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# The use of thermal desorption GC/MS to study weight loss in thermogravimetric analysis of di-acid salts

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**Abstract**

Thermal desorption gas chromatograph mass spectrometry (TD GC/MS) was used to study weight loss in thermogravimetric analysis (TGA). The technique of thermal desorption utilizes the same temperature heating rate as the TGA to thermally desorb volatiles from solid sample matrices. Volatiles were cryo-trapped at −60 °C. After thermal desorption is complete, the trapped volatiles are separated by a GC capillary column and identified by mass spectrometry. In this study, the TD GC/MS was applied in pharmaceutical development to understand the chemical reactions attributed to the weight loss in the thermal decomposition of two dicarboxylic acid salts of a drug substance. These two salts exhibited different thermal stabilities. The thermally induced chemical reactions obtained from these two salts included dehydration and decarboxylation. Thermal degradation compounds were identified and reaction pathways for decomposition were proposed. The stability of the salts is dependent on the identity of the dicarboxylic acids from which they were generated. The information obtained from TD GC/MS helps better understand the weight loss process in thermogravimetric analysis.


*Keywords:* TGA; Thermal desorption; GC/MS; Dicarboxylic acid; Thermal stability

## 1. Introduction

Thermogravimetric analysis, which measures the weight loss as a function of temperature, is an useful analytical tool in pharmaceutical development as it helps characterize the thermal behavior of drug substances and drug products. When multiple species are released during a single weight loss event in a TGA, only the total weight loss is observed from the thermogram. It is therefore interesting to know how the weight loss is distributed among the various components and to understand the chemistry behind the weight loss. In addition, it is important to know in formulation development whether a drug substance has bound or unbound solvent molecules and at what temperature solvent molecules are released. TGA can only provide partial answers but cannot indicate positive identity. In some cases, increasing temperature results in a sharp decline in the thermogram, indicative of thermal decomposition of testing materials. Compounds released by thermal degradation cannot be positively identified by TGA. As a result, an analytical technique is needed to facilitate the identification of components produced in thermal degradation processes as these degradation products may have relevance for characterization of drug substance and product stability. In addition, identification of all volatile components can reveal the suitability of TGA data for measuring residual solvent content of active pharmaceutical ingredients when decomposition is suspected.

The technique of TGA/MS has been in the market for years. It permits the direct mass analysis of volatiles released from solid matrices. Various applications have been reported in the literature. For example, TGA/MS has been used to study the decomposition or thermal degradation of polymers [1–8], oxidation of materials [9,10], and characterization of various types of materials [11–18]. The technique, however, has limited capabilities of identifying unknown components since it has no column separation prior to MS detection. It is therefore not practical to use this technique to identify un-

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knowns if multiple components are released from solid matrices at the same time. That is why the majority of TGA/MS applications are operated or displayed in the selected ion mode (not in the scan mode) to monitor the targeted ions in the TGA process. There are only a few reports on the use of TGA/MS for identification purposes, mainly for polymer degradation studies. Howell and coworkers used thermogravimetry (TG) GC/MS equipped with a cryotrap to study the thermal degradation of polystyrenes [19,20]. Jang and Wilkie applied a cold trap to collect the evolved products in a sniffer prior to GC/MS analysis of bisphenol A polycarbonate [3,21]. A latex was studied by Reggers et al. using the off-line combination of TG–GC–MS [22]. All these studies showed positive identification of unknown thermal degradation products. However, there has been little reported in the literature on the use of these techniques in the pharmaceutical industry [23,24].

This thermal desorption technique permits direct analysis of volatiles from solid matrices without any prior solvent extraction or other sample preparation. The combination of TD and GC/MS has been used to test residual solvents in bulk pharmaceuticals [23,24]. It also has a wide application in environmental control testing, such as insecticide fernitrothion in forestry atmospheres [25], polycyclic aromatic hydrocarbon in aerosols from wood combustion [26], pesticides in the atmosphere [27,28], and identifying and quantifying trace levels of volatile organic compounds using sorbent tubes [29].

The purpose of this study is to describe the application of thermal desorption GC/MS to the study of chemical reactions responsible for weigh losses observed in thermogravimetric analysis of pharmaceutical drug substance salts. Two drug substance salts formed with succinic acid and acetylenedicarboxylic acid were used as examples to show the application of this technique in pharmaceutical development. There have been a number of papers reported on the degradation of dicarboxylic acids [30–32]. In this study, the thermally released multiple components were separated by a gas chromatograph capillary column and detected by mass spectrometer. The peaks of interest were identified through the NIST mass spectrometry library search. The TD GC/MS technique provides additional information on the identity of the compounds released from solid matrices in the thermogravimetric process, which is especially important in pharmaceutical formulation development.

## 2. Experimental

A short path thermal desorption unit (Model TD-4, Scientific Instrument Services Inc., Ringoes, NJ, USA) sits directly on the injector/septum area of the gas chromatograph. A cryotrap cooled by liquid carbon dioxide (Welding Supply Co. Inc., NJ, USA) was installed inside the GC oven under the GC injection port to permit the trapping of volatiles at the front of the capillary column. A separate digital dual temperature controller permits the accurate temperature setting and regulates both the cooling and the heating temperatures of the cryotrap. Control of the thermal desorption system is accomplished through the following variables: desorption times, desorption temperatures and temperature ramps for purge, injection, desorption, focusing, and start delay (Table 1).

Table 1
Conditions for the thermal desorption unit

| | |
|---|---|
| Purge time | 30 s |
| Injection time | 30 s |
| Desorption time | 5–10 min depending on temperature heating ranges |
| Start delay | 30 s |
| Desorption temperature | Varied |
| Temperature ramp | 10 °C/min |
| Purge flow | >60 ml/min, Helium |
| Desorption flow | 20 ml/min, Helium |
| Cryotrap temperature | <−60 °C |
| Cryoheat temperature | 230 °C |

The thermal desorption analysis proceeds through the following steps. About 5–10 mg of solid is transferred into the desorption tube, which has been previously packed with silane-treated glass wool (PN 2-0411, Supelco Co., Bellefonte, PA, USA), After adding solid samples, another segment of glass wool is packed on the top of the samples. A desorption tube is then mounted onto the thermal desorption assembly. Prior to desorption, the heater block is quickly heated up to the set temperature and a cryofocus trap is cooled to −60 °C or lower. After reaching the desired temperatures for oven, heater block, and cryofocus trap, the desorption tube is dry purged with helium gas to remove oxygen and nitrogen. The desorption assembly is then pneumatically lowered (injection mode) so that the desorption tube needle is in the GC injection port. The heater blocks are positioned around the tube so that the combination of the heat applied and the carrier gas flow through the tube purge the volatile components into the GC injection port and into the front of the GC column. Upon completion of the desorption process, the heater block is opened and the normal carrier gas flow to the GC injection is initiated. The desorption tube is removed from the GC flow path and the cryofocus trap is rapidly heated to 230 °C to provide a narrow injection band. At the same time, GC/MS is triggered to start the analysis.

The gas chromatograph was TRACE GC-2000 (Thermo-Electron, San Jose, CA, USA) equipped with a split/splitless injector. The capillary column used was a ZB-WAX 30 m × 0.25 mm i.d. ×0.25 μm film thickness (Phenomenex, Torrance, CA, USA). The carrier gas was high purity helium (99.999%, Welding Supply Co. Inc., NJ, USA) under a constant column flow rate of 1 ml/min. A gas purifier (VICI, Fisher, PN 05730-2) and a moisture trap (VICI, Fisher, PN 05-730-9) were connected in series on the helium line to remove hydrocarbon impurities and trace water in the helium gas. The initial column temperature was set at 35 °C, and held for 2 min. The temperature was then ramped at a rate of 10 °C/min to reach the final temperature of 200 °C, and held at that temperature for 10 min. The injector temperature was set at 220 °C while the injection was operated in a

split mode with a split ratio of 10:1. The GC/MS interface was set at 280 °C. The PolarisQ Ion Trap Mass Spectrometer (ThermoFinnigan, San Jose, CA, USA) was operated in the electron impact (EI) mode with ionization energy of 70 eV. The mass spectral scans were carried out continuously from 15 to 500 amu during GC analysis. The ion source temperature was set at 220 °C. Before the analysis, the following bake-out procedure was applied to ensure the cleanness of the system. The desorption block was heated to 250 °C, the injection temperature was heated to 300 °C with a 200:1 split ratio, and the oven temperature was held at 250 °C for 1 h prior to analysis.

A high resolution 2950 (TA Instruments, New Castle, DE, USA) thermogravimetric analyzer was used to determine the thermal stability of drug substance di-acid salts. Experiments were carried out on about 3 mg samples under nitrogen, at a flow rate of 20 ml/min and a heating rate of 10 °C/min.

## 3. Samples

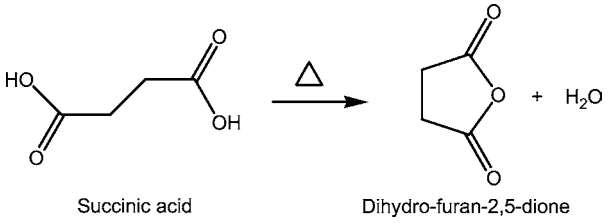
Two salts were produced from the same basic drug substance using succinic acid and acetylenedicarboxylic acid. One of the important tests of salt formation is to analyze the product mixture for thermal stability by thermogravimetric analysis. Reference compounds of these dicarboxylic acids were purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin, USA) for comparison. TD GC/MS was used to test these two acids together with their corresponding salts.

## 4. Results and discussion

Fig. 1 shows TGA thermograms for the decomposition of two drug substance (DS) salt forms. Each salt has a unique thermogram, the sample weight loss as a function of temperature. The DS succinic acid salt starts to lose weight at 105 °C (melting point of salt) and the weight loss becomes severe from 150 to 200 °C (the onset temperature for weight loss is 182 °C). In comparison, the DS acetylenedicarboxylic acid salt has a sharp weight loss from 135 to 165 °C. Since the same drug substance is used to form these salts, the different thermograms observed are due to the different chemical nature of these di-acids and their interaction with the drug substance. It is of great importance to know why the thermograms of these salts are different, and what types of chemical reactions are related to the weight loss observed in these thermograms.

### 4.1. Succinic acid salt

Fig. 2 shows a chromatographic comparison of the decomposition of succinic acid and the DS succinic acid salt. Both chromatograms contain a strong peak at an elution time of 19.1 min. The compound corresponding to this peak was identified as butanedioic anhydride resulting from the dehydration of succinic acid. The mass spectrum of this anhydride is shown in Fig. 3. No carbon dioxide was released from either succinic acid or the DS succinic acid salt. The chromatographic pattern of the DS succinic salt is similar to that of succinic acid, indicating that thermal decomposition of the salt is comparable to that of the precursor acid. The onset of decomposition for succinic acid is approximately 182 °C within the DS salt and 169 °C as the free acid. The higher temperature of decomposition within the salt is interesting because succinic acid is within a liquid matrix above 105 °C while the free acid has a higher melting point (169 °C) but decomposes with melting. The major reaction in this temperature range is the dehydration of succinic acid.



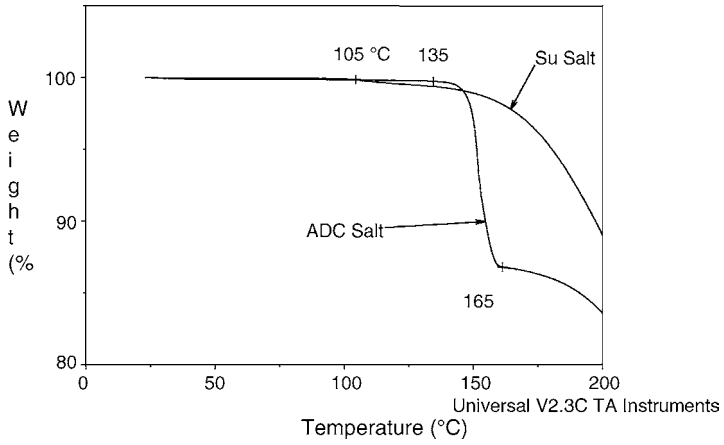




Fig. 1. Thermograms for the decomposition of salts of a drug substance with two dicarboxylic acids generated by thermogravimetric analysis: SU salt (succinic acid salt), ADC salt (acetylenedicarboxylic acid salt).

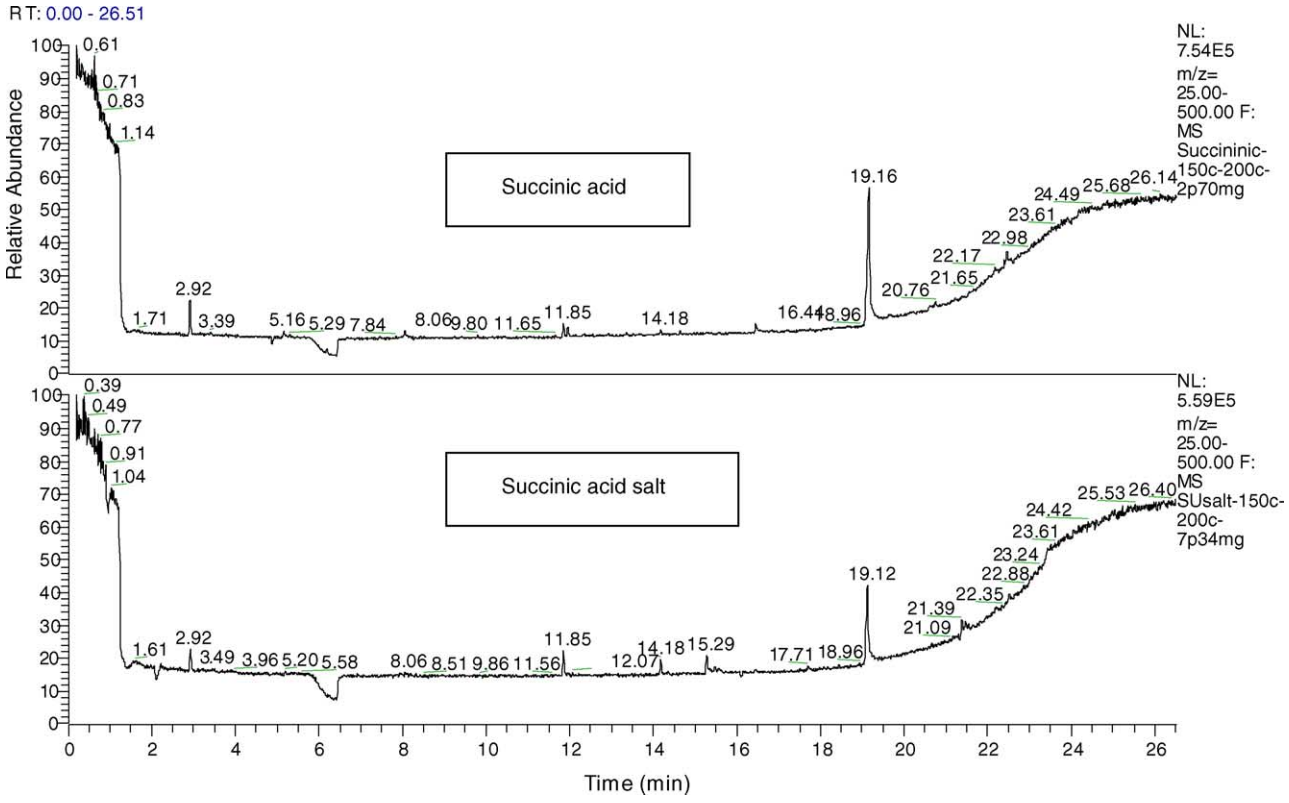



Fig. 2. Top: chromatogram of the product mixture obtained from succinic acid decomposition over a temperature range from 150 to 200 °C. Bottom: chromatogram of the product mixture obtained from the drug substance succinic acid salt decomposition over a temperature range from 150 to 200 °C.

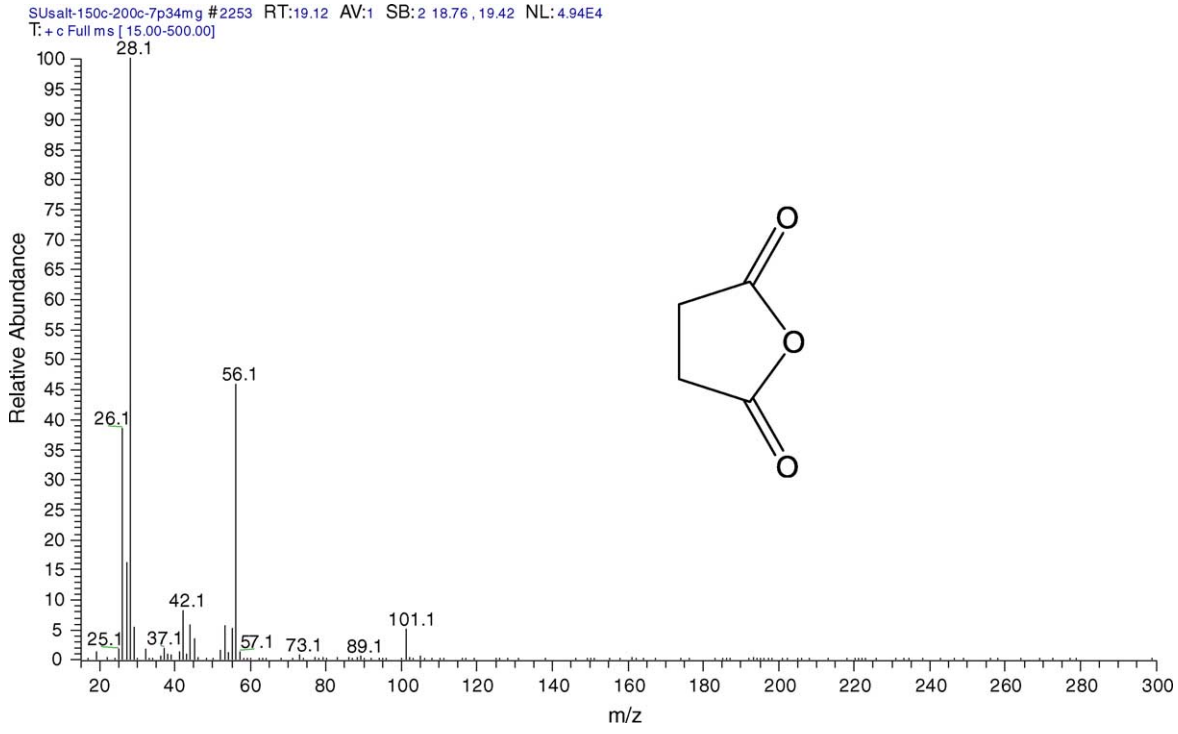



Fig. 3. Mass spectrum of butanedioic anhydride, a major compound generated from the thermal decomposition of both succinic acid and the corresponding DS salt.

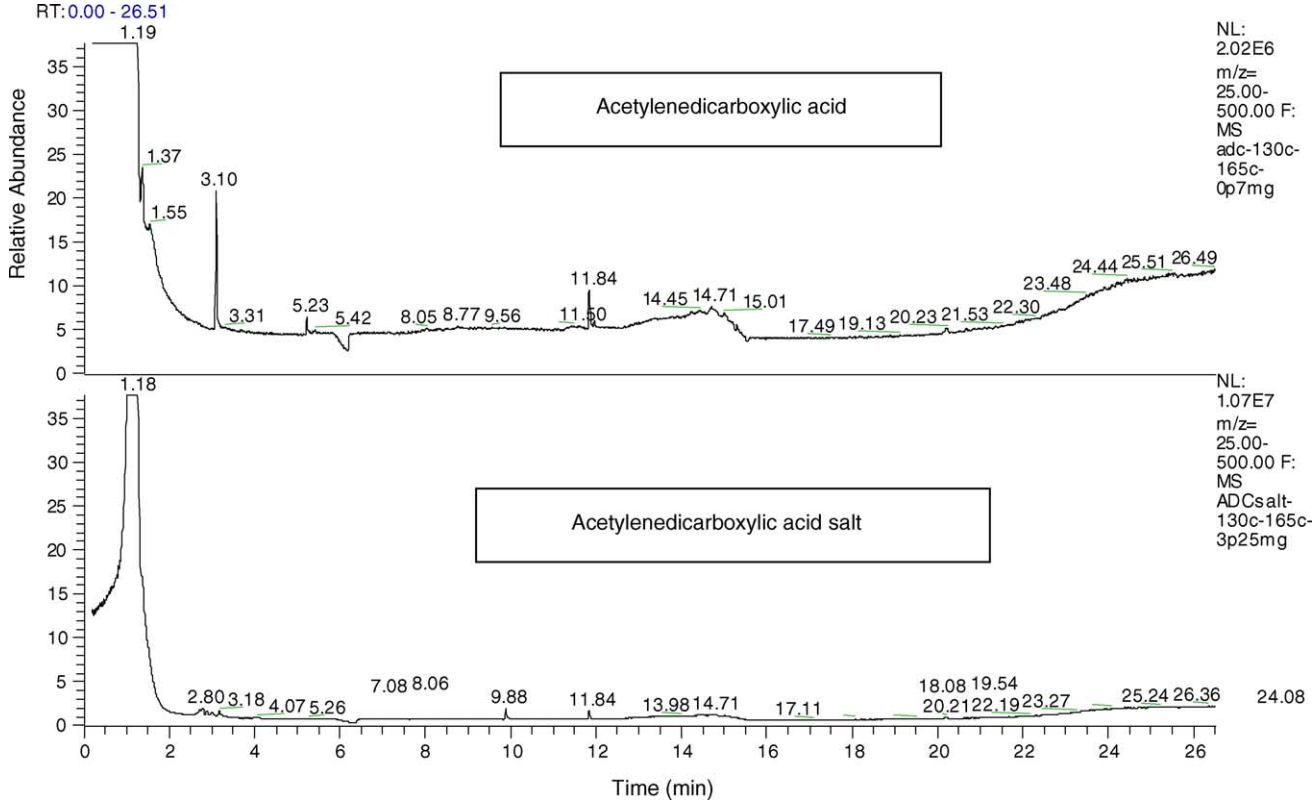
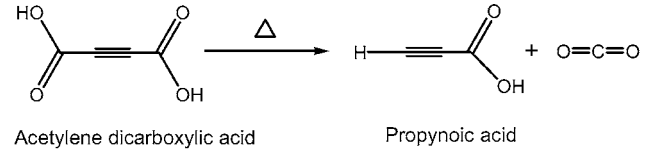



Fig. 4. Top: chromatogram of the product mixture obtained from the thermal decomposition of the acetylenedicarboxylic acid over temperature range from 130 to 165 °C. Bottom: chromatogram of the product mixture obtained from the thermal decomposition of the drug substance acetylenedicarboxylic acid salt over temperature range from 130 to 165 °C.

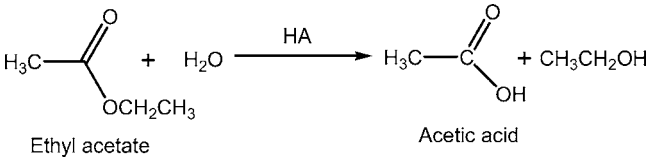
### 4.2. Acetylenedicarboxylic acid salt

The TGA thermogram of the DS acetylenedicarboxylic acid salt shows a slight weight loss from 30 to 135 °C while the weight displays a sharp drop from 135 to 165 °C. Using TD GC/MS under the same temperature range from 130 to 165 °C, the chromatograms of acetylenedicarboxylic acid reference compound and its DS salt are shown in Fig. 4. It was noted that the peaks at 3.10 and 5.23 min observed in the top chromatogram of Fig. 4 (ACD reference compound) were due to column bleeding. The weight loss between 130 and 165 °C observed in the TGA is due to multiple chemical reactions. It is also noted that both acid and its salt samples have similar chromatographic patterns over the temperature range.

A major peak was observed at around 1.2 min within the temperature range of 130–165 °C. This peak was identified as carbon dioxide ($CO_2$) resulting from the thermal degradation (decarboxylation) of acetylenedicarboxylic acid. Due to the presence of an αβ-unsaturated bond, the resulting propynoic acid can undergo further decarboxylation to form acetylene, which was detected at 1.5 min in the chromatograms of both acetylenedicarboxylic acid and its salt.




Acetic acid, observed at a retention time (RT) of 11.8 min in the chromatogram of the DS salt, may result from the hydrolysis of ethyl acetate (RT = 2.80 min in the lower trace), which was the solvent used for crystallization of the drug substance.




The resulting ethanol and propynoic acid could react with each other to form a propynoic acid ethyl ester, which elutes

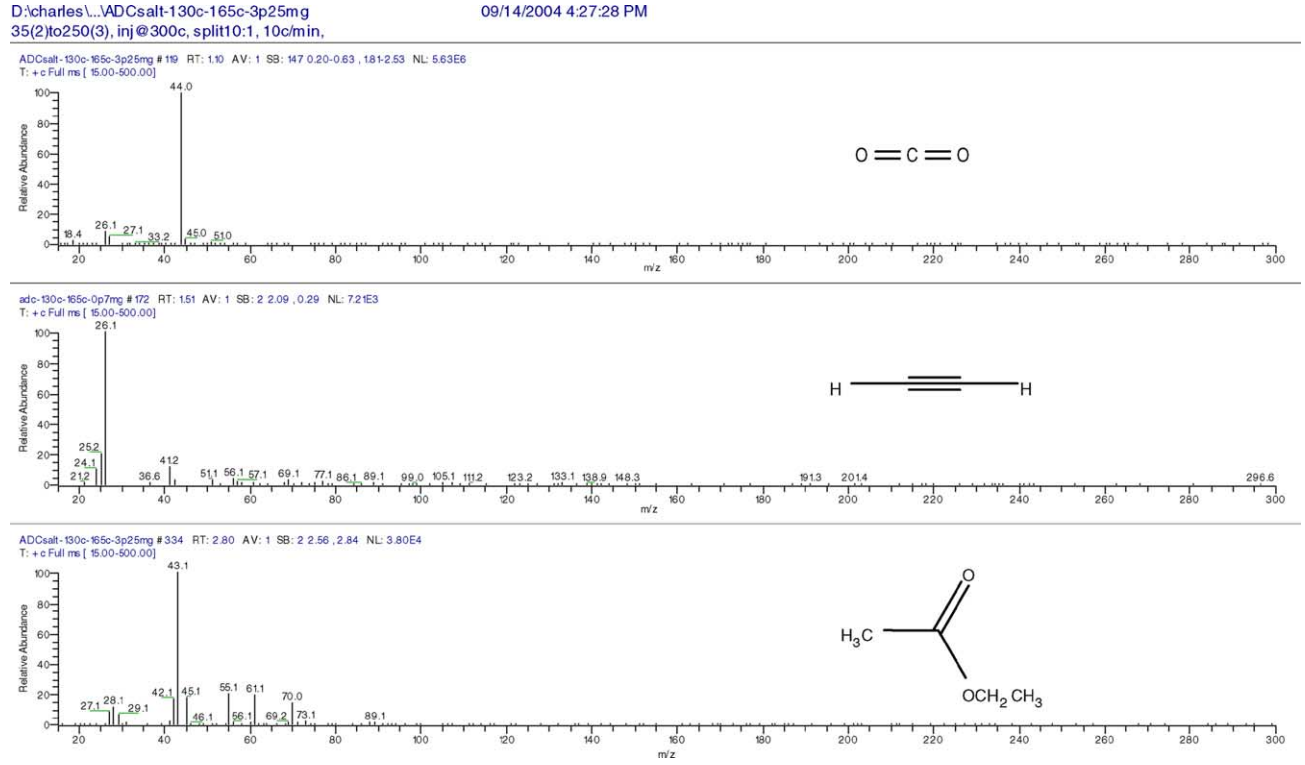



Fig. 5. Mass spectra of compounds generated by the thermal decomposition of the drug substance acetylenedicarboxylic acid salt. Top: mass spectrum of carbon dioxide, a compound eluted at 1.1 min. Middle: mass spectrum of acetylene, a compound eluted at 1.5 min. Bottom: mass spectrum of ethyl acetate, a compound eluted at 2.8 min.

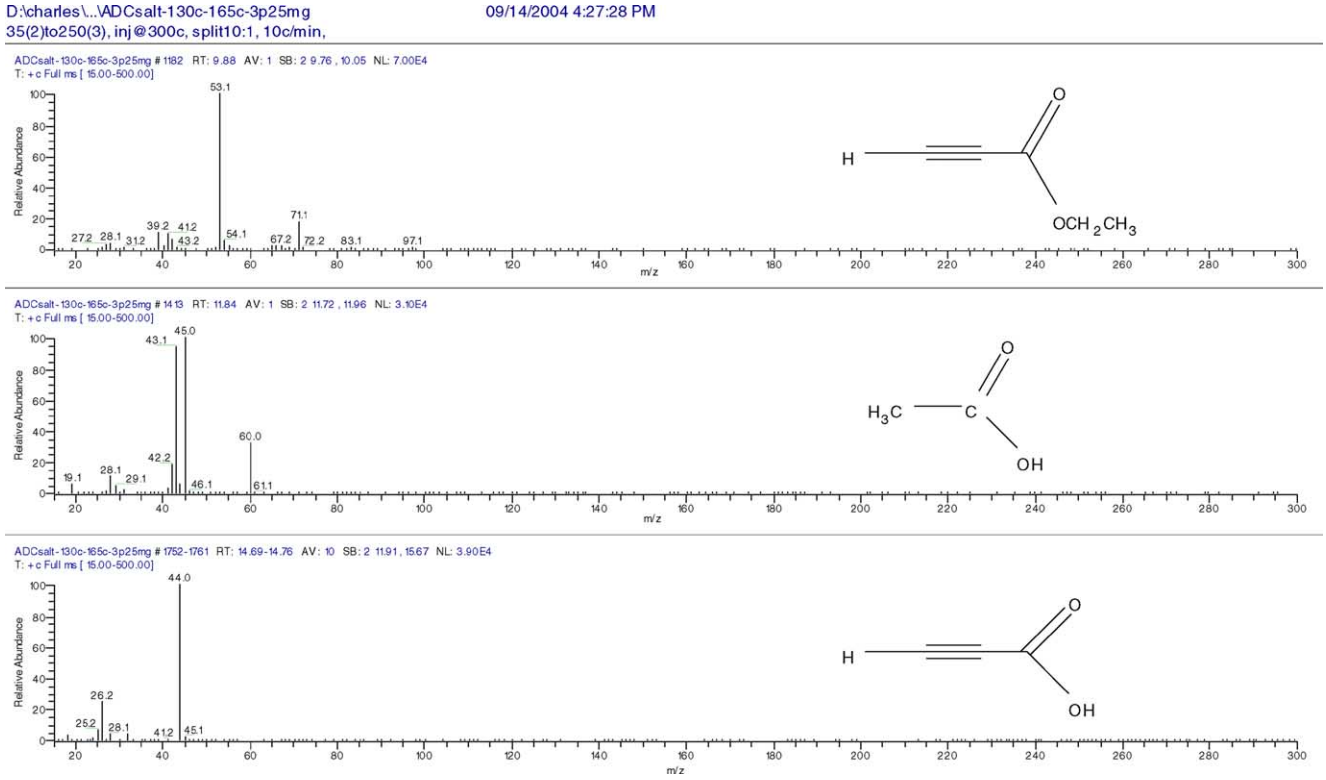
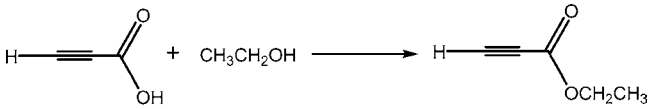



Fig. 6. Mass spectra of compounds generated by the thermal decomposition of the drug substance acetylenedicarboxylic acid salt. Top: mass spectrum of propyonic acid, a compound eluted at 9.9 min. Middle: mass spectrum of acetic acid, a compound eluted at 11.8 min. Bottom: mass spectrum of propyonic acid ethyl ester, a compound eluted at 14.8 min.

at around 9.9 min as shown in the chromatogram of the DS salt.




Propynoic acid Propynoic acid ethyl ester

Figs. 5 and 6 show the mass spectra of the compounds generated by the thermal decomposition of the drug substance acetylenedicarboxylic acid salt (M.P. 138.2 °C) in the temperature range from 130 to 165 °C. Note that the acetylenedicarboxylic acid begins to decompose 52 °C lower within the salt than as the free acid (M.P. 190 °C). It seems that the high decomposition temperature does not change the products of decomposition but does change their relative intensities.

## 5. Conclusions

Thermal desorption GC/MS has been successfully used to study the chemical reactions responsible for the observed weight losses in thermogravimetric analyses of two dicarboxylic acid salts. Thermal degradation compounds resulting from the decomposition of these salts were identified by GC/MS. The related chemical reactions and the reaction pathways were elucidated to better understand the weight loss behavior for these dicarboxylic acid salts in thermogravimetric analysis.

The DS succinic acid salt mainly undergoes dehydration to form an anhydride, which is responsible for the observed weight loss in the temperature range from 150 to 200 °C. Succinic acid starts to decompose from the solid state at 169 °C while the acid within the salt does not start to decompose till 182 °C even though the salt melted before 110 °C. However, there would appear to be no significant difference in their thermal decomposition products between succinic acid and its DS salts.

The DS acetylenedicarboxylic acid salt mainly undergoes decarboxylation in the temperature range from 130 to 165 °C. No dehydration was observed. Multiple reactions were present during the TGA process. Their reaction pathways were identified. The ADC salt decomposes at a lower temperature than does the succinic acid salt.

The study has demonstrated that the combination of thermal desorption and GC/MS is a simple hyphenated technique, but it could provide valuable information on the thermal decomposition behavior of pharmaceutical drug substances and the salt formation/decomposition in formulation development. It could be used to explain and understand, from the chemistry point of view, the weight losses observed in thermogravimetric analysis process. Identification of volatiles and thermal degradation products by TD GC/MS helps to better understand the chemical reactions attributed to a weight loss process, making a direct connection between the physical property observed in TGA and the chemical property obtained by MS. This is important and valuable information for chemical and formulation development in the pharmaceutical industries.

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