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Sibutramine hydrochloride monohydrate

Thermal behavior, decomposition kinetics and compatibility studies

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Abstract In the present work, the thermal decomposition of sibutramine hydrochloride monohydrate (SBT) (an appetite suppressant agent) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). Solid-state characterization was carried out by diffuse reflectance infrared fourier transform spectroscopy (DRIFT), scanning electron microscopy (SEM) and X-ray powder diffraction (XRPD). Isothermal and non-isothermal methods were employed to determine the kinetic data of decomposition process. From isothermal experiments, activation energy (*E*a) can be obtained from slope of ln t versus $1/T$, and the value obtained was 96.06 and 101.43 kJ mol^{-1} in N_2 and air atmospheres, respectively. For non-isothermal method *E*a can be obtained from plot of logarithms of heating rates, as a function of inverse of temperature, resulting in a value of 96.56 and 98.22 kJ mol^{-1} in N_2 and air atmospheres, respectively. The compatibilities of several commonly used pharmaceutical excipients (microcrystalline cellulose, magnesium stearate, colloidal silicon dioxide, lactose monohydrate) and empty hard-gelatin capsules with SBT were evaluated using DSC. The 1:1 physical mixtures of these excipients with SBT showed physical interaction of the drug with magnesium stearate. On the other hand, DRIFT results did not evidence any chemical modifications.

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Introduction

Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight—at least 300 million of them clinically obese—and is a major contributor to the global burden of chronic disease and disability. Often coexisting in developing countries with under-nutrition, obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups [1, 2].

Sibutramine (SBT) represents a new class of compounds for the treatment of obesity that acts inhibiting the reuptake of serotonin and norepinephrine, thus increasing satiety and adrenergic activity [3]. SBT (Fig. 1) exists as the racemic mixture of the (+) and (−) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N*,*N*-dimethyl-A-(2-methylpropyl)-, hydrochloride monohydrate. It is a white crystalline powder with a solubility of 2.9 mg mL^{-1} in pH 5.2 water and molecular weight of 334.33 Da [3, 4].

Thermal analysis is used in the pharmaceutical industry as a quick and reliable technique for studying and predicting pharmaceutical stability, quality control and for development of new pharmaceuticals [5]. It can be applied successfully to investigate different materials from solids to semi-solids, which have pharmaceutical relevance [6]. The technique is used for determination of purity, stability studies and polymorphism evaluation. Also, kinetic parameters (activation energy, frequency factor and reaction order) can be measured by thermoanalytical methods according to progress of reactions [7–9]. Thermoanalytical techniques are widely applied alone or combined with

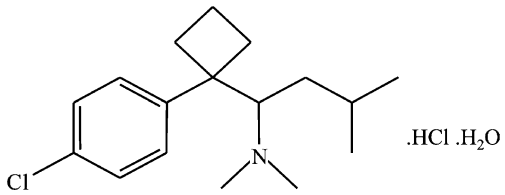

Fig. 1 Chemical structure of sibutramine hydrochloride monohydrate

microscopy, spectroscopy (UV, IR), X-ray powder diffractometry, and mass spectrometry.

The successful formulation of a stable and effective solid dosage form depends also on the careful selection of the excipients [10, 11]. The excipients are considered inert, but incompatibilities (solid-state interactions) with the active pharmaceutical ingredient (API) are commonly possible. The inadequate use of pharmaceutical excipients in solid oral dosage forms can cause serious biopharmaceutical implications, modifying the release mechanism and absorption characteristics as well as the bioavailability [6, 12–15]. Differential scanning calorimetry (DSC) has been increasingly used for quick evaluation of possible incompatibility through comparison of the thermal curves of pure substances with those obtained from a binary mixture (1:1; m/m) [7, 16–19].

The aim of this work was to perform the characterization of SBT using a variety of techniques including thermal analysis (TG/DTG and DSC), diffuse reflectance infrared fourier transform spectroscopy (DRIFT), scanning electron microscopy (SEM), and X-ray powder diffraction (XRPD), and to carry out compatibility studies, to improve the solid-state characterization and, consequently, the quality control of this important active pharmaceutical ingredient.

Materials and methods

Materials

The SBT raw material was kindly donated by Medley S/A Pharmaceutical Industry (Campinas, SP, Brazil). Commercial formulations (generic, reference and similar) were purchased from distinct laboratories within their shelf life period and were designed as I, II and III. The pharmaceutical excipients tested were: microcrystalline cellulose (Blanver, Itapevi, SP, Brazil), magnesium stearate (M. Cassab, São Paulo, SP, Brazil), colloidal silicon dioxide (Galena, Campinas, SP, Brazil), and lactose monohydrate (Galena, Campinas, SP, Brazil). The empty hard-gelatin capsules were also included in the compatibility test.

Methods

Differential scanning calorimetry (DSC)

The DSC curves were obtained on a Shimadzu DSC-60 cell (Kyoto, Japan) using aluminum crucibles with about 2.0 mg of samples. The temperature range was from 30 to 400 °C at a heating rate of 10 °C min^{-1} in dynamic N_2 atmosphere with the flow rate of 50 mL min^{-1}. The DSC equipment was preliminarily calibrated with standard reference of indium (m.p. 156.6 °C; $\Delta H_{fus} = -28.54$ J g^{-1}) and zinc (m.p. 419.5 °C).

The compatibility studies were performed with binary mixtures (1:1; m/m) of SBT and each excipient present in the commercial capsules, as well as the empty capsules and the commercial formulations.

Thermogravimetric (TG) analysis

TG experiments were measured on a Shimadzu thermobalance model TGA-50 (Kyoto, Japan) in the temperature range from 30 to 400 °C, using platinum crucibles with approximately 4 mg of samples, under dynamic N_2 and air atmospheres (50 mL min^{-1}) at a heating rate of 10 °C min^{-1}. The equipment was preliminarily calibrated with standard reference of calcium oxalate. Non-isothermal kinetic investigation of SBT was performed from TG data by application of Ozawa's method [20]. The graph of mass loss versus temperature of five TG curves was obtained at different heating rates (2.5, 5, 10, 15, and 20 °C min^{-1}), under N_2 and air atmospheres. For isothermal method, the temperature was from 140 to 180 °C, with 10 °C temperature increment, in N_2 and air atmospheres. A graphic of ln t versus $1/T$ (K^{-1}) was plotted and linear regression was applied.

X-Ray powder diffraction (XRPD)

For characterization of crystallinity, X-ray diffraction patterns were obtained on a Siemens diffractometer model D 5000, with tube of CuKα, voltage of 40 kV and current of 40 mA, in the range of 3–40 (2θ) with a pass time of 1 s.

Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT)

The DRIFT spectra were measured in a Shimadzu spectrophotometer (Prestige), in a scan range of 400–4,000 cm^{-1} with an average of over 32 scans at a spectral resolution of 4 cm^{-1} in KBr. A background spectrum was obtained for each experimental condition.

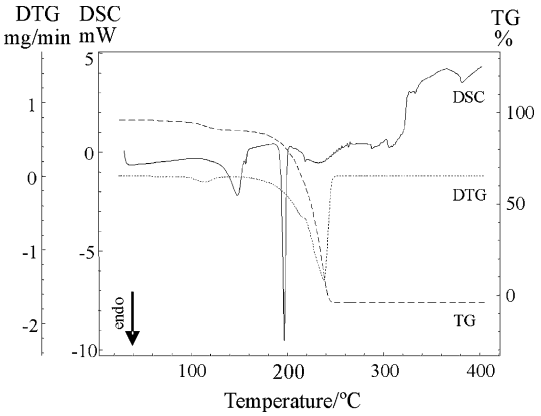

Fig. 2 DSC and TG/DTG curves of SBT in dynamic nitrogen atmosphere (50 mL min^{-1}) and heating rate of 10 °C min^{-1}

Scanning electron microscopy (SEM)

The photomicrographs of SBT were observed in a Phillips scanning electron microscope, model XL30. Samples were mounted onto metal stubs using double-side adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E 5000 and directly analyzed under SEM (50× and 200×).

Results and discussion

DSC curve of SBT (Fig. 2) showed a broad endothermic event (T_{peak}) at 148.09 °C ($\Delta H_{fusion} = -103.01$ J g^{-1}), corresponding to the SBT dehydration process, and a sharp endothermic event (T_{peak}: 196.93 °C; T_{onset}: 193.62 °C; $\Delta H_{fusion} = -91.57$ J g^{-1}) corresponding to melting point. The T_{onset} value is in agreement with the range of 193–195.5 °C cited by the literature [21]. The TG/DTG curves confirmed the water loss ($\Delta m = -5.27\%$, i.e., 17.6 Da) in the range of 112.1–124 °C. The thermal decomposition was defined in two simultaneous and overlapped stages, better visualized in DTG curve, in the following temperature range: 168.2–217.6 °C ($\Delta m = 29.2\%$) and 217.6–251.5 °C ($\Delta m = 64.8\%$).

Non-isothermal kinetic analysis was based on TG experiments performed at five different heating rates: 2.5, 5, 10, 15, and 20 °C min^{-1}, in N_2 and air atmospheres. Therefore, Ozawa's method was applied in order to determine the activation energy (*E*a), Arrheniu's frequency factor (A) and reaction order at the beginning of the thermal decomposition step, at around 165–200 °C. The superposition of the TG curves of SBT is shown in Fig. 3a and c. The TG curves shifted to higher temperatures with increasing heating rates. In N_2 and air atmospheres, the *E*a calculated was 96.56 and 98.22 kJ mol^{-1}, and the Arrheniu's frequency factor was 3.040 and 5.137 × 10^9 min^{-1}, respectively. The order of reaction followed a zero order reaction ($n = 0$) in both N_2 and air atmospheres.

The isothermal TG curves of SBT carried out at 140, 150, 160, 170, and 180 °C are illustrated in Fig. 3b and d. These curves were used to obtain a graphic plot of ln *t* versus the reciprocal of temperature $1/T$ (K^{-1}). The equation obtained from this linear regression method was

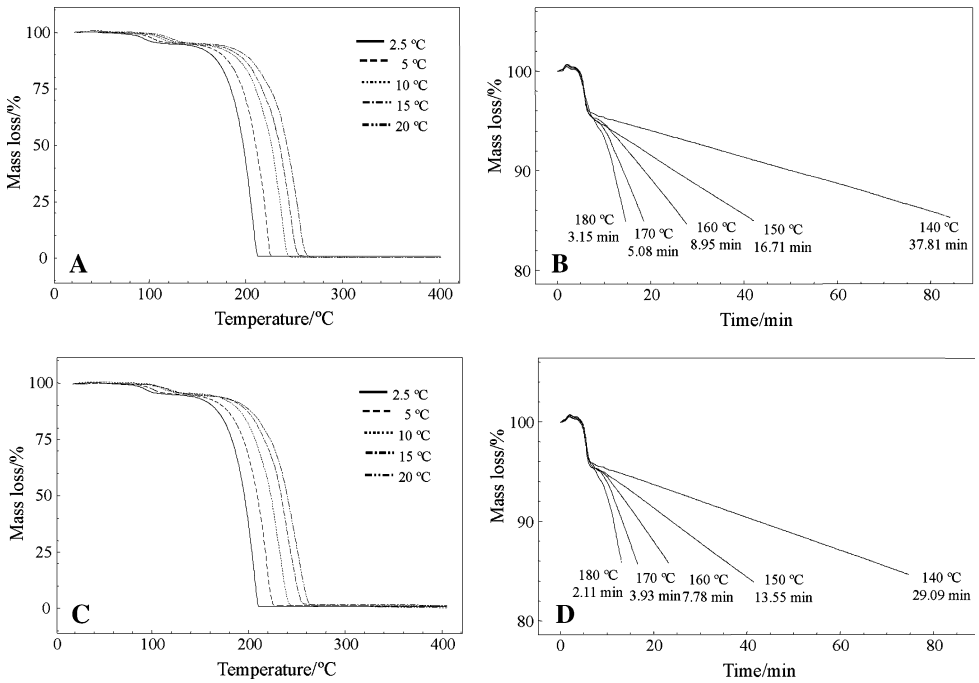

Fig. 3 TG curves obtained for the non-isothermic study of SBT at 2.5, 5, 10, 15, and 20 °C min^{-1} in N_2 (**a**) and air (**c**) atmospheres. Isothermal TG curves of SBT obtained between 140 and 180 °C, with a temperature increment of 10 °C in N_2 (**b**) and air (**d**) atmospheres

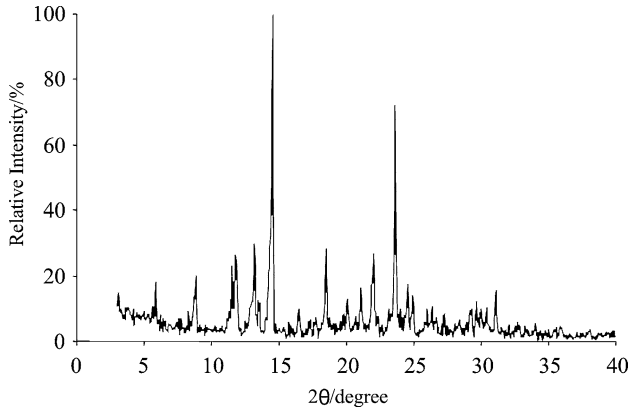

Fig. 4 XRPD spectra of SBT

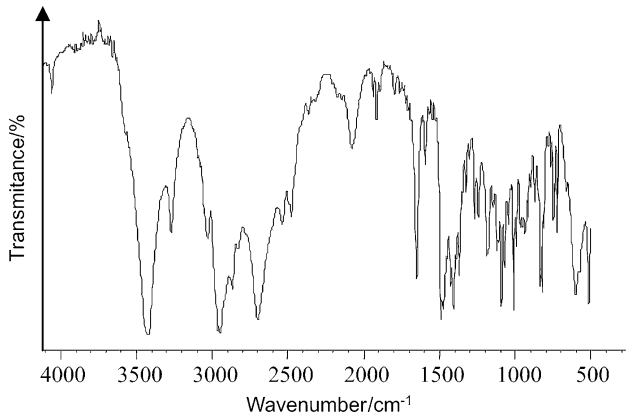

Fig. 5 DRIFT spectra of SBT

$y = -11.554x + 24.429$ ($R = 0.9943$) for N_2 atmosphere and $y = -12.200x + 26.173$ ($R = 0.9984$) for air atmosphere. The activation energy value can be calculated from the product of slope with the molar gas constant ($R = 8.314$), this energy was $Ea = 96.06$ and 101.43 kJ mol^{-1} for N_2 and air atmospheres, respectively. These results are in agreement with the values obtained from the dynamic method.

X-ray powder diffraction studies were performed in order to obtain more information about the crystalline characteristics. The 2θ values of the diffraction peaks (Fig. 4) for SBT were $2\theta = 5.87$, 8.82, 11.78, 13.28, 14.53, 16.48, 18.48, 20.08, 21.08, 22.03, 23.63, 24.53, and 31.13.

The DRIFT spectrum of SBT is showed in Fig. 5, the absorption bands at 3,271 and 1,651 cm^{-1} were attributed to aromatic ring. The bands in the region of 2,962, 1,499 and 1,408 cm^{-1} corresponded to the stretching vibrations of alkane C–C molecules. The absorption band at 2,700 cm^{-1} is assigned to tertiary salt present in SBT chemical structure. The band referent to halogen appears in DRIFT spectrum at 1,188 cm^{-1}.

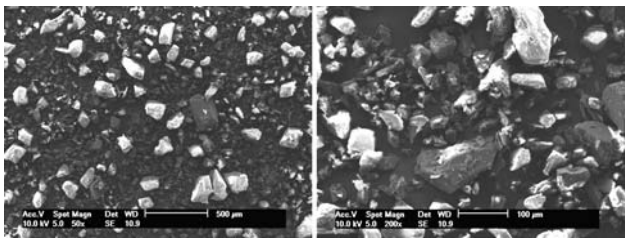

Fig. 6 SEM of SBT at a magnification of 50× and 200×

Based on the photomicrographs obtained from scanning electron microscopy (Fig. 6), the crystal structure and a particle size variation can be visualized.

The selection of adequate excipients for a formulation is based on the characteristics of the drug and its compatibility with other components. Moreover, excipients can influence the dissolution profile affecting the drug bioavailability [22]. The excipients tested were selected based on the product information [4]. The DSC curves (Fig. 7) can be considered as superposition of the curves of pure compounds for most excipients evaluated, indicating that there was no interaction, and therefore no physical-chemical incompatibility. The exception was the binary mixture between SBT and magnesium stearate, in which occurred the displacement of characteristic SBT fusion peak. However, it must be considered that lubricants are generally present in pharmaceutical formulations at very low concentration (0.5–2%), which is very

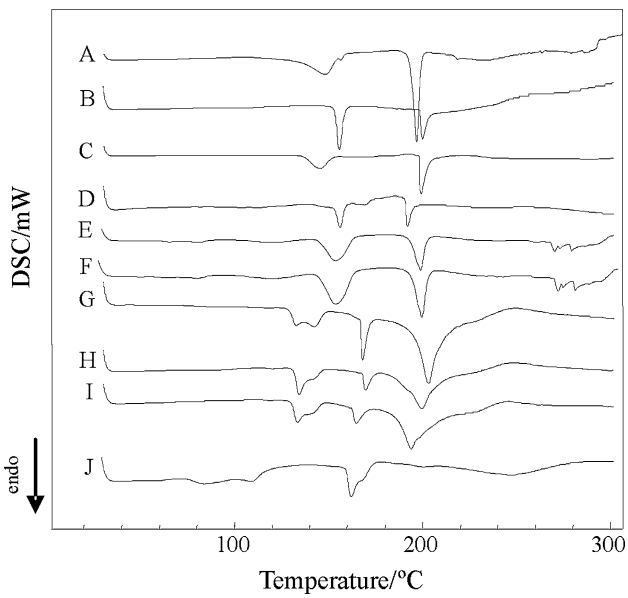

Fig. 7 DSC curves of SBT and excipients mixtures (1:1; m/m). A: pure SBT; B: microcrystalline cellulose; C: lactose monohydrate; D: colloidal silicon dioxide; E: white capsule; F: blue capsule; G: commercial formulation I; H: commercial formulation II; I: commercial formulation III; J: magnesium stearate

different from the examined situation (1:1; m/m). Differences in the thermal curves of other drugs with magnesium stearate were described in the literature suggesting a solid–solid interaction, but not necessarily an incompatibility [7, 23–27]. In fact, the thermal behavior of SBT was maintained in all analyses of the pharmaceutical formulations with magnesium stearate in real proportions (Fig. 7). In order to identify possible chemical interactions between SBT and magnesium stearate, these compounds and the binary mixture were analyzed by DRIFT. The obtained spectrum was the superposition of the spectrum of the individual compounds and no additional band was observed (Fig. 8).

The obtained data for compatibility studies are demonstrated in Table 1. In these mixtures, it could be observed some broadening of endothermic events leading to changes in the onset and peak temperatures, which occur simply due to physical mixing of the components without indicating any significant interaction. However, a displacement of the SBT T_{onset} (157.14 °C) was observed for the binary mixture of SBT and magnesium stearate (1:1; m/m).

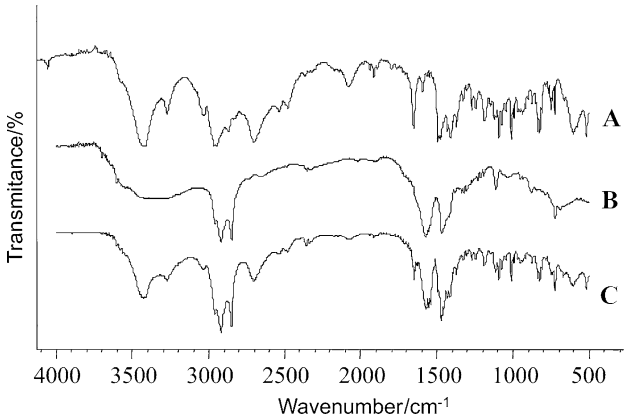

Fig. 8 DRIFT spectra of: A: SBT; B: magnesium stearate; C: binary mixture (1:1; m/m)

Table 1 Onset and peak temperatures of fusion events observed in the DSC curves of SBT and binary mixtures (1:1; m/m)

Samples	T_{onset} (fusion/°C)	T_{peak} (fusion/°C)	Entalphy (fusion) J/g
Drug			
Sibutramine	193.62	196.93	91.57
Drug/excipient			
Microcrystalline cellulose	197.02	201.13	39.91
Colloidal silicon dioxide	190.54	192.87	34.20
Magnesium stearate	157.14	159.94	84.92
Lactose monohydrate	198.09	199.33	43.28
Drug/capsules			
White	191.75	197.20	85.23
Blue	194.00	197.29	87.07
Formulations			
I	196.71	203.22	181.47
II	188.86	194.08	121.51
III	191.48	199.94	147.51

Conclusions

The thermal behavior and the solid-state characterization of sibutramine were carried out by means of DSC, TG/DTG, DRIFT, SEM, and XRPD. The obtained isothermal and non-isothermal kinetic parameters can be used as reference values for the routine quality control of SBT. The results demonstrated the applicability of DSC as a fast screening tool for selection of adequate excipients at the early stages of pre-formulation studies. No interaction was observed for SBT in the commercial pharmaceutical formulations, showing that the physical interaction of SBT with magnesium stearate did not compromise the quality of the final product.

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