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THERMAL BEHAVIOR STUDY AND DECOMPOSITION KINETICS OF SALBUTAMOL UNDER ISOTHERMAL AND NON-ISOTHERMAL CONDITIONS

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The thermal decomposition of salbutamol (β_2 – selective adrenoreceptor) was studied using differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG). It was observed that the commercial sample showed a different thermal profile than the standard sample caused by the presence of excipients. These compounds increase the thermal stability of the drug. Moreover, higher activation energy was calculated for the pharmaceutical sample, which was estimated by isothermal and non-isothermal methods for the first stage of the thermal decomposition process. For isothermal experiments the average values were E_{act}=130 kJ mol^{-1} (for standard sample) and E_{act}=252 kJ mol^{-1} (for pharmaceutical sample) in a dynamic nitrogen atmosphere (50 mL min^{-1}). For non-isothermal method, activation energy was obtained from the plot of log heating rates *vs.* $1/T$ in dynamic air atmosphere (50 mL min^{-1}). The calculated values were E_{act}=134 kJ mol^{-1} (for standard sample) and E_{act}=139 kJ mol^{-1} (for pharmaceutical sample).

Keywords: *activation energy, DSC, kinetic method, salbutamol, TG, thermal behavior*

Introduction

Salbutamol (it is also known as albuterol, 1-(4-hydroxy-3-hydroxyphenyl)2-*tert*-butylaminoethanol) is a β_2-adrenoceptor agonist and currently one of the most frequently prescribed bronchodilators for treatment of bronchial asthma [1, 2]. It is normally used in sulfate form. β_2-adrenoceptor has been illegally used as doping agent in animal feed to increase the meat production. Due to its anabolic effect the International Olympic Committee (IOC) included β_2-adrenoceptor as a banned drug in sport lists [3, 4].

To monitor its therapeutic use as well as to control the illegal use of β_2-adrenoceptor several methods the identification of this drug in pharmaceutical formulations and in biological samples have been reported. These include chromatography, spectrophotometry, capillary electrophoresis (CE), amperometry coupled to batch injection analysis (BIA) [1, 2, 4–6]. On the other hand, several studies have been done to enhance the efficiency of delivery of salbutamol particles in human organism. For example, the effect of the properties of carriers that are usually the main component of dry powder inhalers (DPI) formulations; particle size distribution; morphology; surface roughness and electrostatic charge and study of the inclusion complex of salbutamol with native cyclodextrins (CDs) [7–12] has been studied. CD, due to its hydrophobic character that may help to avoid incompatibility troubles with other drugs or excipients in their preformulations, reduce the local irritance or haemolysis of a drug as well as cavity which provides a protection. In these studies several methods were used such as differential scanning calorimetry (DSC), thermogravimetry (TG), nuclear magnetic resonance, X-ray diffraction, scanning electron microscopy, infrared and mass spectroscopy.

Thermal decomposition of solid samples as well as effective activation energy can be determined from TG experiments (isothermal method). Therefore, in these experiments only the heating rate was measured (β). It is valid only for an ideal system because there are no changes in reaction process as a function of heating rate [13].

The Arrhenius plot of ln$k$ *vs.* $1/T$ (where k is the rate constant and T is temperature in Kelvin) should give a straight line. The kinetic parameters such as activation energy (E_{act}, J mol^{-1}) and pre-exponential factor (A, s^{-1}) are obtained from the slope $-E_a/R$ (where R is the gas constant, 8.314 J mol^{-1} K^{-1}) and intercept ln$A$, respectively [14, 15].

Wall, Ozawa and Flynn proposed another method to obtain the activation energy by linear heating rate (isoconversional method). This non-isothermal method employs TG/DSC curves as well as Arrhenius equation. Moreover, for different heating rates (β) with a constant degree of conversion (α) a linear relationship is observed between logβ and $1/T$. Arrhenius kinetic parameters (E_{act}, A) relative to thermal decomposition of salbutamol are determined

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by the Ozawa method (Shimadzu software) from the temperature (K) and heating rate data [16–18].

In our work, thermal analysis (TG and DSC) and Ozawa dynamic method as well as isothermal method were used to determine kinetic parameters and thermal decomposition of salbutamol.

Experimental

Standard sample of salbutamol (2-(hydroxymethyl)-4-[1-hydroxy-2-(*tert*-butylamino)ethyl]phenol) was obtained from Boehringer Ingelheim of Brasil, lot No. 292180. Pharmaceutical product was purchased in a local drugstore. This latter sample contains lactose (Henrifarma, lot No. 870), magnesium stearate (Iquego, lot No. 17199/001) and corn starch (LAFEPE, lot No. 003). The mixed samples consisted of equal masses of salbutamol and each excipient was weighed individually into amber glass flasks to originate mass of 20 g of mixture. Physical mixtures were prepared in proportion (m/m) 1:1 (salbutamol:excipient) by simple mixing.

TG/DTG curves were performed in a TGA-50 Shimadzu instrument under dynamic N_2 atmosphere (50 mL min^{-1}) at a heating rate of 10°C min^{-1}. The sample masses both for pharmaceutical product and standard sample were about 4.5 mg and were weighed to Pt crucibles. DSC measurements were performed in a dynamic nitrogen atmosphere (50 mL min^{-1}) at heating rate of 10°C min^{-1} using a DSC-50 Shimadzu cell. Either for standard sample or pharmaceutical product approximately 1.7 mg sample masses in Al crucibles were used. DSC cell was calibrated with indium (m_p=156.6°C, ΔH_{fus}= 28.54 J g^{-1}) and zinc (m_p=419.6°C). These conditions were used for initial thermal decomposition study in the 25–600°C temperature range.

TG/DTG curves were obtained in the same Shimadzu instruments between 150–180 and 180–200°C for standard sample and pharmaceutical product, respectively. The applied heating rates are summarized in Table 1 under dynamic air atmosphere (50 mL min^{-1}). These conditions were employed for isothermal degradation method.

Ozawa dynamic method was applied using TG kinetic analysis program installed in Shimadzu data acquisition system. Six different heating rates were used: 2.0, 5.0, 7.5, 10, 15 and 20°C min^{-1} under dynamic air atmosphere (50 mL min^{-1}).

Results and discussion

Thermal behavior and kinetic study of salbutamol

Figure 1 presents TG/DTG and DSC curves of standard salbutamol sample in the temperature range of 25–600°C at a heating rate of 10°C min^{-1}. DSC curve shows a sharp endothermic peak at 201°C with ΔH=212 J g^{-1} enthalpy change that corresponds to melting followed by the thermal decomposition of the sample. TG/DTG curves indicate that standard sample is thermally stable up to 180°C. Between 180 and 600°C successive mass losses Δm_1=18%, DTG_{peak}=204°C (thermal decomposition beginning); Δm_2=3.7%, DTG_{peak}=299°C (corresponding to thermal decomposition with carbonization of sample) and Δm_3=10.7%, DTG_{peak}=580°C, due to elimination of carbonization product were observed.

Figure 2 shows the TG/DTG and DSC curves of the commercial pharmaceutical product using the same experimental conditions in relation to standard sample with a different thermal profile caused by presence of excipients. DSC curve shows two endothermic events (T_{peak}=53 and 133°C), which are due to dehydration of magnesium stearate. The third

Table 1 Data (β and $T_{isothermal}$) used in isothermal kinetic calculations for standard and commercial pharmaceutical product of salbutamol

Sample	β/ °C min^{-1}	$T_{isothermal}$/ °C	*t*/min for Δm=5%
Standard	20	($T_{isothermal}$–10)	–
	5	$T_{isothermal}$: 150	202
		170	90
		180	38
		185	26
		190	18
Pharmaceutical product	20	($T_{isothermal}$–10)	
	5	$T_{isothermal}$: 180	315
		185	158
		190	73
		195	36
		200	19

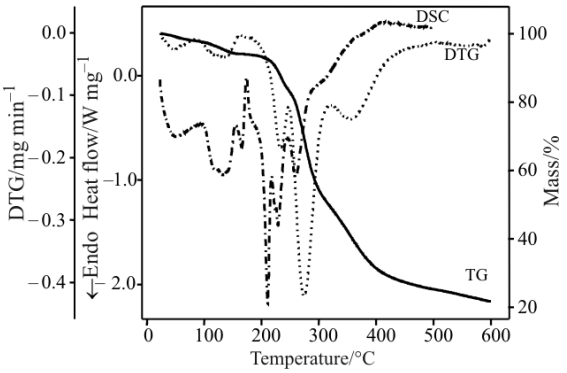

Fig. 1 DSC and TG/DTG curves of salbutamol standard sample

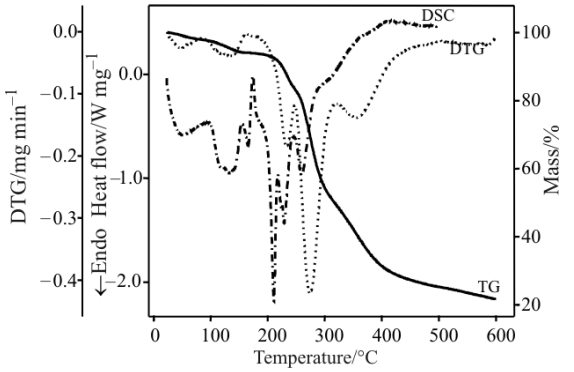

Fig. 2 DSC and TG/DTG curves of commercial pharmaceutical product

endothermic event, T_{peak}=165°C corresponds to lactose dehydration. The exothermic event observed at T_{peak}=174°C is due to the structural transformation of anhydrous lactose (α→β) [13]. Other endothermic events occur from T_{onset}=196°C (T_{peak}=211°C) which corresponds to the melting of lactose which stabilizes the salbutamol. TG/DTG curves indicate that thermal decomposition of the commercial pharmaceutical product takes place in different temperature ranges causing the respective mass losses: Δm_1=3.3% (DTG_{peak}=46°C), Δm_2=4.0% (DTG_{peak}=139°C) corresponding to hydration water, Δm_3=8.9% (DTG_{peak}=234°C), Δm_4=31.3% (DTG_{peak}=276°C) and Δm_5=27.4% (DTG_{peak}=358°C). After polymorphic transition melting followed by the thermal decomposition of sample with carbonization takes place.

Isothermal TG curves for salbutamol standard were recorded at 150, 160, 170, 175 and 180°C (Fig. 3a). Table 1 presents the necessary times for 5% of thermal decomposition. These curves were used to obtain the ln*t vs.* 1/*T* (K^{-1}) plot for salbutamol standard sample (Fig. 4). From linear regression method ln*t*=15601.6 (1/*T*)–31.6 and R^2=0.99975 were obtained. For activation energy (E_{act}) from product of 15601.6 (angular coefficient) with molar gas constant (R=8.314 J mol^{-1} K^{-1}) E_{act}=130 kJ mol^{-1} was calculated.

The isothermal TG curves for commercial salbutamol pharmaceutical product sample were recorded at 180, 185, 190, 195 and 200°C (Fig. 3b). From these curves, ln*t vs.* 1/*T* (K^{-1}) plot was constructed (Fig. 4). 5% mass loss after dehydration steps was taken into account. The necessary times for 5% of sample thermal decomposition are summarized in Table 1. The equation used for the calculation was ln*t*=30265.8 (1/*T*)–61.0 with R^2=0.99959 resulted E_{act}=252 kJ mol^{-1} of activation energy.

Figures 5 and 6 show the TG curves of salbutamol standard sample and the pharmaceutical product recorded at different heating rates, respectively. In these experiments, TG curves are shifted to higher temperatures when the heating rates were increased.

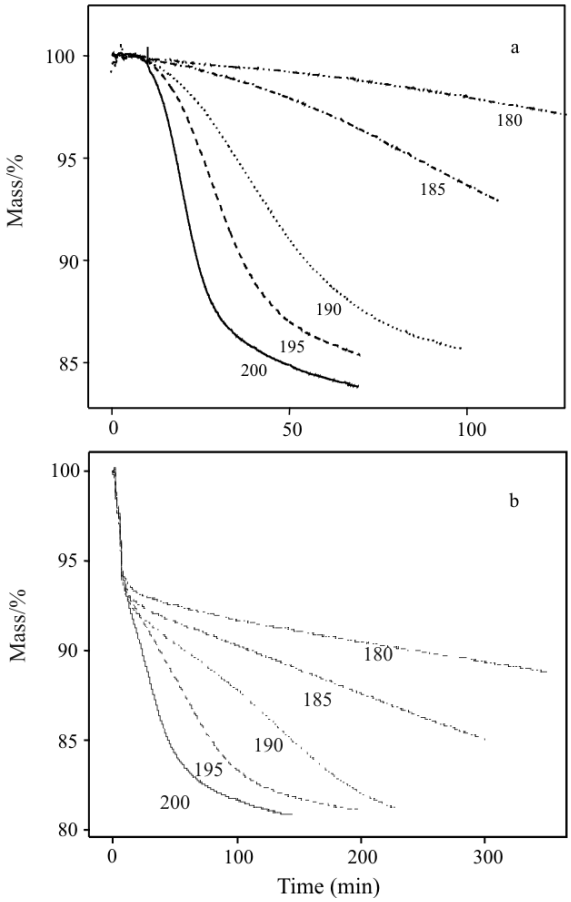

Fig. 3 a – isothermal TG curves salbutamol standard at 150, 160, 170, 175 and 180°C, b – isothermal TG curves of commercial pharmaceutical product at 180, 185, 190, 195 and 200°C

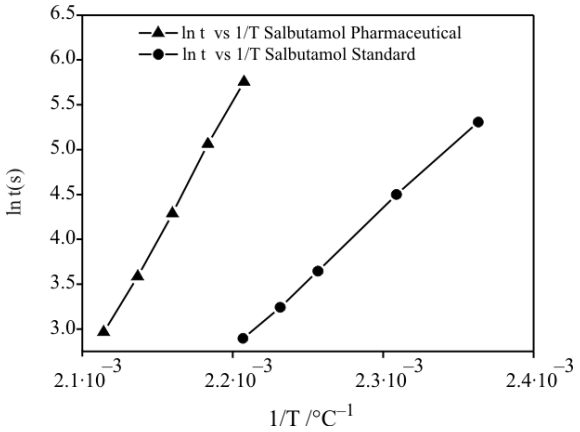

Fig. 4 ln*t vs.* 1/*T* plot of salbutamol standard and commercial pharmaceutical product obtained using Arrhenius equation

In order to determine the activation energy (E_{act}) at the beginning of the main thermal decomposition step from 165 to 189°C (standard sample) and 193 to 203°C (commercial pharmaceutical product), Ozawa's method was applied The calculated plots

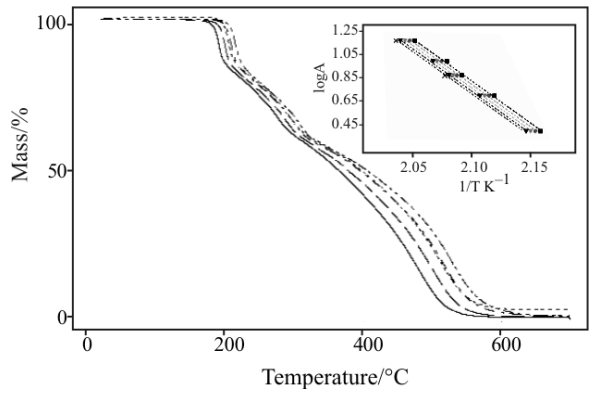

Fig. 5 TG curves of salbutamol standard at 2.5, 5.0, 7.5, 10, 15 and 20°C min^{-1} (insert shows Ozawa´s plot)

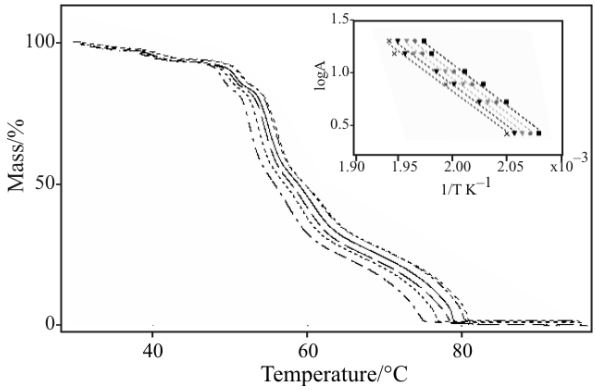

Fig. 6 TG curves of commercial pharmaceutical product obtained at 2.5, 5.0, 7.5, 10, 15 and 20°C min^{-1} (insert shows Ozawa´s plot)

were inserted into figures presented demonstrating a fairly good correlation at five heating rates. For this first stage of thermal decomposition the calculated E_{act} was 134 and 139 kJ mol^{-1} for standard and pharmaceutical samples in air atmosphere, respectively. The E_{act} values found through non-isothermal Ozawa method are in good agreement to the results of isothermal kinetic analysis.

Conclusions

The study of thermal behavior of the two salbutamol samples evidenced that the presence of excipients increase the thermal stability of this drug. It was confirmed through the kinetic study that indicated a lower value of activation energy for the standard sample. The activation energy values obtained by using isothermal and non-isothermal approaches can be used in the preformulation and production steps for quality control of medicines. Finally, kinetic study can be a fast alternative or a complementary method to estimate the self-life of medicines.

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