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Thermoanalytical Study of Atenolol and Commercial Tablets

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SUMMARY. A thermoanalyical study of pure atenolol and a commercial tablets containinf the drug were carried out using thermogravimetric (TG) and differencial scanning calorimetry (DSC) techniques. Non-isothermal method was employed to determine kinetics data of decomposition process. In order to evaluate interaction observed in the commercial tablets, compatibility studies of drug and excipients (microcrystalline cellulose, sodium starch glycolate, magnesium stearate, mannitol and silicon dioxide) were performed. The binary drug-excipient mixture (1:1) suggest a physical interaction of the drug with mannitol. The DSC provides a rapid, safe and accurate method for purity determination of atenolol.

RESUMEN. "Estudio Termoanalítico del Atenolol y de Comprimidos Comerciales". Se realizó el estudio termoanalítico del atenolol puro y de comprimidos comerciales utilizando técnicas de termogravimetría (TG) y calorimetría diferencial de barrido (DSC). El método no isotérmico fue empleado para determinar los datos cinéticos del proceso de descomposición. Para evaluar la interacción observada en los comprimidos comerciales, se realizó un estudio de compatibilidad entre la droga y los excipientes (celulosa microcristalisada, glicolato de amidón sódico, estearato de magnesio, manitol y dióxido de silicio). La mezcla binaria de la droga-excipiente (1:1) sugiere una interacción física entre la droga y el manitol. El DSC provee un método rápido, seguro y preciso para la determinación de la pureza del atenolol.

INTRODUCTION

The β-blockers are an antihypertensives category of drugs that have been shown to reduce morbidity and mortality in patients with hypertension [1]. Atenolol is the frequently used, β_1-seletive-antagonist drug in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infaction and the prophylactic treatment of migraine [2,3]. Chemically, atenolol is a phenylacetamide [(4-2'-hydroxy-3'-isopropylaminopropoxy) phenilacetamide] [2]. It is a white powder with a melting point between 152 °C and 156,5 °C [4].

Many drugs intended for oral administration, and the mostly used are solid dosage forms such as tablet, capsules and powders. For rational dosage form development, it is essential to characterize the physical chemical properties as well as to assess its compatibility with excipients during processing and storage, in order to develop stable, safe and effective final drug product [5-9].

Thermoanalysis has been used for the rapid evaluation of purity, kinetics decomposition and physical property of drugs [10,11]. Moreover, this technique was provided an alert for compatibility problems and it was indicated the most favorable directions to pursue for a successful formulation [12-14]. The most widely used thermoanalytical techniques are differential scanning calorimetry (DSC) and thermogravimetry/derivate thermogravimetry (TG/DTG) in which a physical property of a substance and/or its reaction product is measured as a function of a controlled temperature program [15,16].

Few studies with this drug has been published used these techniques. Pyramides *et al.* [17] studied the combined use of DSC and TG for

KEY WORDS: atenolol, Compatibility study, DSC, Kinetic analysis, TG.
PALABRAS CLAVE: Análisis cinético, atenolol, DSC, Estudio de compatibilidad, TG.

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the thermoanalysis of atenolol tablets (100 mg), analyzing the finished dosage forms and their components. Marini *et al.* [18] studied the atenolol - excipient compatibility by physical-chemical techniques, suggesting a modification only the thermal response of the drug in the magnesium stearate-rich mixtures and strong interaction between polyvinylpyrrolidone - atenolol. The results of Abou-Sekkina *et al.* [19] studies indicated a high resistence of atenolol against gamma-irradiations. Based on published data there is few evidence of incompatibility with a single concentration of atenolol and excipients in commercial formulations.

The aim of this work was to characterize the physical chemical properties of atenolol as well to investigate a possible interaction drug-excipient in a 50 mg commercial tablet market in Brazil.

MATERIALS AND METHODS

Materials

The pure atenolol was kindly provided by Purifarma. A 50 mg atenolol tablet (Atenorm®, Cifarma), containing microcrystalline cellulose, sodium starch glycolate, mannitol, magnesium stearate and colloidal silicon dioxide, was purchased in local pharmacy.

The excipients used in the compatibility study were microcrystalline cellulose (Avicel® Ph-102), sodium starch glycolate (JRS), magnesium stearate (Mallinckrodt), mannitol (Merck) and colloidal silicon dioxide (Aerosil®, Galena).

Thermogravimetric and Differencial Scanning Calorimetry Analysis

The TG/DTG measurement was performed on thermobalance TGA-50 (Shimadzu), under dynamic nitrogen atmosphere with the flow rate of 50 mL/min. Approximately 5 mg of sample was placed in platinum pan and heated from 25 °C to 900 °C in heating rate of 10 °C/min.

The DSC measurement was performed in DSC-60 cell (Shimadzu), under dynamic nitrogen atmosphere with the flow rate of 50 mL/min. Approximately 2 mg of sample was weight out and placed in a sealed aluminum pan. The analysis was scanned from 25 °C up to 500 °C with heating rate of 10 °C/min.

The study of a 50 mg atenolol tablet was analyzed at the same conditions mentioned above. In addition, a compatibility study was performed with a simple mixture of atenolol-excipient in weight ratio of 1:1.

Determination of Purity

The purity determination was determined by DSC [20] and compared with potentiometric titration [21]. The DSC analysis was performed using approximately 2 mg of sample, heated at 2 °C/min in the temperature range from 25 °C to 180 °C, under nitrogen atmosphere with flow rate of 50 mL/min. The analysis was carried out with triplicate [11].

Nonisothermal Kinetic Study

The non-isothermal kinetic study of atenolol was evaluated by thermogravimetric analysis. Approximately 5 mg of atenolol raw material placed in platinum pan and heated at 2.5, 5, 10, 15, 20 °C/min within the temperature range of 25-900 °C under dynamic nitrogen atmosphere with the flow rate of 50 mL/min. The kinetics parameters were determined through Ozawa's method using Shimadzu TASYS software [22].

RESULTS AND DISCUSSION

Thermogravimetric and Differencial Scanning Calorimetry Analysis

The TG/DTG and DSC curves of the atenolol are seen in Fig. 1. The DSC curve exhibit a single sharp endothermic peak from 152 to 157 °C corresponding to atenolol's melting event T_{peak} = 155.04 °C and ΔH_{fusion} = - 126.42 J/g. In addition the decomposition event starts at 200 °C. The DSC data corroborate with TG data, which was evidenced a thermal stability up to 200 °C with a small mass loss (Δm = 0.56 %) corresponding to volatile material. This is confirmed by infrared drying (Δm = 0.6 %), using an OHAUS balance model MB45.

The thermal decomposition process of atenolol occurs in three stages in the following temperature range and mass loss: 201-333 °C (Δm = 28 %), 333-507 °C (Δm = 46.6 %) and 507-900 °C (Δm = 12.7 %).

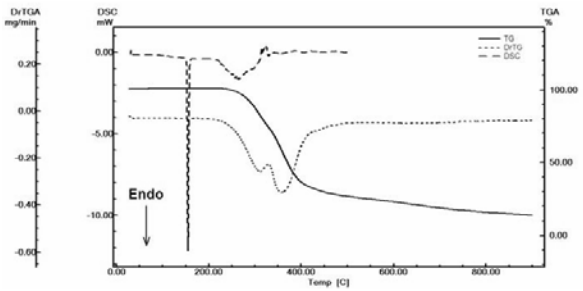

Figure 1. TG/DTG and DSC curve of pure atenolol at 10 °C/min in dynamic nitrogen atmosphere.

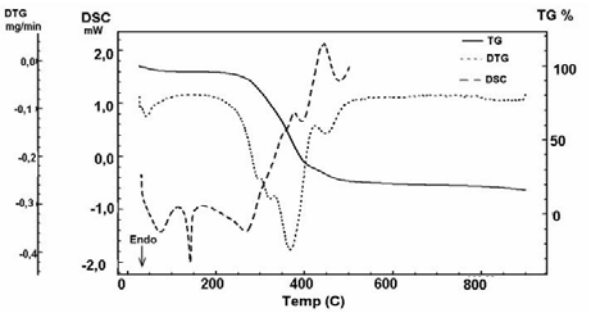

Figure 2. TG/DTG and DSC curve of commercial tablet at 10 °C/min in dynamic nitrogen atmosphere.

The TG/DTG and DSC curves of the 50 mg atenolol tablet are seen in Fig. 2. The DSC curve showed a broad endothermic event (30-105 °C) before the melting peak which refers to the loss of volatile material, demonstrated in the TG curve (Δm = 3.86 %) and confirmed by infrared drying (Δm = 3.98 %), using an OHAUS balance model MB45.

The thermal decomposition process of commercial tablet occurs in four steps in the following temperature range and mass loss: 180-303 °C (Δm = 14.04 %), 303-335 °C (Δm = 11.9%), 355 - 422 °C (Δm = 38.7%) and 422-900 °C (Δm = 14.3%). The DSC curve showed the presence of drug fusion event in temperature range of 133-147 °C (T_{peak} = 141.75 °C and ΔH_{fusion} = -35.69 J/g). Therefore it was observed that the fusion event occurs at temperatures about 13 °C less than pure atenolol, suggesting an interaction, but not necessary corresponding to incompatibility. In this case, this could be associated with a possible lowering of the activation energy in the mixture.

In order to evaluate the commercial tablets interaction with excipient, a compatibility study was performed. The DSC and TG curves of the pure atenolol and the drug-excipient (1:1) physical mixtures are shown in Figs. 3 and 4. The thermal profiles of the mixtures can be considered as a superposition of the curves of the atenolol active ingredient and excipients. Differences were observed in the case of atenolol-mannitol mixture (Fig. 5).

The atenolol melting peak in the binary mixture of drug-mannitol was displaced about 13 °C less than the melting peak of pure atenolol. In this context, the interaction evidenced in the commercial tablet is due to the presence of mannitol in the formulation.

Determination of Purity

The purity determination is based on the assumption that an impurity will depress the melting point of a pure material whose melting is characterized by a melting point (T_0) and an enthalpy of fusion (ΔH_f). The melting transitions of a pure, 100 % crystalline material, should be infinitely sharp, but impurities or defects in the crystal structure will broaden the melting range and lower the final melting point to a temperature lower than T_0 [23]. The effect of an impurity on T0 of the pure atenolol was determined by DSC method basing on the Van't Hoff equation [**1**],

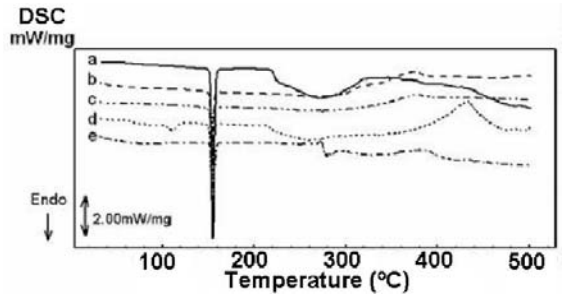

Figure 3. Stacked overlay of DSC curves of atenolol and 1:1 physical mixtures: (**a**) atenolol; (**b**) 1:1 atenolol/microcrystalline cellulose; (**c**) 1:1 atenolol/colloidal silicon dioxide; (**d**) 1:1 atenolol/magnesium stearate; (**e**) 1:1 atenolol/sodium starch glycolate.

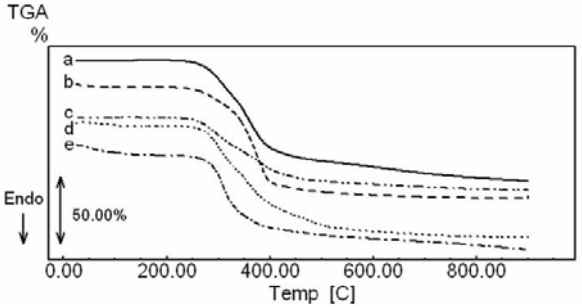

Figure 4. Stacked overlay of TG curves of atenolol and 1:1 physical mixtures: (**a**) atenolol; (**b**) 1:1 atenolol/microcrystalline cellulose; (**c**) 1:1 atenolol/colloidal silicon dioxide; (**d**) 1:1 atenolol/magnesium stearate; (**e**) 1:1 atenolol/sodium starch glycolate.

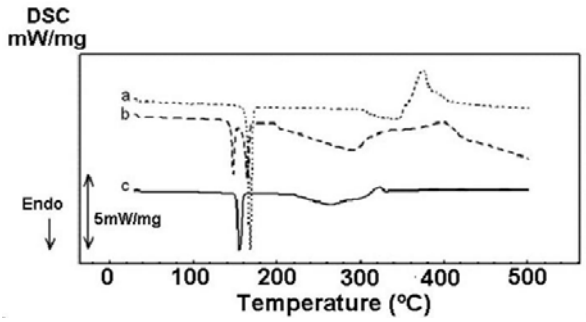

Figure 5. DSC curves of (**a**) mannitol , (**b**) 1:1 mannitol/atenolol mixture and (**c**) atenolol.

$$T_s = T_0 - \frac{RT_0^2 X}{\Delta H_f F} \qquad \text{Eq. [1]}$$

where T_s is the sample temperature at equilibrium *(K)*, T_0 is the melting point of the pure component *(K)*, R is the gas constant, X is the concentration of impurity (mole fraction) and F is the fraction molten at T_s.

The DSC curve showed at Fig. 6 exhibits an endothermic event corresponding to the melting point of atenolol (ΔH_{fusion}= - 146.67 J/g). The calculated purity was 99.24 ± 0.07 % obtained from triplicate analysis. The result obtained in DSC was compared to the official method (98.7 ± 0.6 %) and both obtained results were similar.

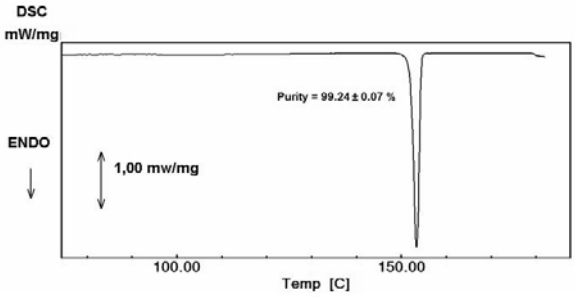

Figure 6. DSC curve of pure atenolol at 2.0 °C/min in dynamic nitrogen atmosphere.

Nonisothermal Kinetic Study

The kinetic data were extracted from plotting mass loss vs. temperature (TG curves) obtained to several heating rates for pure atenolol. Fig. 7 demonstrate the superposition of TG curves and the inserted figure presents the correlation of reaction mechanism.

Ozawa's method was applied in five TG curves in order to determine the activation energy *(E)* and Arrhenius frequency factor (Z). The activation energy was obtained from a plot of logarithms of heating rates (A) as a function of the inverse of temperature (1/*T*) for a constant

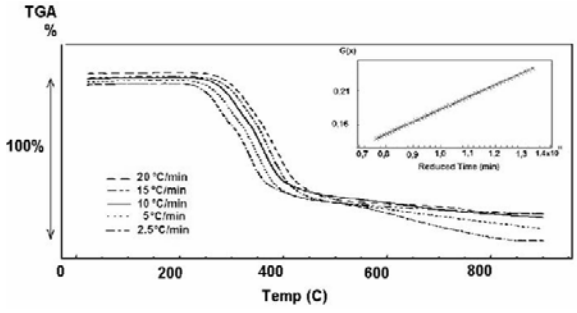

Figure 7. TG curves of atenolol obtained at different heating rates under dynamic nitrogen atmosphere.

G(x), where G(x) is the integrated form of the conversion dependence function, *f*(x). The kinetics parameters obtained were: activation energy *(E)* of 124.03 kJ/mol and frequency factor (Z) of 1.805 x 10^{10} min^{-1}.

CONCLUSION

In the development of solid dosage forms, the pre-formulation study is important to ensure the quality, stability, safe final product and drug-excipient compatibility. The DSC was a rapid, safe and accurate method for purity determination. Through non-isothermal conditions, the activation energy for the first step of decomposition reaction of atenolol was determined. The DSC and TG techniques proved to be suitable analytical tools to provide information about potential interaction between pure atenolol and mannitol.

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