Thermal Stability of Piroxicam – Active Substance and Tablets

I. Kinetic study of the active substance under non-isothermal conditions

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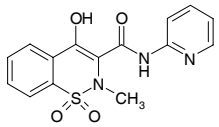
The thermal methods of analysis are widely employed in the study of stability and thermal decomposition of substances used in medicine, especially drugs. Kinetic studies have become a crucial point in thermal analysis, having as main purpose to determine the kinetic model of thermal decomposition and to calculate the parameters of the Arrhenius equation. The present work reports the study of thermal behaviour of piroxicam active substance and tablets, based on the thermoanalytical curves, respectively the determination of the kinetic parameters. The kinetic study regarding the piroxicam – active substance's thermal decomposition was performed under non-isothermal conditions, in a nitrogen atmosphere, at five heating rates: 2.5; 5; 7.5; 10 and 15°C/min. The kinetic parameters of thermal decomposition process were obtained from thermogravimetric curves using the following differential methods: Friedman isoconversional and Freeman-Caroll, respectively integral methods: Flynn-Wall-Ozawa, Kissinger-Akahira-Sunose, Starink and Tang.

Keywords: piroxicam, thermal stability, kinetic study, non-isothermal conditions

Piroxicam [4–hydroxyl–2–methyl–N–(2–pyridyl)–2H–1,2–benzothiazine–3–carboxamide–1,1–dioxide], with the formula:



is a non-steroidal anti-inflammatory drug (NSAID) used for inflammatory and painful diseases of rheumatic and non-rheumatic origin.

The anti-inflammatory activity of NSAID's and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostagladins, which are mediators of the inflammatory process [1,2]. Piroxicam is a potent inhibitor cyclo-oxygenase (Cox) in *vitro* and in *vivo*, thereby decreasing the synthesis of prostaglandins, prostacyclin, and thromboxane products, because this enzyme is responsible for the conversion of arachidonic acid to prostaglandins [3,4].

The cyclo-oxygenase enzyme exists in two isoforms: Cox-1 is present and active in all tissues, while Cox -2 is present and active only in the kidney, brain and ovaries. During the inflammatory process the concentration of Cox-2 increases in the affected tissues thus producing prostaglandins, which explains the increased interest for the synthesis of some specific compounds of Cox-2 [5,6].

Thermal analysis is one of the most frequently used instrumental techniques, especially in fields of growing importance, inclusively in the pharmaceutical field. The application of thermal methods, especially thermo-gravimetry/ derivative thermogravimetry (TG/DTG) and differential scanning calorimetry (DSC) is of great importance in solving pharmaceutical problems such as the determination of purity, the qualitative and quantitative analysis of drug formulation, stability tests, compatibility, kinetic parameters determination etc [7-12].

Thermogravimetry is an analytical, quantitative and comparative method, capable of producing fast and reproducible results. It can be used in the quality control of drugs, with a view to improvement of the final product and for the determination of drug quality via technological parameters [13-18].

The DSC technique, which is frequently used instead of the DTA, can be used in pharmaceutical research as an analytical tool of great importance for the identification and purity testing of active drugs and especially to elucidate the miscibility/ incompatibility with its effects on thermal stability, yielding results rapidly and efficiently [8,19-22].

The thermal stability of drugs is a very important factor since their instability affects the therapeutic efficiency, toxicity, biodisponibility and the process of obtaining the tablets. Thermal stability can be characterized by the thermal behaviour, respectively by the kinetic analysis.

Kinetic studies have become a crucial point in thermal analysis, during which the main purpose is to determine the mechanisms of pyrolysis reaction and to calculate Arrhenius parameters. The kinetic parameters, the rate constant (k), the activation energy (E), the pre-exponential factor (A), and the reaction order (n), can provide the mechanism and the rate of the decomposition reaction, the storage conditions, especially lifetime, half-life time, and shelf-life time [23-28].

Isoconversional methods are amongst the more reliable kinetic methods for the treatment of thermoanalytical data [29-33].

The major information produced by these methods is the dependence of the apparent activation energy with the extent of conversion, called the E_α-dependency. This dependency is important for detecting and treating multistep kinetics. On the other hand, the E_α-dependencies evaluated by isoconversional methods allow for meaningful mechanistic and kinetic analysis as well as for reliable kinetic predictions. One of the main advantages of these methods is that they provide a way of obtaining

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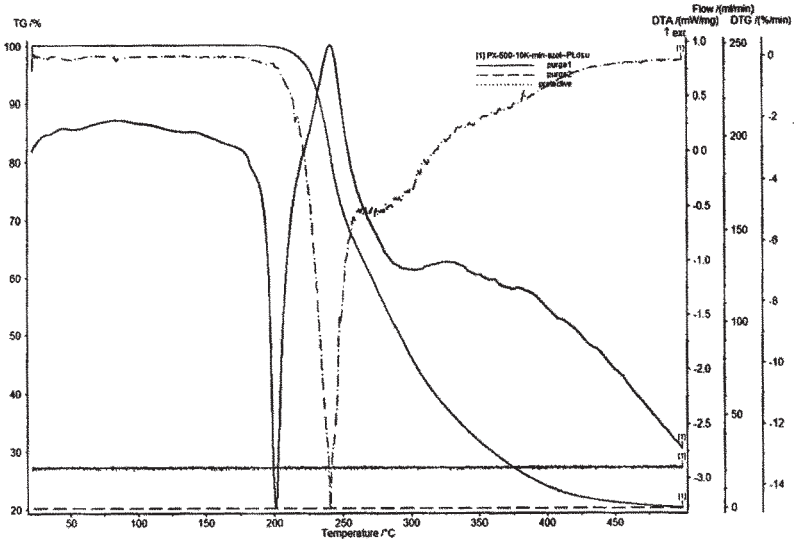

Fig. 1. TG/DTG and DTA curves of PX-AS.

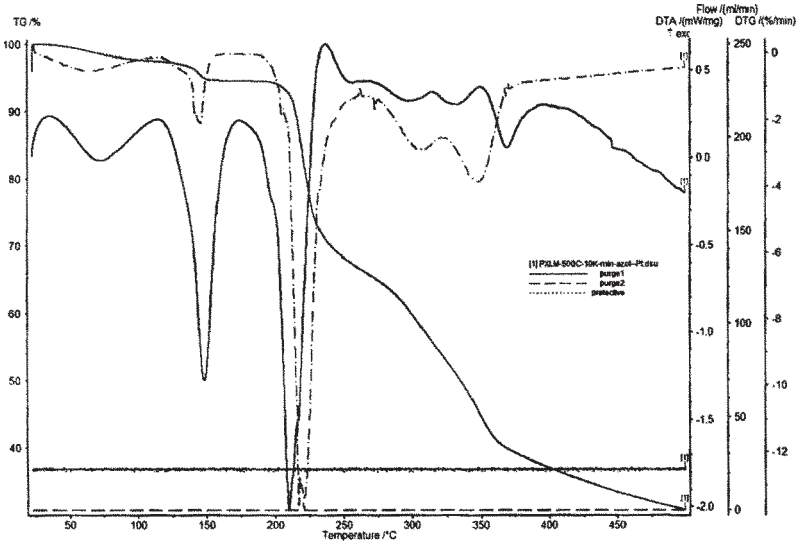

Fig. 2. TG/DTG and DTA curves of PX-M.

kinetic parameters without any assumption on the reaction mechanism. For this reason they are sometimes called "model-free".

In our previous papers [34-44], we provided the importance and utility of the kinetic analysis in estimations on the thermal behaviour of different pharmaceuticals.

The purpose of the present paper is to evaluate the thermal behaviour of piroxicam, active substance and tablets, respectively the determination of the kinetic parameters, for the active substance under non-isothermal condition, because these represent a criterion for the estimation of its thermal stability.

Experimental part

Materials and methods

The substances examined by thermal analysis were:

- piroxicam (PX) – active substance (AS) or drug;
- piroxicam (PX) – tablets (M).

The active substance was available as pure compound able to be used for medical purposes. It was obtained from Nantog Jinghua Pharmaceutical Co.Ltd, China, lot PRX 2006001. The pharmaceuticals (tablets) were commercial products, containing different excipients, like: corn starch hydrated, microcrystalline cellulose, lactose monohydrate, povidone K30, magnesium stearate, talc, etc.

TG/DTG/DTA experiments were performed with a Netzsch-STA 449 TG/DTA instrument in the temperature range of 20–500°C, using platinum crucibles with ≈ 20 mg of samples under dynamic nitrogen atmosphere (20 mL×min^{-1}) and the heating rates of 2.5; 5; 7.5; 10 and 15°C × min^{-1}.

Results and discussions

Thermal behaviour

Some of the thermal curves of the two substances, obtained under dynamic temperature conditions, at heating rate of 10°C·min^{-1} and a nitrogen atmosphere, are presented in figures 1 and 2.

According to the TG/DTG curves, it can be said that the thermal decomposition of PX-AS occurs in one stage, but through a complex process, especially after a mass loss of about 30-35%, with successive and /or concomitant reactions (fig.1). The corresponding decomposition temperature range is between 200 and 450°C with a mass loss of about 80% and $T_{peak\ DTG}$=240.2°C.

The PX-M thermal behaviour is more different from that of PX-AS, being clearly more complex. The TG/DTG curves show four areas of thermal instability, the last of them being the most complex. In the 35-104°C, respectively 118-153°C ranges, there have been held the first processes of mass loss of 2.92% and 2.08%, and the peak temperatures of DTG are 63.7, respectively 147.4°C. It follows a first process of thermal decomposition between 200 and 265°C, with a pronounced effect on the DTG curve ($T_{peak\ DTG}$=218.5°C) and the mass loss is about 28%. The second process of decomposition can be considered to occur between 265-400°C, with a succession of two peaks on the DTG curve ($T_{peak\ DTG}$=307.4°C, respectively 350.0°C), even if the DTA curve indicates a more complex process. The mass loss in

this interval is approximately 30%. After 400°C, the mass loss continues, so that up to 500°C, about 6% it is lost.

The DTA curve shows a first broad peak ($T_{peak\ DTG}$=72.2°C) followed by a sharp one at 153.0°C. Both are likely endothermic peaks. The next peak, the most pronounced one, of endothermic nature and with $T_{peak\ DTA}$=208.9°C which corresponds to the melting. As in case of PX-AS, the melting is followed by an exothermic peak ($T_{peak\ DTA}$=234.4°C), which is the beginning of thermal decomposition. It follows a succession of three slightly exothermic peaks at 272.2; 317.0 and 350.0°C, and finally, a little more pronounced one, of endothermic nature at 372.2°C.

By comparison of the thermal curves, it shows that PX-AS is more thermally stable than the PX-M, due to the presence of excipients in PX-M, respectively their possible interactions with the PX-AS.

Kinetic analysis

Also, the *thermal stability* was characterized by using the *kinetic parameters,* on the basis of the kinetic study performed under non"isothermal conditions, which sustained the present facts.

The kinetic parameters, the rate constant (k), the activation energy (E), the pre"exponential factor (A) and reaction order (n) were determined from the TG/DTG curves, by using the differential methods, Friedman isoconversional (Fd) [45] and Freeman–Carroll (FC) [46] respectively integral methods, Flynn–Wall–Ozawa (FWO) [47,48], Kissinger–Akahira–Sunrose (KAS) [49, 50], Starink [51] and Tang [52].

From the equation of reaction rate:

$$\frac{d\alpha}{dt} = k(T)\cdot f(\alpha) = A\cdot\exp\left(-\frac{E}{R\cdot T}\right)\cdot f(\alpha) \quad (1)$$

for non-isothermal conditions $d\alpha/dt$ is replaced with $\beta\cdot d\alpha/dT$, where β is the heating rate, giving:

$$\beta\cdot\frac{d\alpha}{dT} = A\cdot\exp\left(-\frac{E}{R\cdot T}\right)\cdot f(\alpha) \quad (2)$$

where: α is the conversion degree, t is the time, $f(\alpha)$ is the reaction model and T is the temperature.

The *isoconversional Friedman method* is based on the equation:

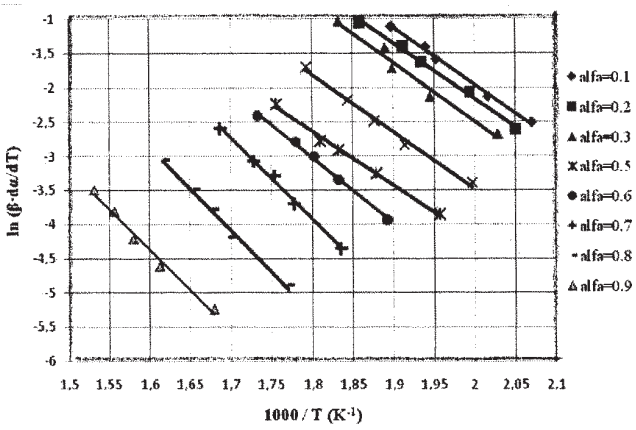

Fig. 3. Friedman's plot for piroxicam at different heating rates

$$ln\left(\beta\cdot\frac{d\alpha}{dT}\right) = ln[A\cdot f(\alpha)] - \frac{E}{R\cdot T} \quad (3)$$

In order to evaluate the activation energy more precisely, the term $ln(d\alpha/dT)$ was obtained by numerical derivation of the curve α vs. *T* with respect to T and subsequent taking logarithms.

For α=constant and using various heating rates, the plot $ln(\beta\cdot d\alpha/dT)$ vs. $(1/T)$ is linear (fig.3). The values of the activation energy as obtained from the slopes of the straight lines are listed in table 1.

The Freeman-Carroll method is one of the most commonly used methods, particularly for the calculation of reaction order. The method uses the most simple conversion function, corresponding reaction order, $f(\alpha) = (1-\alpha)^n$, and the formula that describes the Freeman-Carroll method is:

$$\frac{\Delta ln(\beta\frac{d\alpha}{dt})}{\Delta(\frac{1}{T})} = n\cdot\frac{\Delta ln(1-\alpha)}{\Delta(\frac{1}{T})} - \frac{E}{R} \quad (4)$$

By the comparison of the E values †obtained by two differential methods, it is showed that there is a good agreement for Freeman-Carroll and Friedman methods, but only for $0.1\leq\alpha<0.6$. For $\alpha>0.6$, the variation of E is more pronounced, indicating the complexity of the decomposition, according to the thermal curves.

The value of n > 1.000 indicates that the reaction mechanism does not correspond exactly to a rection kinetic model of order 1.

Method	E / kJ·mol^{-1}, for conversion degree, α									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	Main
Fd	68.6 ±1.3	67.3 ±1.1	71.2 ±1.0	69.6 ±0.8	66.2 ±0.6	81.7 ±1.2	100.4 ±1.4	102.2 ±1.3	98.4 ±1.1	80.6±5.1
FWO	79.0 ±0.8	72.7 ±0.7	73.5 ±0.9	71.0 ±0.6	71.7 ±0.8	91.1 ±1.1	97.9 ±1.2	94.7 ±0.9	89.1 ±1.3	82.3±3.6
KAS	74.7 ±0.4	67.9 ±0.5	68.7 ±0.4	66.0 ±0.6	66.5 ±0.7	86.7 ±0.9	93.6 ±0.7	89.9 ±0.5	89.0 ±0.8	78.1±3.8
Starink	75.0 ±0.6	68.9 ±0.4	89.7 ±0.8	71.4 ±1.1	89.6 ±0.9	95.9 ±1.1	70.5 ±0.8	71.5 ±0.7	68.2 ±0.5	77.9±3.6
Tang	75.1 ±0.5	69.0 ±0.4	89.8 ±0.7	71.5 ±0.9	89.7 ±1.0	96.0 ±1.2	70.6 ±0.9	71.6 ±0.7	68.3 ±0.4	78.0±3.6

Table 1
VALUES OF THE ACTIVATION ENERGY OBTAINED BY THE FRIEDMAN (Fd), FLYNN–WALL–OZAWA (FWO), KISSINGER–AKAHIRA–SUNOSE (KAS), STARINK AND TANG METHODS FOR ACTIVE SUBSTANCE.

Flynn–Wall–Ozawa's isoconversional method is based on the measurement of the adequate temperature to certain values of the conversion α, for experiments effectuated to different rates of heating β. The equation corresponding to this method is:

$$\ln\beta = \ln\frac{A\cdot E}{R\cdot g(\alpha)} - 5.331 - 1.052\cdot\frac{E}{R\cdot T} \qquad (5)$$

where g(α) is the conversion integral.

The plot *lnβ vs. (1/T)* is linear (fig.4) and from the slopes of the straight lines (–E/R), the values of the activation energy (E) were obtained (table 1).

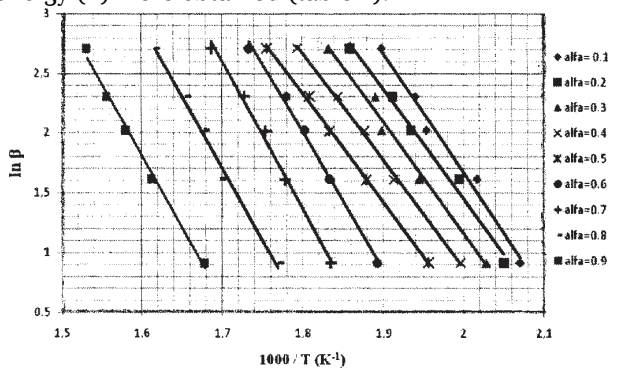

Fig. 4. The Flynn–Wall–Ozawa isoconversional diagrams

The *Kissinger–Akahira–Sunose* method, is one of the best isoconversional methods and it is based on the equation:

$$\ln\frac{\beta}{T_\alpha^2} = \ln\frac{A\cdot R}{E\cdot g(\alpha)} - \frac{E}{R\cdot T_\alpha} \qquad (6)$$

This method utilises the adequate temperatures (T_α) to certain values of the conversion α for experiments effectuated to different rates of heating, β.

From the slopes of the straight lines obtained by the representation graphic of the ln(β/T^2) *vs.* ($1/T_\alpha$) was determined the activation energy (table 1).

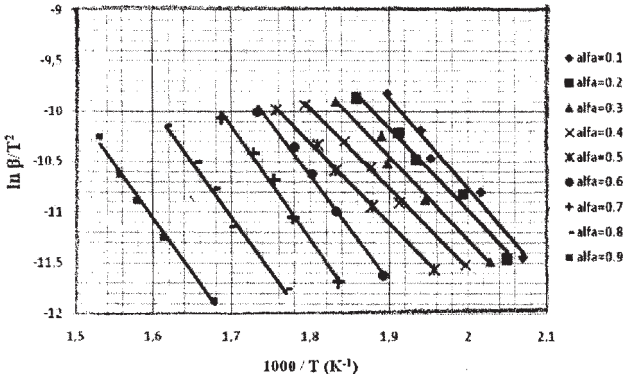

Fig. 5. The Kissinger–Akahira–Sunose diagrams for piroxicam at different conversion degrees

The approximation suggested by Starink for the temperature integral is $p(x) = \exp\frac{-1{,}0008x - 0{,}312}{x^{1.92}}$. In this case, k = 1.92 and at constant conversion a, the general linear equation becomes:

$$\ln\frac{\beta}{T^{1.92}} = -1{,}0008\frac{E}{RT} + C \qquad (7)$$

The approximation proposed by Tang for the temperature integral is:

$$\ln p(x) = -0.3777 - 1.8947 \ln x - 1.0015\, x$$

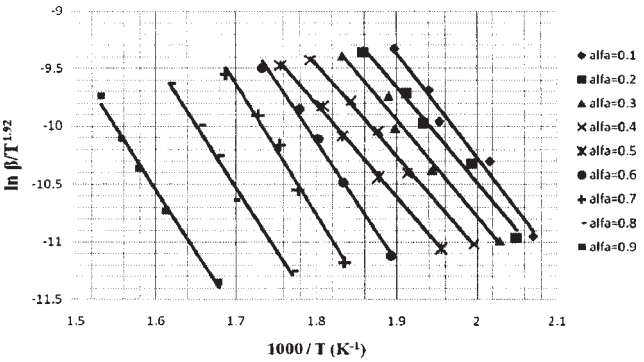

Fig. 6. The Starink diagrams for piroxicam at different conversion degrees

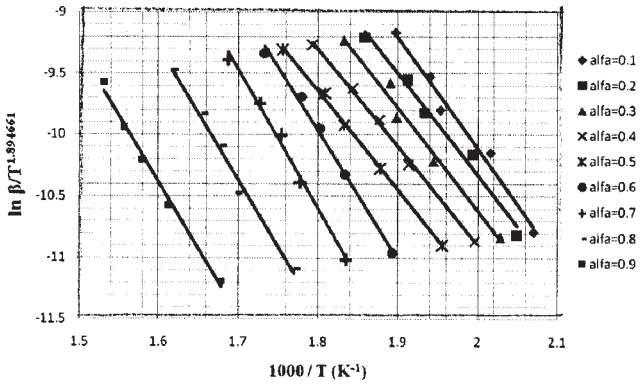

Fig. 7. The Tang diagrams for piroxicam at different conversion degrees

For this method, (k=1.8947) and at constant conversion, α, the general linear equation becomes:

$$\ln\frac{\beta}{T^{1.8947}} = -1{,}0015\frac{E}{RT} + C \qquad (8)$$

Conclusions

There was performed a thermal study: thermal behaviour of piroxicam active substance and their pharmaceutical form, respectively and kinetic analysis under non-isothermal conditions for the piroxicam active substance.

There have been observed differences between the thermal curves of the pure compound and those of the pharmaceutical product, due to the presence of the excipients in drug and due to the possible interactions with the active substance.

The study of thermal behaviour of the two piroxicam samples evidenced that the presence of excipients decreases the thermal stability of this drug.

The kinetic study was done only for the active substance, because the thermal behaviour of different pharmaceutical products differs due to the function of the excipients present in formulation, and then the assignment of the kinetic parameters' values to a certain process should be irrelevant.

The values of the kinetic parameters, determined with integral and differential methods (especially Fd), are in fair good agreement.

From Table 1, it is found that E varies with á in some degree, which shows the complexity of the decomposition process, with successive and/ or concurrent reactions, but without highlighting the existence of a multistage process.

The values of E, in the 72-82 kJ·mol^{-1} range, show a low thermal stability of piroxicam-active substance.

The kinetic study through values of kinetic parameters (especially E) can be used in the preformulation and

production steps for quality control of medicines, together with the melting point, which characterizes their purity.

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