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Evolved gas analysis during thermal degradation of salbutamol sulphate

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Corresponding Author:	Fabio Sonvico AUSTRALIA
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Corresponding Author's Secondary Institution:	
First Author:	Fabio Sonvico
First Author Secondary Information:	
Order of Authors:	Fabio Sonvico Victoria Coleman, PhD Daniela Traini, Professor Paul M Young, Professor
Order of Authors Secondary Information:	
Abstract:	Crystalline Salbutamol sulphate (SS) is a common β 2-agonist used in dry powder inhalers for the treatment of asthma. The solid-state characteristics of SS are important since they govern the stability and thus efficacy of the drug when incorporated in inhalation medicine. Previous studies have investigated the thermal properties of SS and the complex array of thermal events have been attributed a mixture of melting and/or degradation mechanisms. In order to ascertain the exact thermal transformation processes that SS undergoes we utilised a combination of differential scanning calorimetry coupled with quadrupole mass spectrometry and thermogravimetric analysis coupled with Fourier transform infrared spectroscopy over the temperature range 25-500 °C. Based on the coupled thermal analysis data we proposed that SS undergoes a multi-step degradation mechanism in which the molecule dehydrates losing water initially, followed by the break up of the secondary amine group and lastly develops sulphur dioxide. When used in conjunction, the analytical techniques offered significant advantages over the use of thermal analysis alone, offering a better understanding of the transformations occurring to SS following heating.
Response to Reviewers:	Responses attached as a file

Sydney, 27 May 2014

Graduate School of Health

Pharmacy

General inquiries

T: +61 9514 8303

F: +61 9514 8300

E: Pharmacy@uts.edu.au

Fabio Sonvico

Senior Lecturer in Pharmaceutics

T: +61 2 9514 9296

E: Fabio.Sonvico@uts.edu.au

PO Box 123

Broadway NSW 2007

Australia

www.pharmacy.uts.edu.au

Dear Professor Szilágyi,

I'm submitting with this letter the revised version of the manuscript "Evolved gas analysis during thermal degradation of salbutamol sulphate" we submitted for publication in the Journal of Thermal Analysis and Calorimetry.

The comments of the referees helped to improve the manuscript especially in the part relative to the mass spectrometry analysis of the evolved gases from the heating of the β_2 -agonist drug. A point-by-point answer to all comments is attached at the end of this letter.

Yours sincerely,



Fabio Sonvico

Senior Lecturer in Pharmaceutics

The authors would like to thank the editor and the reviewers for the useful suggestions. The comments have been used to improve the manuscript and the answers to the specific queries are reported here below.

Reviewer #1

- 1) Page 1: The title should be change to Evolved gas analysis during thermal degradation of salbutamol sulphate. There is no solid state property of SS in this manuscript.

The title has been modified according to the suggestion. The new title is “Evolved gas analysis during thermal degradation of salbutamol sulphate”.

- 2) Page 5: How the authors select the mass for analysis at 12, 18, 28, 29, 32, 44, 48, 56, 58, 64, 73, 78, 92 and 94 amu? Why the authors select these mass?

The masses have been selected on the basis of a preliminary scan of the signals obtained with the DSC/MS equipment. The small and volatile molecular fragments obtainable from the molecule are within this range and the sensitivity of the instrument is limited when studying molecular weights above 100 amu.

- 3) Page 5: The authors have used argon with TG-MS, on the other hand, nitrogen with TG-FTIR, why they used different gases?

Argon was initially selected because it provides a signal at 40 amu in the MS spectrum analysis not interfering with evolved gases from salbutamol sulphate. Nitrogen on the other hand is giving a signal at 28 amu masking the signal of carbon monoxide. We decided ran the experiment again in a nitrogen atmosphere. The thermal results reflected what was obtained with argon.

As a consequence of the comments of both referees on the use of Argon and nitrogen, results from this new experiment were presented instead.

The authors have now removed Carbon monoxide results from the Table 1.

- 4) Page 7: The authors have determine thermal degradation up to 500°C and the residue is 40%, there is no characterization for this residue, the authors should run TGA up to 800 or more to see more volatile products using FTIR and MS, or this residue can characterized by elemental analysis, FTIR or NMR.

The objective of the research presented was to correlate the main thermal events of the analysis of salbutamol sulphate with the evolved gases with the aim to investigate the first degradation steps of the molecule.

A full characterization of the degradation of SS at higher temperatures, where there are not evident peaks corresponding to thermal events is beyond the scope of the paper.

- 5) Page 10: The results of MS spectra is not clear and need to rewrite and supported by the right figures, such there is no information for the formation of hydrocarbon, MeOH etc.

A new version of Figure 2 was proposed in the revision including most of the evolved gases producing a signal. The text was modified accordingly.

Reviewer #2

However, some explanation should be done:

1. The thermal studies were performed under inert atmosphere (argon, nitrogen). However, the authors believe that oxidation process of evolved larger volatile organic molecule is possible (page 8, line 12). Please explain this supposition in a little more detail.

Despite the inert atmosphere used for this study, a small quantity of oxygen is present in the gases used for the experiments. It is envisaged that oxygen in combination with temperature, pyrolysis and the ionization during MS analysis are contributing to oxidation processes, explaining the relevant signal of carbon dioxide detectable throughout the steps of decomposition of the molecule.

2. During thermal decomposition of salbutamol sulphate, the emission of CO and CO₂ is also observed. However, the formation of those gaseous products is not included in the decomposition mechanism (Fig. 4). Please explain.

As explained above, carbon dioxide represents the final product of carbonization/oxidation processes. Figure 4 has been modified to include carbon dioxide formation.

3. Reference citations in the text should be identified by numbers in square brackets [].

The citations have been formatted according to the style of the journal

Editorial comments:

- 1) TG: The Journal prefers the term TG and DTG instead of TGA and DTGA, so please change it throughout the manuscript (except in the trademark names).

The terms have been changed throughout the manuscript as requested.

- 2) May I call your attention to the crucial importance of recent citations beside the original sources in order to present relevant and substantial literature background of a paper published in the Journal of Thermal Analysis and Calorimetry. Please, visit www.springeronline.com/10973 with special focus on the papers published in the last 2 years (2013–2014, Online First). – At this moment the paper contains no references from JTAC, however, to show that the manuscript fits our journal it is necessary to give proper and recent references.

As suggested some relevant and recent citations from JTAC have been added to the references (Citations 4, 5, 6 and 14).

- 3) Figure axes: Please, give all Figure axes and Table headings according to the standards of our Journal. Example: Temperature/K, Heat flow/mW or Heat capacity/J g⁻¹K⁻¹. A style guide is included at the "For authors and editors" menu on the website of the journal ("Sample Figure JTAC.tif" and "Tips for text editing in JTAC.pdf" files).

Figure axes have been modified according to Journal standards.

- 4) Weight: Our Journal prefers the term of "mass" instead of "weight", so please substitute weight by mass throughout the manuscript even in the figures and tables as well. (Example: sample mass, m/m, mass%, mass loss etc.).

The term has been changed in the whole manuscript.

1 Evolved gas analysis during thermal degradation of salbutamol sulphate

2 Fabio Sonvico^{1,#}, Victoria Coleman², Daniela Traini^{3,4}, Paul M Young^{3,4}

3
4
5
6
7 ¹ Graduate School of Health - Pharmacy

8
9 University of Technology Sydney

10
11 Broadway, Sydney, NSW 2007, Australia

12
13
14
15
16
17 ² Nanometrology Section, National Measurement Institute Australia, West Lindfield,
18
19 NSW 2070, Australia

20
21
22
23
24 ³ Respiratory Technology, Woolcock Institute of Medical Research.
25
26
27 431 Glebe Point Road, Glebe, NSW 2037, Australia

28
29
30
31 ⁴ Discipline of Pharmacology, Sydney Medical School, The University of Sydney
32
33 University of Sydney, NSW 2006, Australia

34
35
36
37
38
39 #To whom correspondence should be addressed

40
41 Dr. Fabio Sonvico

42
43 Graduate School of Health – Pharmacy, University of Technology Sydney

44
45
46 15 Broadway, Ultimo, Australia

47
48 Email: fabio.sonvico@uts.edu.au

49
50
51 Phone: +61 2 9514 9296

52
53 Fax: +61 2 9514 8300

Abstract

1
2 Crystalline Salbutamol sulphate (SS) is a common β 2-agonist used in dry powder
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4 inhalers for the treatment of asthma. The solid-state characteristics of SS are import
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6 since they govern the stability and thus efficacy of the drug when incorporated in
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8 inhalation medicine. Previous studies have investigated the thermal properties of SS
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10 and the complex array of thermal events have been attributed a mixture of melting
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12 and/or degradation mechanisms. In order to ascertain the exact thermal transformation
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14 processes that SS undergoes we utilised a combination of differential scanning
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16 calorimetry coupled with quadrupole mass spectrometry and thermogravimetric
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18 analysis coupled with Fourier transform infrared spectroscopy over the temperature
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20 range 25–500 °C. Based on the coupled thermal analysis data we proposed that SS
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22 undergoes a multi-step degradation mechanism in which the molecule dehydrates
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24 loosing water initially, followed by the break up of the secondary amine group and
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26 lastly formation of sulfur dioxide. When used in conjunction, the analytical
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28 techniques offered significant advantages over the use of thermal analysis alone,
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30 offering a better understanding of the transformations occurring to SS following
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32 heating.
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47 **Keywords:** Salbutamol sulphate, DSC, TG, FTIR, MS, Evolved Gas Analysis
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1. Introduction

Asthma and chronic obstructive pulmonary disease are characterized by an acute or chronic bronchoconstriction. Smooth muscle contraction caused by cholinergic stimulation can be reversed by the activation of β_2 -adrenoceptors. Inhaled β_2 -agonists are effective bronchodilators and have become the standard approach for the management of diseases which obstruct the airway [1]. Salbutamol sulphate, the emisulphate of 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino) ethanol, is a short-acting β_2 -adrenergic agonist with a rapid onset of action (<15 minutes) and receptor stimulation lasting up to 4–6 hours. First commercialized as a solution for nebulization in 1968, it has since been reformulated and proposed as a pressurised metered dose inhaler (pMDI), and more recently as a inhalable dry powder, becoming the most common bronchodilator used in the management of asthma [2, 3]. The formulation of pulmonary administered drugs as inhalable powders offer clear advantages: a chemically stable solid form, absence of propellants (required in pMDIs) and reduced treatment time associate with conventional nebulizers. However, for the active pharmaceutical ingredients (API) to be efficiently deposited within the lung it has to have well-defined morphology, appropriate density and size distribution. Furthermore, a careful choice of formulation excipients and a suitable aerosolizing device is also needed. The synthesis or processing of the API into particles with an aerodynamic particle size lower that 5 μm is pivotal for inhalation to ensure efficient deposition in the airways. Solid-state properties, morphology, surface chemistry, cohesiveness, dissolution rate are all factors that affect an API therapeutic efficacy, toxicity, bioavailability and stability [4].

1 Recently, a renewed attention has been focused on the solid-state characterization and
2 development of drug salts and polymorphs with the ultimate aim to improve their
3 biopharmaceutical characteristic and therapeutic efficacy [5,6]. In recent papers, the
4 thermal properties of salbutamol sulphate have been investigated using differential
5 scanning calorimetry [7-14]. The authors presented a series of endothermic events that
6 were attributed either to the melting of the crystal followed by degradation or to
7 various stages of the degradation process of the drug. However, the exact explanation
8 of the observed thermal events could not be provided.
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21 In this study classical thermal analysis techniques, such as differential scanning
22 calorimetry and thermogravimetric analysis, have been coupled with mass
23 spectrometry (MS) and Fourier transform-infrared (FT-IR) spectroscopy and are used
24 to obtain a complete characterization of the thermal transformational properties of
25 salbutamol sulphate.
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2. Materials and Methods

2.1 Materials

Salbutamol sulphate (SS) was a kind gift of Nanomaterials (Singapore).

2.2 Evolved Gas Analysis Methods

2.2.1 *Differential scanning calorimetry and thermogravimetric analysis coupled with mass spectrometry*

Differential scanning calorimetry and thermogravimetric analysis were carried out with a thermogravimetric differential thermal analysis/differential scanning calorimetry (TG-DTA/DSC) system (Setsys 16/18, SETARAM Instrumentation, Caluire, France) coupled with a quadrupole mass spectrometer (ThermoStar™ Balzers, Pfeiffer, Asslar, Germany). Samples (15 - 20 mg) were equilibrated in platinum crucibles at 25 °C for 2 minutes before heating at a rate of 5 °C·min⁻¹ up to 500 °C in a non-oxidising, high-purity nitrogen gas flow (20 ml min⁻¹). A transfer capillary, heated at 198 °C, transferred the evolved gas to the mass spectrometer. The peaks in the mass spectra chosen for analysis were at 12, 17, 18, 28, 29, 32, 44, 48, 56, 58, 64, 73, 78, 92 and 94 amu, to study the presence of water, ammonia, methanol, CO₂, SO₂ and other volatile organic compounds produced by the sample molecule degradation (see Table 1). **The selection of the ions was based on a preliminary scan of the most abundant ions evolved and on the structure of the salbutamol sulphate.**

2.2.2 Thermogravimetric Analysis coupled with Fourier transform infrared

spectroscopy

The infrared spectra of the evolved gasses from the thermogravimetric analysis (TG) of SS were obtained by coupling a thermogravimetric analyzer (STA 6000, Perkin Elmer, Glen Waverly, Victoria, Australia) and a Fourier transform infrared (FT-IR) spectrometer (Frontier FT-IR, Perkin Elmer). A transfer line (TL 8000, Perkin Elmer), heated at 270 °C to prevent condensation, was used to transfer evolved gases from the TG to the FT-IR cell. TG was carried out at a temperature range of 25–500 °C in high purity nitrogen with a flow rate of 20 ml·min⁻¹ and a heating rate of 5 °C·min⁻¹.

Sample mass varied between 15 and 20 mg, and samples were weighed in ceramic pans. The FT-IR scan range was from 450 to 4000 cm⁻¹. FT-IR spectra and TG data were coupled using Spectrum Timebase™ software. Spectra of the evolved gases were compared for identification to reference gas spectra available through the NIST Chemistry Web book [15].

3. Results and Discussion

The DCS and TG traces obtained for salbutamol sulphate (SS) are presented in Fig. 1.

As reported by other authors, the DSC thermogram presents three main endothermic peaks at 197, 265 and 290.5 °C, respectively. Contrary to reports by some authors, no melting was observed in correspondence of the first endothermic peak at 197 °C [8,10,11,14,16]. The three endothermic events correspond to three distinct mass losses, accounting for the 12.9, 18.4 and 16.3 % of the sample mass, respectively. The loss of mass associated with the thermal events supported the hypothesis that these events correspond to three subsequent steps of the degradation process of SS, as previously suggested [13,14]. The derivative of thermogravimetric analysis (DTG) obtained for SS and the ion currents recoded for selected ion fragments analysed by mass spectrometry (see Table 1) are shown in Fig. 2. The derivative of TG data provides peaks that correspond to the maxima in mass loss rate (Fig. 2). Those peaks occur at temperatures relatively close, but generally few Celsius degrees higher, to the temperatures at which peaks were registered for differential scanning calorimetry.

The first degradation step appeared to be related to the release of water vapour occurring mainly around 200 °C, as shown in Fig. 2a. The high temperature at which the water is released, as well as the relevant mass loss registered, eliminated the possibility of an eventual loss of residual water associated with the SS crystals.

Interestingly, the first degradation step corresponded to the loss of a percentage of the molecule molar mass (12.9% of 576 Da for salbutamol sulfate, approximately 72 Da) which corresponds almost exactly to the loss two molecules of water (approx. 72 Da).

The first degradation step was then attributed to a dehydration of the molecule of salbutamol releasing two molecules of water for each molecule of salbutamol.

1 The signal of ammonia shown in Figure 2a is partly masked by water, which has a
2 signal at 17 amu when deprotonated. This is evident in the peak around 200 °C that
3
4 closely matches the evolved water. It seems however, that a second peak appearing at
5
6 260 °C and referable to the weight loss from salbutamol sulphate at that temperature
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8 could be attributed exclusively to ammonia. On the contrary, methanol is not one of
9
10 the evolved gases, its signal not changing from background values.
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14 Figure 2b shows the signal of evolved carbon dioxide and sulfur dioxide. The signals
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16 of carbon (12) and sulfur monoxide (48) closely matched the signal of carbon dioxide
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18 and sulfur dioxide respectively but with lower current intensities (data not shown).
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20 Carbon dioxide started to be evolved in correspondence to the first mass loss,
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22 attaining a peak around 270 °C and continued to be detected up to 500 °C. The main
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24 degradation steps are characterized by the development of an important amount of
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26 carbon dioxide and carbon. The peak in DTG occurring at 290°C is clearly associated
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28 to an abrupt and sharp increase in evolved sulfur oxides.
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33 Higher molecular mass ions signals, related to more complex organic molecule
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35 fragments, are shown in Fig 2c. The most relevant one was found to be the 2-methyl-
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37 1-propene (MPE) fragment, presenting a main peak at 260°C and a second one at
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39 400°C. Other fragments such as 2-methylpropane (MPA) and *tert*-butylamine (TBA)
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41 presented similar profiles but at lower intensities. Aromatic fragments such as phenol,
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43 and to a lesser extent benzene, showed mass spectra with intensities much lower than
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45 other organic ions, increasing at temperatures above 400°C. The low signals could be
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47 due to the fragmentation and/or oxidation of evolved larger volatile organic molecule
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49 during the MS ionization process.
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55 The FT-IR spectra measured during the three main endothermal events recorded with
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57 DSC are reported in Fig. 3 and support the results obtained by coupling the DSC with
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1 mass spectrometry. In Fig. 3a the spectrum collected at 196 °C is dominated by the
2 absorption of gaseous water. The reference spectrum of water presented in Fig. 3d is
3 characterized by the presence of three complex series of peaks: the peaks from 3500
4 to 4000 cm^{-1} are related to the symmetrical and asymmetrical stretching of the water
5 molecules, the peaks from 1200 to 2000 cm^{-1} characterized by a maximum at 1508
6 cm^{-1} are related to the 'in plane' bending of OH bonds, while the peaks from 450 to
7 700 cm^{-1} are attributed to 'out of plane' bend of the OH bonds. The gaseous water
8 spectrum does not present the classic broadening of absorption peaks linked to
9 hydrogen bonds.
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24 Apart from the water absorption peaks, two other peaks are evident in the spectra in
25 Fig. 3a, which can be related to other evolved gases. The broad peak at 2300-2400
26 cm^{-1} is characteristic of carbon dioxide absorption, while the second peak at 2965 cm^{-1}
27 cm^{-1} appears more relevant to determine salbutamol sulphate degradation pattern and
28 could be found also in the spectrum acquired at 265 °C. In the spectrum presented in
29 panel b of figure 3, the absorption peaks characteristic of 2-methyl-1-propene (Fig.
30 3e) are clearly identifiable: the methyl C-H asymmetric and symmetric stretching is
31 responsible for the peaks between 2850 and 2950 cm^{-1} , gem-dimethyl bending for the
32 doublet at 1350-1400 cm^{-1} , while vinylidene pendant C-H is responsible for the
33 characteristic peaks at 3085 cm^{-1} (stretch) and at 885 cm^{-1} (out of plane bending) [17].
34 The absorption peak of carbon dioxide is still evident, while the other absorption
35 peaks can be attributed to ammonia (Fig. 3f). The spectrum of gas-phase ammonia is
36 complex and shows multiple band structures, the peaks of ammonia are evident in the
37 spectrum collected at 265 °C where the peak around 3300 cm^{-1} and the two intense
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1 peaks at 930 and 965 cm⁻¹ can be attributed to the stretching and bending of N-H
2 bonds, respectively.
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7 The spectrum collected at 290 °C (Fig. 3c) presents the same peaks present at the
8 lower temperature except for a sharp doublet appearing between 1300 and 1400 cm⁻¹.
9 This absorption frequency is characteristic of sulfur-oxy compounds and was
10 attributed to sulfur dioxide (Fig. 3f). At higher temperatures the absorption peaks of
11 carbon dioxide dominated the FT-IR spectra.
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21 The use of FT-IR associated with TG helped to refine the data obtained by the
22 coupling of thermal analysis with mass spectrometry. The latter technique failed to
23 provide reliable information on higher molecular weight organic ions, for which the
24 signal was weak in comparison to the small volatile molecules. The combination of
25 the two analytical techniques together helped to clarify the degradation mechanism of
26 SS that was hypothesized by Larhrib et al. [13]. In this work it was suggested that the
27 most likely group to be released upon heating was the *tert*-butylamine group. The
28 degradation of SS in aqueous solutions at elevated temperatures has been extensively
29 studied varying pH, buffer species and concentration [18-20]. In these conditions, the
30 main degradation product observed was the 4-hydroxy-3-hydroxymethylbenzoic acid,
31 suggesting the fragmentation of the molecule with loss of the *tert*-butylamino group
32 and oxidation to carboxylic acid of the residual fragment. More recently, the chemical
33 instability of SS in ethanolic solutions has been studied in order to elucidate the
34 instability of the molecule in pMDI formulations containing ethanol as co-solvent. In
35 this case, the main degradation products were found to be ethyl ether derivatives
36 obtained through a dehydration process [21]. The thermal analysis conducted here in
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1 conjunction with mass spectrometry and FT-IR showed that the mechanism of
2 degradation of SS in its solid form by heating is different from the one initially
3 proposed. The degradation steps proposed are presented in Fig. 4. Even if the steps
4 are partially superimposed, the relative abundance of the different volatile compounds
5 is clearly visible in the mass spectrometry analysis coupled with the data obtained by
6 DSC. Furthermore, the correct identification of these compounds was possible by
7 coupling the **TG** with FT-IR.
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19 As a consequence, we propose that the degradation mechanism for SS is characterized
20 by a first step in which the molecule dehydrates, losing two molecules of water. This
21 latter rearrangement of the molecule facilitates a subsequent fragmentation step that
22 involves the secondary amine group of the molecule. However, *tert*-butylamine is not
23 formed because the fragment is immediately broken into ammonia and 2-methyl-1-
24 propene. **The aromatic fragments remaining are then decomposed during the**
25 **carbonization.**
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4. Conclusions

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2 These analytical techniques used in conjunction offered significant advantages over
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4 the use of stand-alone thermal analysis. These novel thermo analytical techniques
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6 offered a better understanding of the transformations occurring to salbutamol sulphate
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8 following heating, via the identification of the gases evolved at different temperatures
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10 and their coupling to the thermal events.
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26 help on the use of DSC/MS.
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Table 1. Evolved gas analysis by mass spectrometry: fragment molecules

Fragment mass/amu	Molecular formula	Relative molecule
12	C	Carbon
17	NH ₃	Ammonia
18	H ₂ O	Water
32	CH ₃ OH	Methanol
44	CO ₂	Carbon dioxide
48	SO	Sulfur monoxide
56	C ₄ H ₈	2-methyl-1-propene (MPE)
58	C ₄ H ₁₀	2-methylpropane (MPA)
64	SO ₂	Sulfur dioxide
73	C ₄ H ₁₁ N	<i>Tert</i> -butylamine (TBA)
78	C ₆ H ₆	Benzene
94	C ₆ H ₆ O	Phenol

Figure Captions

1
2 **Fig. 1.** DSC and TG data obtained for salbutamol sulphate at an heating rate of 5 °C
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4 min⁻¹
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9 **Fig. 2** Salbutamol sulphate derivative of thermogravimetry curve (DTG, dotted line)
10 and ion currents signals obtained by MS (solid lines) for the following molecular
11 fragments: (a) ammonia 17 amu, water 18 amu, methanol 29 amu; (b) carbon dioxide
12 44 amu, sulfur dioxide 64 amu; (c) 2-methyl-1-propene (MPE) 56 amu, 2-
13 methylpropane (MPA) 58 amu, *tert*-butylamine (TBA) 73 amu, benzene 78 amu,
14 phenol 94 amu.
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26 **Fig. 3** FT-IR Spectra obtained during thermogravimetric analysis of salbutamol
27 sulphate (a, b, c) and reference spectra (c, d, e)
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32 **Fig. 4** Proposed thermal degradation mechanism of SS during heating
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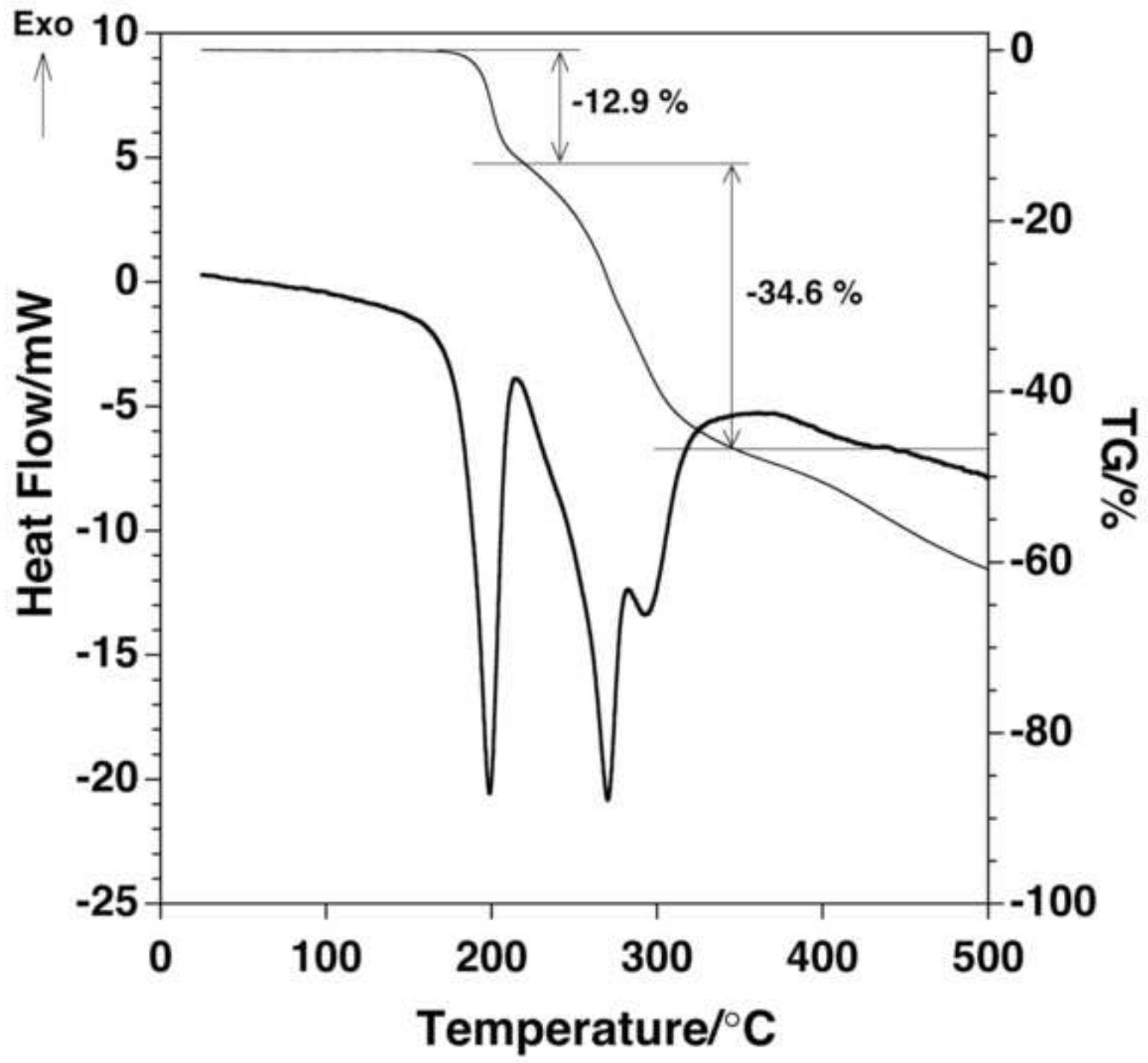


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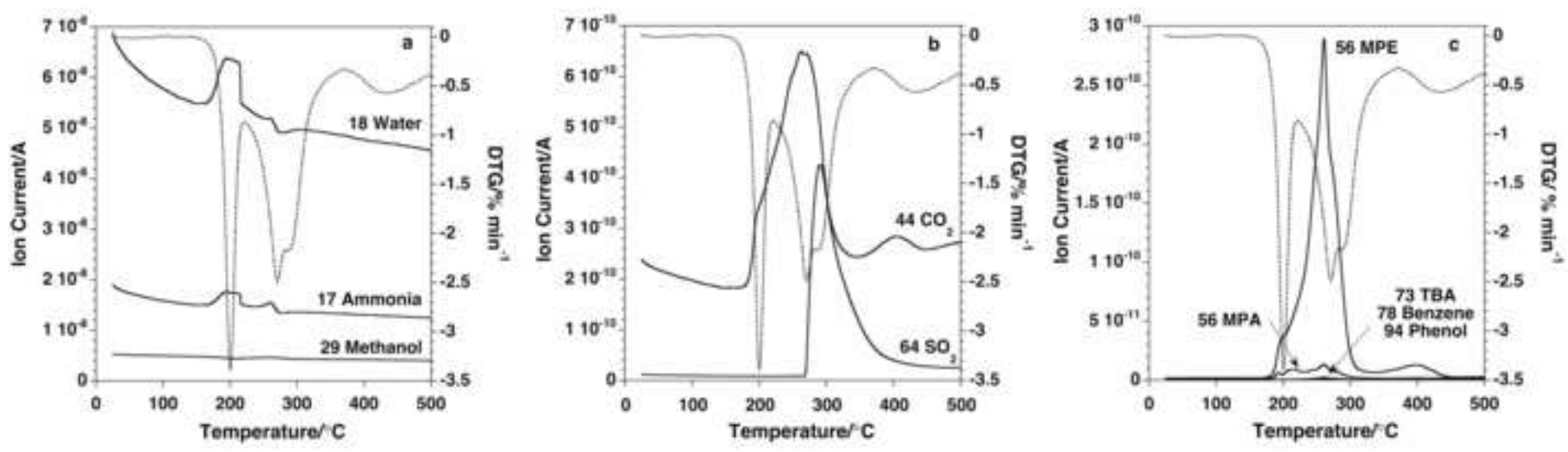


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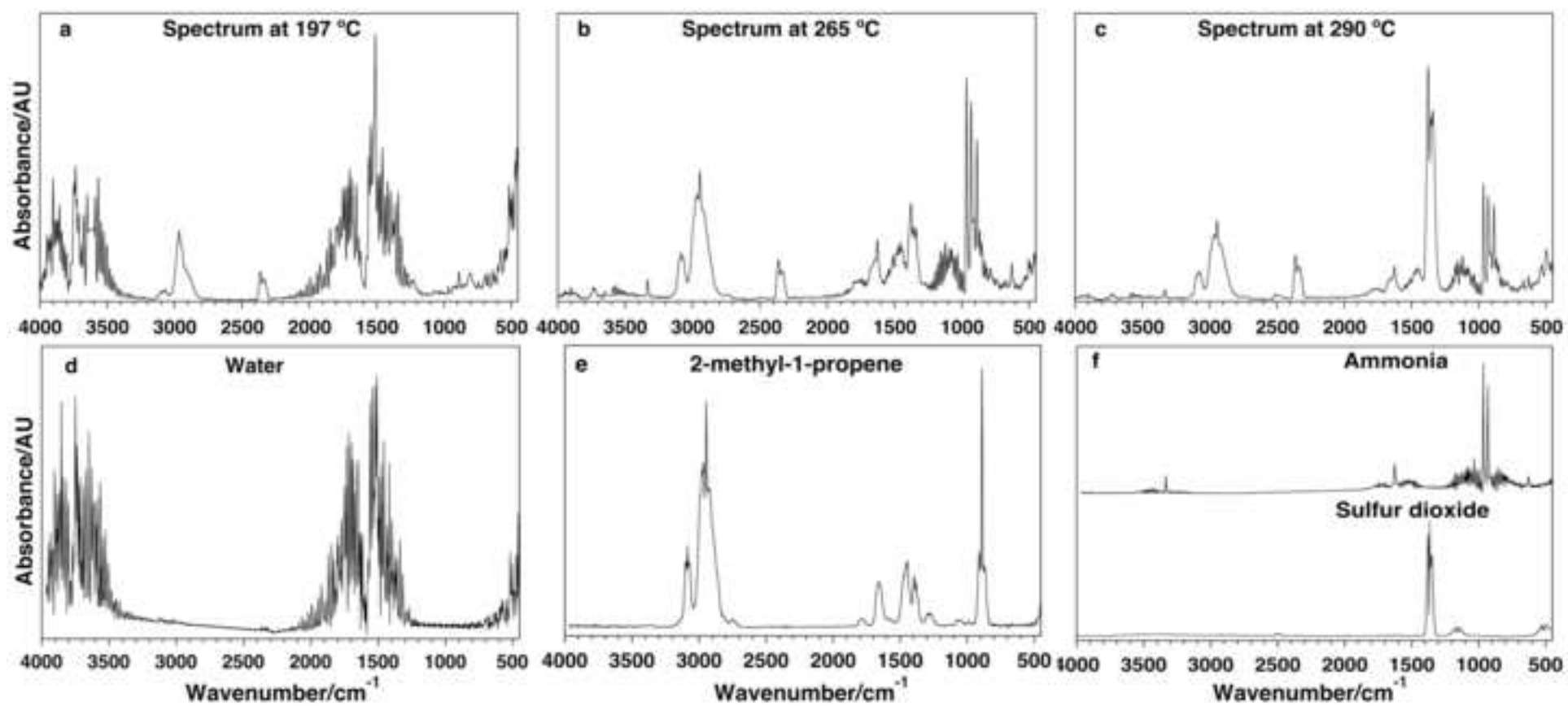
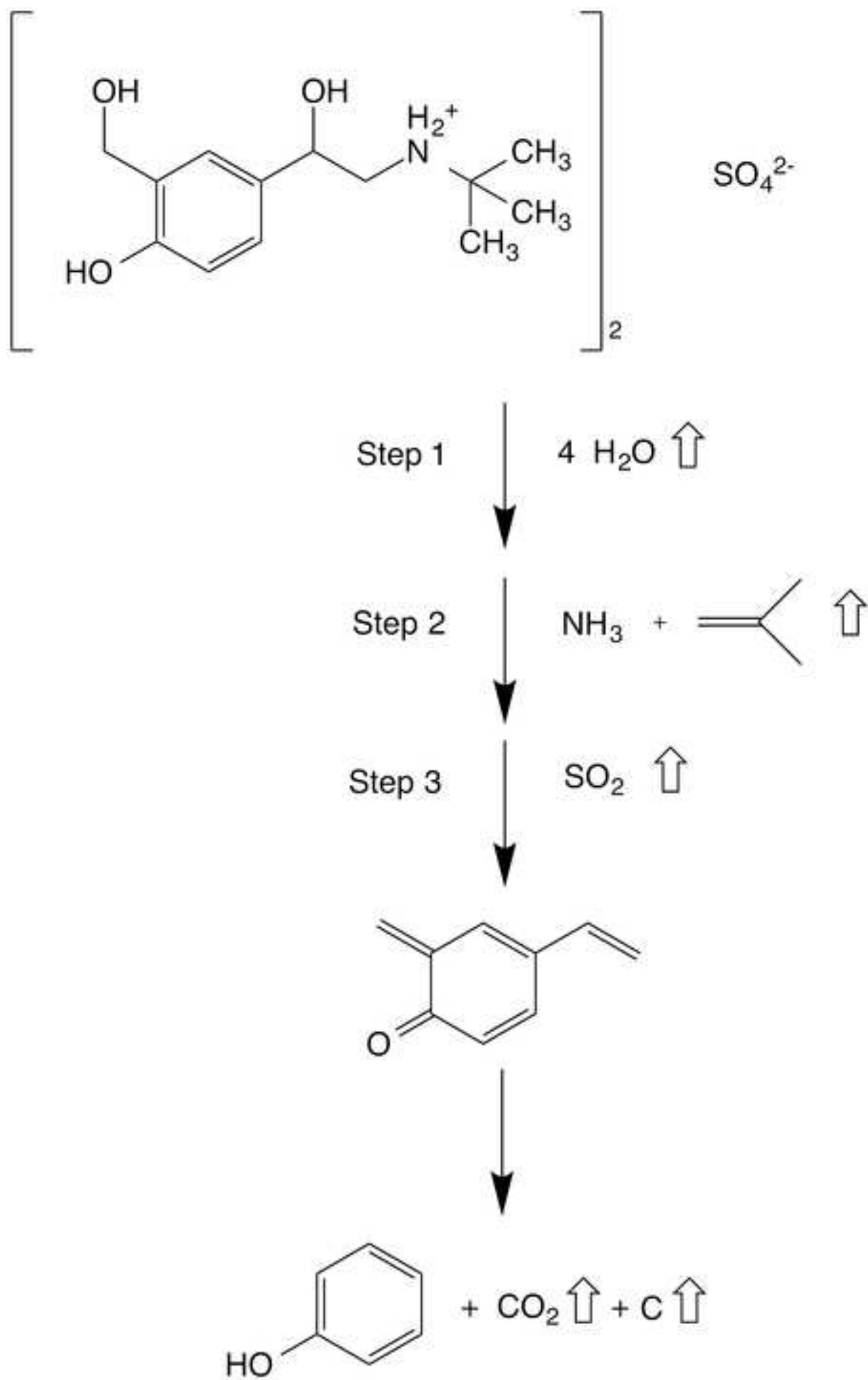


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Name: FABIO SONYICO

Address: GRADUATE SCHOOL OF HEALTH - PHARMACY, 15 BROADWAY, ULTIMO 2007 NSW AUSTRALIA

E-mail address: fabio.sonyico@uts.edu.au

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