following trend was observed.

(a) With increasing concentrations of starch, both the first and second stages of degradation of aspirin were shifted to higher temperatures as seen in Table 5. This is an important observation, because even in the presence of magnesium stearate, which is known to enhance aspirin degradation, starch exerted a stabilizing effect.

(b) In all cases the percentage decomposed during the second step of degradation is more than the first degradation step as seen in Table 4. When the concentration of starch was increased above 5mg per tablet, the fraction decomposed during the first step of degradation, after being exposed to the aqueous environment, was consistently higher than the fraction decomposed in the sample not exposed to the aqueous environment. This effect could be due to the liberation of moisture from the sample, especially the excipients, which then reacts with the aspirin, as mentioned earlier. The second decomposition step, however, showed a decrease in the fraction decomposed after exposure to moisture, because the moisture was used up during the first step of thermal degradation.

(c) The residue that remained after undergoing the thermal program was greater in tablets that were not exposed to an aqueous environment and in

tablets with starch concentrations in excess of 5 mg per tablet, as seen in Table 4.

THE DEGRADATION OF DRY ASPIRIN

Dry aspirin, aspirin in the absence of moisture, also degrades when subjected to a thermal program (Fig. 4). The only documentation of pyrolytic studies of salicylates states that salicyclides are formed during its pyrolysis [9]. As stated earlier, aspirin by itself is hydrophobic and actually exhibits a hydrophobic field around itself when exposed to water in the liquid state [3]. If, in addition to the moisture present in the excipients, a neglibible amount of moisture were allowed to permeate into a container containing aspirin tablets, the degradation pattern for aspirin could be postulated from the TG and DIP–MS results carried out.

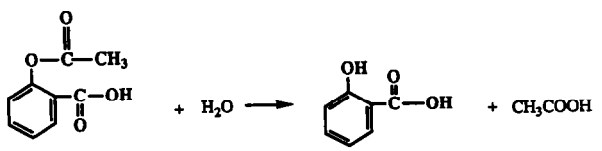
The residue after the first decomposition on the TG curve was subjected to DIP–MS. The degradation pattern for aspirin in the absence of moisture is postulated to be as follows.

The overall picture is that the aspirin melts and then a loss in weight occurs in two stages. In hydrolysis, aspirin reacts to give acetic acid and salicylic acid (Scheme 1)

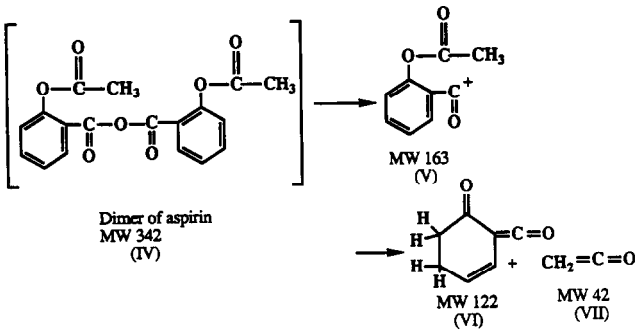
The same products would be expected in the dry state if, on thermal treatment, the aspirin first formed a dimer with the production of water which then reacted as above.

Then the water would react with other aspirin molecules to give salicyclic acid and acetic acid. The dimer formed from the "dry" reaction would be broken down to yield various fragments which could be found in the mass spectrometric studies (Scheme 2).

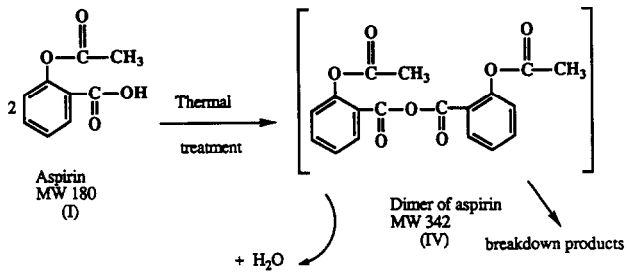
The two-stage decomposition is then explained on the basis of volatilization of acetic acid and salicylic acid with the other products as a result of the breakdown of the dimer. This can follow several routes occurring simultaneously which makes stoichiometric analysis of the TG curve impossible. However, each molecule of water would then be accompanied by the decomposition of three aspirin molecules. Possible degradation routes for



Scheme 1.



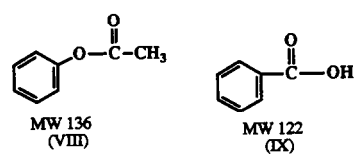
Scheme 2.



Scheme 3.

the dimer (**IV**) are shown in Scheme 3. Other degradation products from the dimer (**IV**) are shown in Scheme 4.

The most pertinent mass spectrometry results were the fragmentation patterns obtained on a sample after the first decomposition on the TG curve. A mass fragment pattern after 2 minutes (when maximum rate of volatilization into the MS unit was observed) showed a maximum peak abundance at an m/z value of 121 followed by 163, 92, and 138 with traces at 180, 65, and 43. After 6 minutes, the maximum peak abundance occurred at an m/z value of 120, followed by 92, with traces recorded at 196, 163, 138, 76, 64, and 43. These fragmentation patterns are consistent with the thermal degradation pattern outlined above: the m/z values can mostly be attributed to the dimer's breakdown products, aspirin, salicyclic acid, and acetic acid.



Scheme 4.

CONCLUSIONS

These findings would help in the preformulation and shelf-life studies of aspirin tablets. The degradation pattern of dry aspirin would explain why the aspirin concentration decreases when aspirin tablets are stored on the shelf at tropical temperatures over a period of time, even in the presence of very small amounts of moisture.

In this study, we have shown that by correlating thermal analysis and mass spectrometric data, it is possible to predict the behavior of the active ingredient in these pharmaceutical tablet mixtures.

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