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THERMOANALYTICAL STUDY OF FLUOXETINE HYDROCHLORIDE

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The thermal behaviour of fluoxetine hydrochloride and five capsules available in Florianópolis, Brazil was investigated. The raw material's purity, kinetic parameters, thermal behaviour and melting characteristics were determined by differential scanning calorimetry and thermogravimetric analysis, as well as the thermal study of the capsules. The purity was 99.12±0.15%. The thermal decomposition followed a zero order kinetic, activation energy of 88.67 kJ mol^{-1} and frequency factor of $3.539 \cdot 10^7$ min^{-1}. DSC curves obtained from the capsules suggest compatibility between the drug and excipient.

Keywords: *DSC, fluoxetine hydrochloride, TG*

Introduction

In the last 20 years, new antidepressant drugs were introduced into the pharmaceutical market, especially those known as serotonin re-uptake inhibitors (SSRIs). Drugs that enhance serotoninergic neurotransmission process through selective inhibition of neuronal reuptake of serotonine in presynaptic neurons and widely prescribed in therapy for depression disorders [1–3].

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) for oral administration. Since its approval and introduction for treatment of depression at the beginning of 1988, fluoxetine has become the most prescribed antidepressant drug around the world [4]. It is the only antidepressant medication that has Food and Drug Administration (FDA) approval for treatment of depression in children and adolescents [5, 6].

Chemically, fluoxetine is unrelated to tricyclic and tetracyclic antidepressant agents, being a secondary amine with one phenyl and one tolyl group in its structure (Fig. 1). It is designed (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-ρ-tolyl)-oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \cdot HCl$ [1, 2, 7].

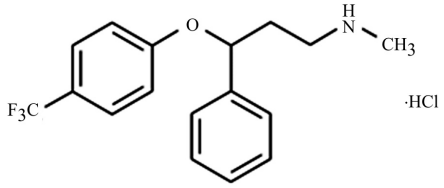

Fig. 1 Structural formula of fluoxetine hydrochloride

The thermoanalysis methods are used in pharmaceutical area for 35 years. It refers to a group of techniques in which a physical property of a substance and/or its reaction products is measured as a function of a controlled temperature program [8–11]. They are established techniques for quality control, preformulation, stability, drug-excipient interactions and purity studies of raw materials and pharmaceutical products [12–16].

The most widely used thermoanalysis techniques are differential scanning calorimetry (DSC) and thermogravimetry/derivative thermogravimetry (TG/DTG), which allows evaluating the physical properties of drugs, including melting and vaporization temperatures and with the corresponding enthalpies, glass transitions, vapor pressures, yielding results rapidly and efficiently [17, 18].

Momo *et al*., in 2005, published the first study of the chemical physical interactions of fluoxetine with phospholipid membranes [19]. In fact, no other reference has been found on the application of TG/DTG and DSC on the thermal behaviour of fluoxetine as raw material and its pharmaceutical dosage forms. Therefore, the main objective of this study is to investigate the thermal behaviour of fluoxetine raw material and five capsules including the innovator drug product, available in Florianópolis, Brazil using the DSC and TG techniques.

Experimental

Materials

Fluoxetine hydrochloride raw material (RM) was provided by Galena Laboratory (Brazil). In this work,

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were used fluoxetine capsules contained 20 mg manufactured by compounding pharmacies from Florianópolis, Brazil (S1, S2, S3, S4) and an innovator product from pharmaceutical industry (P). Each capsule contains 22.4 mg of fluoxetine hydrochloride, which corresponds to 20 mg of fluoxetine base.

Methods

Differential scanning calorimetry (DSC)

DSC curves were measured on Shimadzu DSC-60 cell. Approximately 2 mg of samples were mass out and placed in a sealed aluminum pan. An empty aluminum pan was used as reference. The temperature range was 25 to 500°C and heating rate of 10°C min^{-1} in dynamic nitrogen atmosphere with the flow rate of 50 mL min^{-1}.

The purity determination was performed using heating rate of 2°C min^{-1} in the temperature range from 25 to 185°C in nitrogen atmosphere with flow rate of 50 mL min^{-1}. The T_0, T_s and ΔH_{fusion} were calculated in three replicates by Shimadzu TASYS software. DSC equipment was preliminarily calibrated with standard reference of indium.

Thermogravimetric analysis (TG)

TG/DTG experiments were measured on Shimadzu thermobalance TGA-50. Approximately 4 mg of samples, using a platinum pan, were carried out from 25 to 500°C in dynamic nitrogen atmosphere with the flow rate of 50 mL min^{-1} and heating rate of 5°C min^{-1}.

Non-isothermal kinetic study was performed by application of Ozawa's method [8]. In dynamic experiments heating rates of 2.5, 5, 10, 15, 20°C min^{-1} were used to target temperature 400°C. The equipment was preliminarily calibrated with standard reference of calcium oxalate.

Results and discussion

Thermal characterization of fluoxetine raw material

TG/DTG and DSC curves of the fluoxetine RM are seen in Figs 2 and 3. TG/DTG curves show two thermal decomposition steps. The first step shows a large mass loss (Δm=92.3%) in the interval of 190–297°C, corresponding to fluoxetine's flash point at temperature 192.8±27.9°C calculated from Advanced Chemistry Development Software V8.14 [20]. In addition, it was observed mass loss (Δm=5.03%) in the temperature between 297–365°C. The decomposition is confirmed by DSC curve that indicates an exothermic process in temperature range 235–245°C. The solid product of the first thermal decomposition step has a molecular mass of about 316.8 g mol^{-1}, suggesting the release of 3-phenyl-3-[(α,α,α-trifluoro-ρ-tolyl)-oxy]-propylene (92.3%) by cleavage of the amine group. The second decomposition step suggests the loss of methylene amine (5.03%) and the residue formed (2.67%) refers carbon materials.

DSC curve is typical of a pure crystalline substance, showing a single sharp endothermic peak at temperature range between 154 and 160°C, with a T_{peak} of 157.5°C and ΔH_{fusion} of 98.81 J g^{-1}. Mura *et al*. described a similar relationship between the purity and peak format in 2002, for Naproxen [21]. The endothermic event corresponding to fluoxetine's melting point is in accordance to reported range in the literature (156–157°C) [22].

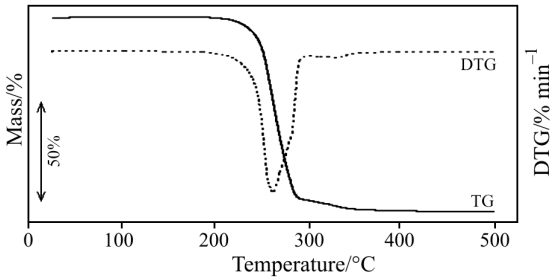

Fig. 2 TG/DTG curves of fluoxetine RM

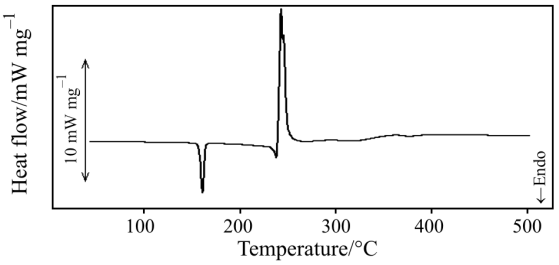

Fig. 3 DSC curve of fluoxetine RM

Thermal characterization of fluoxetine capsules

DSC and TG curves of the different formulations are seen in Figs 4 and 5, respectively. All DSC curves evidence an endothermic peak corresponding to fluoxetine's melting point in the temperature range of 152 to 162°C followed by thermal decomposition (Table 1). This is confirmed by TG curves that indicate mass loss events in temperatures range described in Table 2.

The S4 DSC curve exhibited two shallow broad endothermic peaks between 90–150 and 160–255°C and the TG curve shows a mass loss in three events up to 500°C. It was observed that the drug's melting event occurs with mass loss, suggesting an interaction, but not necessary corresponding to incompatibility. In fact, a similar effect was observed for other drug:excipient mixtures, and was attributed to drug dissolution in the melted excipient [18, 23].

Table 1 Peak (T_p), onset (T_o) and endset (T_e) temperatures and enthalpy change values obtained from dynamic DSC measurements for the melting and decompositon events

Formulation	Melting event				Decomposition event	
	T_p/°C	T_o/°C	T_e/°C	ΔH/J g^{-1}	T_o/°C	T_e/°C
S1	157.19	153.51	160.46	18.92	162 241	241 500
S2	158.09	154.45	161.37	12.96	162 240	240 500
S3	153.78	153.71	160.38	28.08	164 280	280 500
S4	155.87	152.58	159.55	5.75	90 160 255	150 255 500
P	156.19	152.90	159.46	8.04	25 160 260	150 260 500

Table 2 Onset (T_o), endset (T_e) and mass loss data obtained from TG measurements

Formulation	T_o/°C	T_e/°C	Mass loss/%
S1	262 282	282 500	32.37 32.02
S2	162 270	270 500	18.87 39.12
S3	165 280	280 500	24.65 49.33
S4	25 165 265	165 262 500	4.94 24.82 36.66
P	25 160 260	150 260 500	7.71 11.13 58.53

Determination of purity

The determination of purity 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 [24, 25]. Purity determination is officially listed in United States Pharmacopoeia in general chapter on thermal analysis [7].

The effect of an impurity on T_0 of the fluoxetine RM was determined by DSC method basing on the Van't Hoff equation (1).

$$T_s = T_0 - \frac{RT_0^2 x}{\Delta H_f}\frac{1}{F} \quad (1)$$

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.

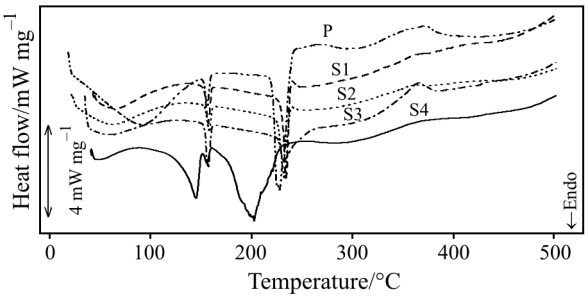

Fig. 4 DSC curves of fluoxetine capsules

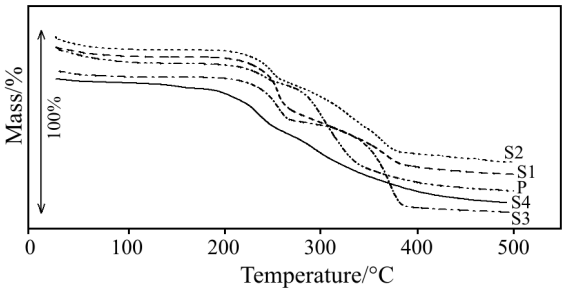

Fig. 5 TG curves of fluoxetine capsules

The obtained DSC curve is shown in Fig. 6, which exhibits the endothermic event corresponding to fluoxetine's melting point (ΔH_{fusion}= –96.6 J g^{-1}). The value of purity found was 99.12±0.15%, confirming low impurity content.

Non-isothermal kinetic study

The kinetic data were extracted from plotting mass loss *vs*. temperature (TG curves) obtained to several heating rates for fluoxetine RM. Figure 7 demonstrate the superposition of TG curves, which are shifted for higher temperatures when heating rates increase. But the amount of mass loss is not changed basically. This result suggests that the various heating rates effect the distribution of heat flux to the crucible and then into

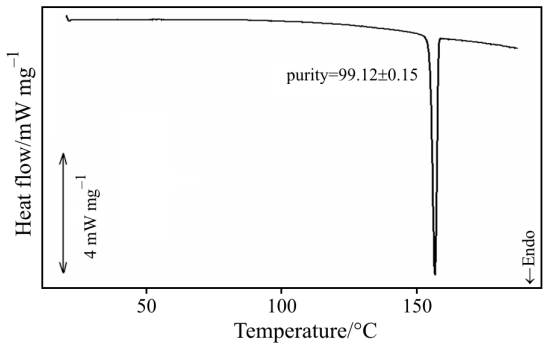

Fig. 6 DSC curve obtained at heating rate of 2ºC min^{-1} in N_2 (50 mL min^{-1})

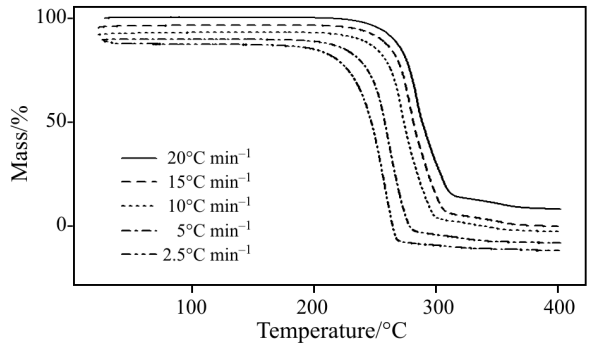

Fig. 7 TG curves obtained at 2.5, 5.0, 10, 15, 20ºC min^{-1} in N_2 (50 mL min^{-1})

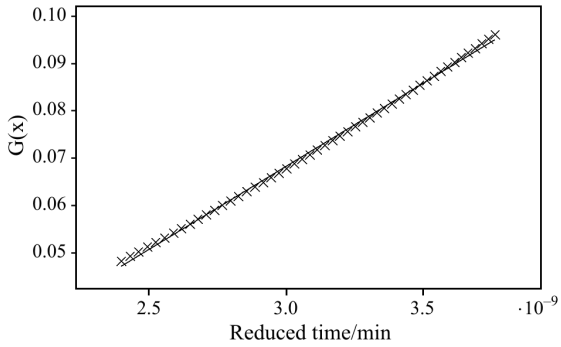

Fig. 8 Integrated form of constant $G(x)$ and the conversion dependence function, $f(x)$

the samples. The effect of heating rates was described by Huang *et al*. in 2001 to drug captopril [26].

Ozawa's method was applied in five TG curves in order to determine the activation energy (E), Arrhenius frequency factor (Z) and order of reaction (n). 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 $G(x)$, where $G(x)$ is the integrated form of the conversion dependence function, $f(x)$ (Fig. 8).

The kinetics parameters obtained were: activation energy (E) of 88.67 kJ mol^{-1}, frequency factor (Z) of $3.539 \cdot 10^7$ min^{-1} and zero order reaction (n =0).

Conclusions

In the development of solid pharmaceutical forms, quality control, stability and compatibility studies are important parameters to ensure the final product quality. Thermoanalysis is a routine method current applied in pharmaceutical industry. In this study, it proved to be a suitable technique to evaluate the quality of fluoxetine hydrochloride capsules and raw material.

DSC provides a rapid method for purity determination, attending value between 98 and 102%, which is in agreement with the official pharmacopoeia [7].

The decomposition process occurs in constant rate, zero order, and is independent of the concentration of the reactants. When the limiting reactant is completely consumed the reaction abrupt stops. The excipients can produce a different environment in which the behaviour of the drug is modified (e.g. fusion heating).

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