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RESEARCH ARTICLE

IDENTIFICATION OF RUPATADINE FUMARATE POLYMORPHIC CRYSTALLINE FORMS IN PHARMACEUTICAL RAW MATERIALS

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ABSTRACT

Polymorphism analysis of pharmaceutical raw materials is considered one of the most relevant evaluations that should be done. As we know, different crystal forms from the same molecule have differences in terms of their physicochemical properties. According to the crystal form used, researchers can obtain benefits for the development of a new product or it can also imply a disadvantage for the formulation of the product. The present study focuses on the identification of crystalline forms in Rupatadine Fumarate raw material samples. The active pharmaceutical ingredient is an antihistaminic, classified as a second-generation selective H1 receptor, which shows advantages in terms of solubility in contrast with the free base and the trichloride form. Analytical techniques employed were: X ray diffraction, differential scanning calorimetry, thermogravimetric analysis, and infrared spectroscopy. The results were analyzed all together and compared with the information found in literature. Based on the results obtained, it was demonstrated that the analyzed drug samples don´t present any other polymorphic form besides A form, which is the only one reported in literature.

INTRODUCTION

Polymorphism in crystalline solids is defined as any material with same chemical composition, but with a different conformations. Diversity of crystalline forms from a pharmaceutical molecule of interest is based on a series of non-covalent interactions, which allow a better control of the chemical stability, dissolution profile, solubility and bioavailability of the API (Rodríguez, 2004). Nevertheless, it is well known that the most thermodynamically stable form of the molecule does not always represent the best option for the development of a new pharmaceutical product. The previous statement justifies the importance of knowing in detail the molecule and the different crystalline forms it may exhibit

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according the conditions under which the production process is carried out (Rodríguez, 2004). Rupatadine fumarate (see Figure 1) is an API, its IUPAC nomenclature is 8-chloro-6, 11-dihydro-11- [1- [(5-methyl-3-pyridyl) methyl] - piperidin-4-ylidene] -5H- benzo [5,6] cyclohepta [1,2-b] pyridine fumarate. [2, 3]

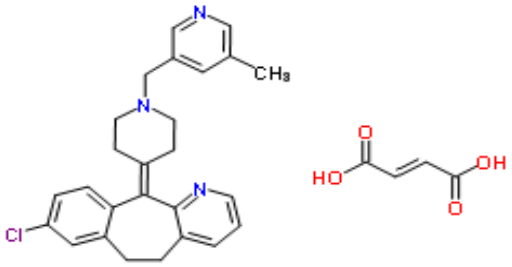

Figure 1. Rupatadine fumarate chemical structure

The compound was first synthesized by a pharmaceutical company named J. Uriach& Cia, S.A in 2003. This API has a dual character, first it is considered a potent antihistaminic classified as second-generation selective H1 receptor, and also represents a platelet activating factor (PAF) antagonist. This pharmaceutical molecule is widely used in the symptomatic treatment of allergic rhinitis and urticaria in adults and children over 12 years of age, with a daily dose of 10 mg (Niu Mingyu, 2014; Shangguan Qing, 2014; Aus, 2009; Katiyar, 2008). The fumarate salt of Rupatadine gives advantages in terms of solubility and security when is compared with the free base form, as it decreases the side effects associated with the API. This molecule has some active metabolites, such as: desloratadine, 3-hydroxidesloratadine, 5-hydroxidesloratadine and 6-hydroxidesloratadine (Katiyar, 2008). Even though, the compound is disclosed in Chinese patent CN 106188008 A, it only mentions the crystalline A form of Rupatadine fumarate. Given the above, it was necessary to study samples of pharmaceutical raw material of this compound for the identification of any other polymorphic forms that haven`t been identified. In order to determine modifications of the solid or crystalline state of the molecule, certain analytic techniques were involved (Niu Mingyu, 2014). The main technique is XDR, because this one determines directly differences in arrangement and conformation of the molecules. Also, TGA with DSC allows the identification of hydrates and solvates (He, 2009). Furthermore, vibrational spectroscopic techniques such as infrared are especially helpful for the characterization of polymorphs, because the patterns of hydrogen bonds vary between functional groups affected by the vibrations, what generates the characteristic signals for each polymorph (Rodríguez, 2004).

MATERIALS AND METHODS

Rupatadine fumarate raw material was produced by Enaltec Laboratories, India, Lot No EL-03/L095/16025 and the samples were provided by a national industry. They were taken randomly and transferred to the test site under controlled conditions of temperature, light and humidity. The conditions and specifications of the equipment used are:

X ray Diffraction

Equipment

- Diffractometer: PANalytical Empyrean.

Conditions

- Temperature: room temperature 25 °C.
- Nickel filter.
- Copper anode source Kα (λ 1, 54 A°).
- Polymethacrylate sample holder.
- Continuous analysis at 0.1° per second in the range of 3° to 40 ° 2θ.
- Gas detector with photodiodes.
- Weight: 10 to 15 mg sample.
- Three replicas.

Differential Scanning Calorimetry

Equipment

- DSC TA Instruments model Q200.

Conditions

- Aluminum capsule.
- 100% Nitrogen Atmosphere 10 psi.
- Flow rate: 40 mL / minute.
- Heating series: isotherm at 20°C for 5 minutes, then increase 10 ° C / minute.
- Temperature range: 20 ° C to 250 ° C.
- Sensitivity Instrument and Recorder: Sensitivity 0.1 uW.
- Temperature precision: ± 0.05 °C.
- Temperature accuracy: ± 1 °C.
- Calorimetric precision: ± 0.1%.
- Calorimetric reproducibility: ± 0.1%.
- Weight: 4 to 5 mg sample.
- Calibration with Indium and distilled water.
- Three replicas.

Thermogravimetric Analysis

Equipment

- TGA TA Instruments model Q500.

Conditions

- 100% Nitrogen 10 psi Atmosphere.
- Volume flow: 40 mL / minute.
- Heating rate: 10 ° C / minute.
- Temperature range: 20 °C to 1000 °C.
- Weight: 4 to 5 mg sample.
- Sensitivity: 0.1 ug.
- Isothermal temperature accuracy: ± 0.1%.
- Isothermal temperature precision ± 0.1%.
- Three replicas.

Infrared Spectroscopy

Equipment

- FTIR Thermo Scientific Nicolet model 6700.

Conditions

- Range: 600 to 4000 cm^{-1}.
- Temperature: 25 °C.

- Relative humidity: 30%.
- 200 scans per replica.
- Three replicas.

RESULTS

The current investigation studies crystalline nature of Rupatadine fumarate pharmaceutical raw material, by making a comparison between the results obtained through different tests applied to the samples, and physicochemical parameters reported on literature and patents. Those results were used to make conclusions about the crystalline or amorphous state of the analyzed samples. Since there´s no pharmaceutical pattern of comparison for the crystalline form, the process of identification must be done according different techniques established in the United States Pharmacopeia (USP 39) for the determination of the physicochemical properties of interest (United States Pharmapoeia Unidos, 2016).

X ray Diffraction

Figure 2 shows the results obtained through the analysis of the samples with X ray diffraction.

Differential Scanning Calorimetry

Figure 3 shows the results of the thermal analysis made to the samples of Rupatadine Fumarate raw material, through differential scanning calorimetry. The thermogram presented in Figure 3 shows an endothermic event at 201,28 ºC which corresponds to the melting point of the substance. Likewise, a decomposition of the sample is visible after the melting, and it is shown as a transition to an exothermic event around 208 ºC. The mentioned melting and decomposition occurs in a narrow range of temperature. There are no other thermal events related with any other decomposition, surface water loss or impurities before the melting point.

Thermogravimetric Analysis

Figure 4 shows the thermogravimetric analysis of Rupatadine Fumarate raw material from Enaltec Laboratories. In order to analyze the results, the thermogram shown in the mentioned figure was divided in three stages: 1) 0 - 150 °C, 2) 150 - 400 °C and 3) 400 - 1000 °C. However, thermal events that take place above 300 °C are not considered relevant for this analysis. There´s no mass decrease in the first stage, which can be interpreted as no loss of surface water, neither as decomposition events in that temperature range.

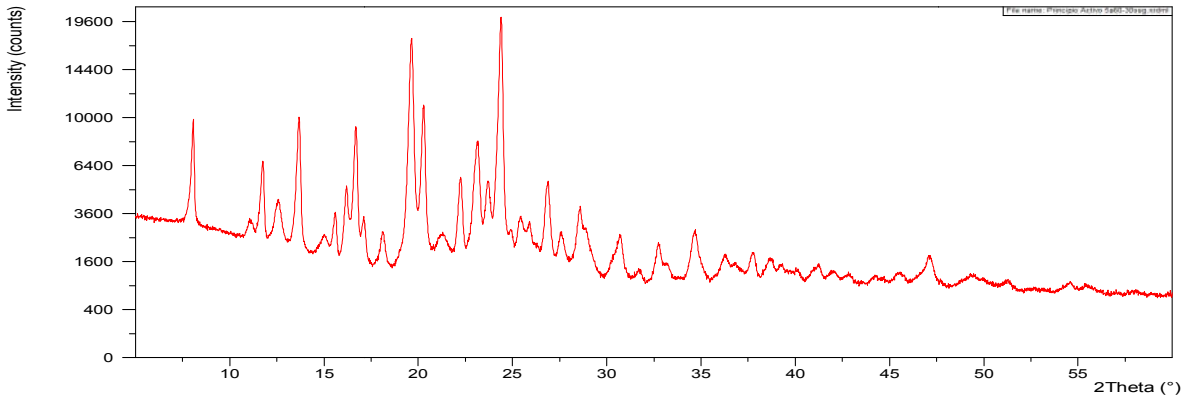

Figure 2. X ray diffractometry for Rupatadine fumarate raw material, Enaltec sample

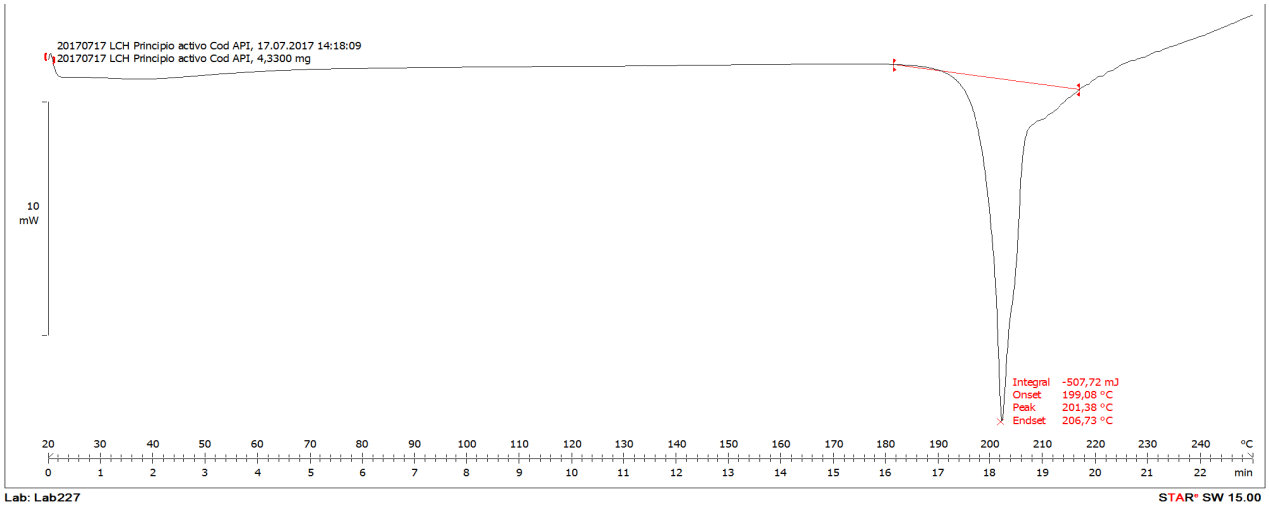

Figure 3. DSC thermogram for Rupatadine fumarate raw material, Enaltec sample

The mentioned figure represents a classic pattern of a crystalline substance. The molecule of interest exhibits two principal peaks, the first one around 20 2θ and the second one is near 25 2θ. Even though, there are four other peaks of lower intensity around 13, 17, 21 and 23 2θ, they are still relevant for the characterization and identification of the crystalline form.

It can also be explained by the lack of hydrates associated with the crystal. This situation is of great interest because the presence of crystallization waters in the samples is usually related to crystalline transitions. The explained behavior of the sample at this stage confirms what is shown by the thermogram of Figure 3. (Billah, 1991 and Madrigal, 2017).

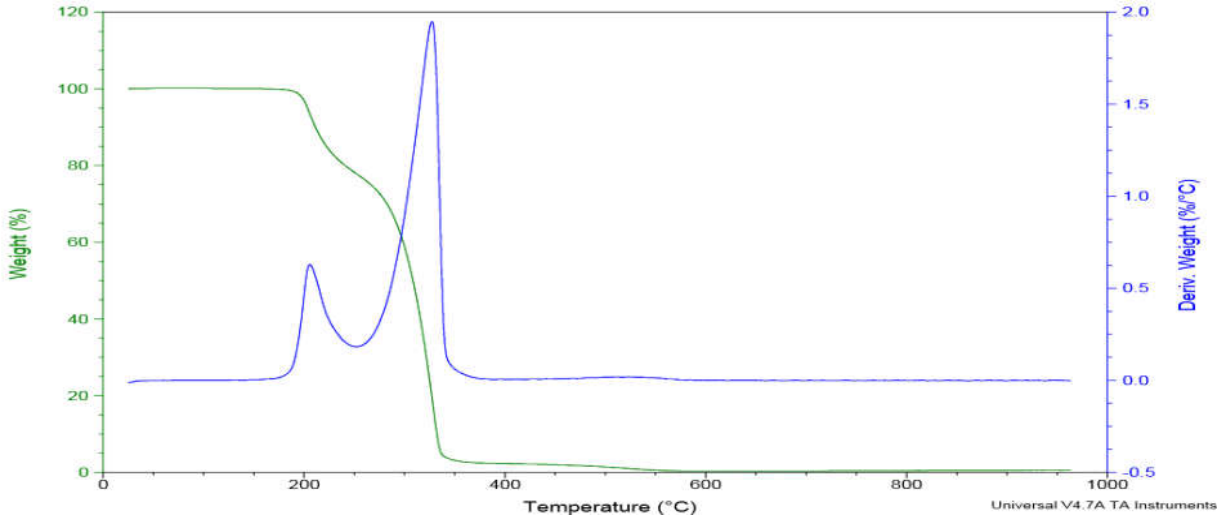

Figure 4. Thermogravimetric analysis for Rupatadine Fumarate raw material, Enaltec sample

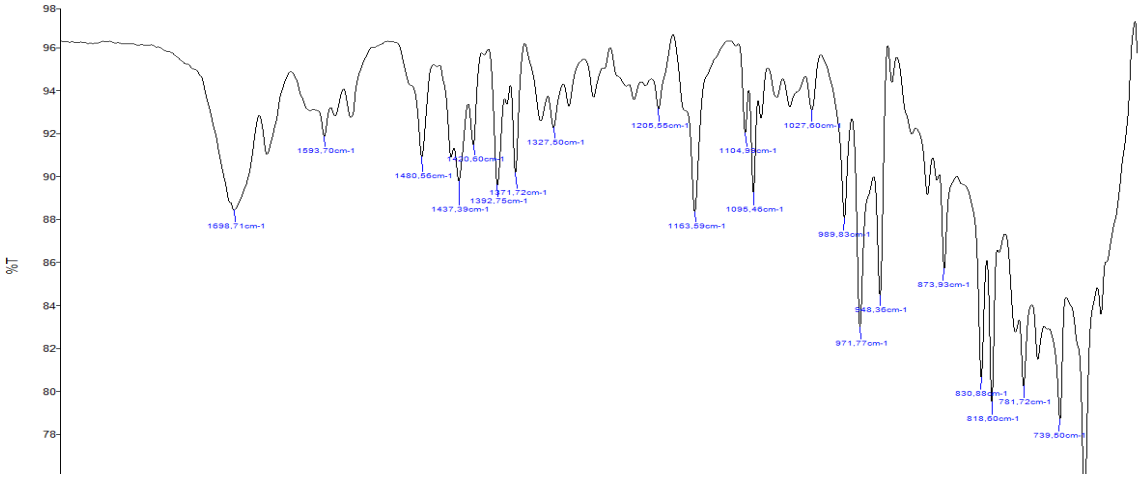

Figure 5. Infrared spectroscopy analysis for Rupatadine Fumarate raw material, Enaltec sample

The analysis of the second stage showed about 20% of mass decrease between 205 °C - 208 °C, which matches with a first decomposition event of the API and it is also in agreement with the decomposition temperature obtained by differential scanning calorimetry analysis of the sample. Then, it is possible to appreciate a second and greater decomposition that takes place around 300 °C and causes the loss of more than 75% of the sample. Finally, there´s a last decomposition event at 350 °C, which basically produces the loss of the remaining mass. It is relevant to say that the test allowed to evaluate and prove the sample´s purity, as there were any decomposition events or mass losses linked with residual solvents or related substances, present in raw material (Fitzpatrick, 2002 and Souza, 2013).

Infrared Spectroscopy

Figure 5 shows the main peaks identified for the API. The wave number at which the absorption bands are presented and the phenomena that occurs are detailed in the table at the end of the article.

DISCUSSION

The results obtained with each one of the executed tests were compared with the state of art found in the cited literature. Therefore, the contrast was done according the following physicochemical parameters: Melting point, X ray diffraction pattern and IR pattern.

XDR

The X ray diffraction analysis of the sample didn´t reveal differences with the established in literature and is in agreement with what is presented in Figure 6. The diffractogram indicates the following characteristic peaks (2θ± 0,2) for Rupatadine Fumarate form A (unique crystalline form reported): 13.6; 17.0; 21.3 and 23.1. However, Figure 6 shows another relevant peaks such as: 11.6; 12.5; 14.9; 15.5; 16.1; 16.6; 18.1; 19.6; 20.2; 22.2; 23.6; 24.3; 24.8; 25.4; 25.8; 26.8; 27.6; 28.5; 28.8; 30.6; 32.7; 33.2; 34.6; 36.2; 36.8 and 37.9 (Mingyu, 2014 and Zhuhai Jin, 2016).

DSC

Literature establishes a melting point for Rupatadine fumarate around 197 - 201 °C. However, experimental reports indicate the beginning of this endothermic event at 194,8°C and its end point at 201,8°C. (Agarwal, 2007 and Carceller, 2017). It is possible to notice in the thermogram of Figure 3, that the melting point obtained through the sample´s analysis (199,08 - 201,38°C) is within the range established in the state of art. (Uriach, 2017).

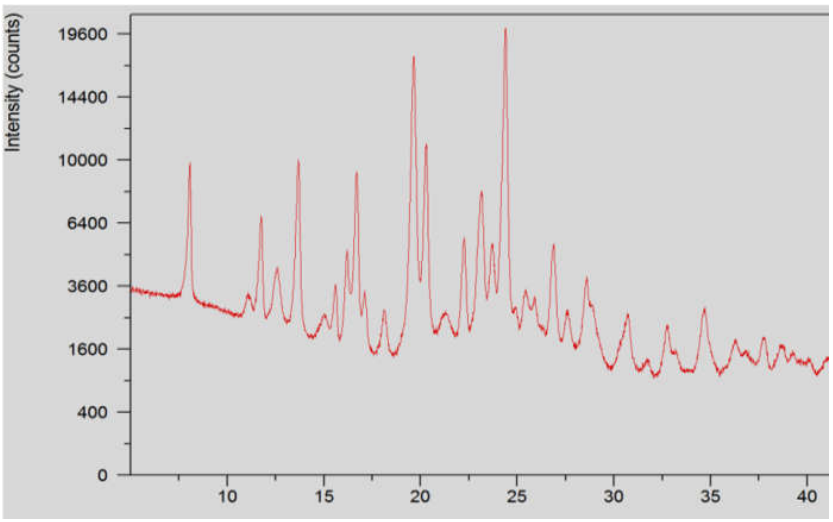

Figure 6. Rupatadine fumarate diffractogram reported in literature (Zhuhai Jin, 2016).

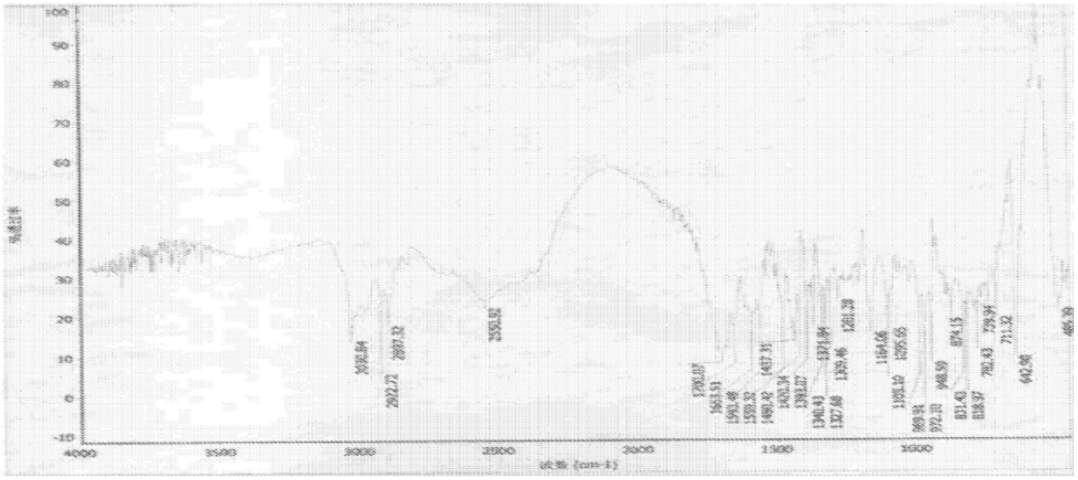

Figure 7. Rupatadine Fumarate infrared spectrogram reported in literature (Niu Mingyu, 2014 and Agarwal, 2007).

TGA

This instrumental technique allows the study of thermal transitions in materials. Whenever a thermal event occurs it manifests itself as a mass change in the sample, as it can be observed in Figure 4. Since it is only possible to attribute mass changes to chemical reactions or water loss, the interpretation of these thermograms can tell us the temperature at which decomposition takes place, but not the melting of the substance (Haines, 1995). Even though there are no studies about thermal analysis of Rupatadine Fumarate by TGA, the realized test confirms the purity of raw material and also a first decomposition event. This was done by comparing the thermal events with the ones presented in the DSC thermogram.

IR

Figure 7 shows the IR spectrogram of API reported in literature. It is possible to distinguish the main peaks or bands from the previous spectrogram: 2922, 2897, 2550, 1700, 1653, 1593, 1559, 1480, 1437, 1420, 1393, 1371, 1340, 1327, 1309, 1281, 1164, 1105, 1095, 989, 972, 948, 874, 831, 818, 782, 739 and 711 cm^{-1}. Both, experimental analysis and literature, exhibit the presence of these peaks in characteristic zones of certain chemical groups present in API´s molecule (Niu Mingyu, 2014 and Agarwal, 2007).

Literature reports the presence of characteristic absorptions related with stretching of C-H bonds of alkanes and aromatic compounds at 2982,02 cm^{-1}. Likewise, peaks near of 1590 cm^{-1} are characteristic of C=C bond stretching from aromatic rings. Absorption bands around 1685 cm^{-1} correspond to the presence of carbonyl groups (C=O) from the fumaric acid (Chavakula, 2013). Although there are some peaks considered characteristic for the substance like the ones close to 1160, 1095 and 971 cm^{-1}, they are unspecific in terms of chemical groups. On the other hand, bands around 839 and 781 cm^{-1} represent stretching and vibration of C-Cl bonds (Agarwal, 2007).

Conclusions

X ray diffraction test showed only the existence of Rupatadine fumarate crystalline form A. That fact is supported by the thermal analysis executed through differential scanning calorimetry, where an endotherm around 201 °C shows the melting point of the mentioned crystalline form, and it is also in agreement with what is established according to literature.
Thermogravimetric assay didn´t present a mass decrease under the first decomposition event of the substance, which suggests the absence of solvents, impurities and crystal/surface water in the sample. Also, this test confirmed the link between the exotherm peak from DSC with the first decomposition event of

the API. Infrared spectroscopy analysis done to pharmaceutical raw material samples, showed characteristic bands of Rupatadine fumarate that are mentioned in literature. According to Figure 1 and in agreement with the experimental results and literature, it can be said that there´s a heterocyclic compound which counts with five rings, three of them aromatic and three with nitrogen as the only heteroatom. Furthermore, one of the aromatic rings presents a bond with a chlorine atom. Also, Figure 1 shows fumaric acid structure, what justifies the appearance of characteristic peaks related with carboxylic acids. Based on the results from the tests performed, the analyzed sample was identified as crystalline Rupatadine fumarate form A, which is also the only one reported in literature. Likewise, no other crystalline forms, neither surface water, residual solvents or impurities were found in the samples.

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