Thermal Behaviour of Acetylsalicylic Acid - active Substance and Tablets

Kinetic Study under Non-isothermal Conditions

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The application of thermal methods is of great importance in the solution of pharmaceutical problems such as the control of raw materials, the determination of purity, the qualitative and quantitative analysis of drug formulation, tests of thermal stability and compatibility, the determination of kinetic parameters etc. The evaluation of thermal stability in the solid state is mostly made by analysing their decomposition under isothermal or non–isothermal conditions. This work reports the study of the thermal behaviour of acetylsalicylic acid active substance and tablets, together with the determination of the melting points and the degree of purity by TG, DTG and DSC. A kinetic study of the thermal decomposition of acetylsalicylic acid active substance was carried out using dynamic TG curves and the differential–isoconversional Friedman method, respectively the non-parametric kinetics method.

Keywords: acetylsalicylic acid, drug, tablets, TG, DTG, DSC.

The thermal analysis is a generic word used for analytical techniques which study the behaviour of a substance to a certain temperature.

Applying the thermal methods is very important for solving pharmaceutical problems as getting the purity, qualitative and quantitative analysis of the medicine formulas, testing the stability and determining the kinetics parameters [1–4].

The thermal stability is a very important problem, because determining the temperature range when a certain medicine substance is stable regarding its structure as well as its pharmaceutical action is crucial for stocking the drugs, for its technological transformations and for the obtaining technology of the right formulas.

Thermogravimetry (TG) and differential scanning calorimetry (DSC) can be used in the pharmaceutical industry to identify and test the purity of the active substances, for the qualitative and quantitative control of the raw materials and of the pharmaceuticals products, in case of possible interactions while medicine processing etc. [5–10]

The actual trend, of using the analytical techniques, consists in using them combined (thermal and of other nature: spectrophotometric first of all, gas-chromatographic, titrimetric techniques), obtaining superior results and in the same time reducing the quantity of material studied [11–12].

Reducing the quantity of substance analyzed can be done, with superior results, by using methods based on the relation between the reaction rate and the concentration of some substances which influence the reaction rate, methods known as kinetics methods.

The kinetic methods contributed to predict some reaction mechanisms, as well as to assess the life–time of the pharmaceuticals, that usually requires weeks or months.

A series of works, even recent ones, show encouraging results regarding the evaluation of the thermal behaviour of pharmaceutical products by the kinetic data obtained in non-isothermal conditions [13–14].

Aspirin (acetylsalicylic acid) is an antiinflamator drug which is able to ease the pain and cure the asthma and the heart diseases. The publications about aspirin and its derivatives had been studied its dissolving kinetics, the obtaining mechanism, the absorption processes, the incompatibility drug–excipients, its pharmacology in body etc [15–16].

Aspirin's formula, acetylsalicylic acid or 2-acetoxy-benzoic acid, is presented in figure 1.
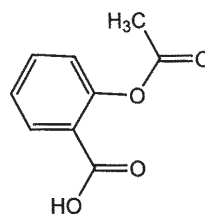

Fig.1. The chemical structure of the aspirin (acetylsalicylic acid)

This paperwork studies the thermal behaviour of aspirin active substance and tablets, having as purpose the evaluation of its thermal stability in solid stage, together with the finding of the melting point and of the purity degree through DSC. Also, it was performed the kinetic study by the thermal decomposition, under non-isothermal conditions.

Experimental part

The substances examined by thermal analysis were:
- acetylsalicylic acid - active substance or drug (AS)
- acetylsalicylic acid (aspirin) - tablets (M)

The active substances (drugs) were obtained from Terapia S.A. / Ranbaxy, Cluj-Napoca, România as pure compounds. The pharmaceuticals (tablets) were commercial products, containing different excipients, like: microcrystalline cellulose, talc, colloidal anhydrous silica dioxide.

TG/DTG experiments were performed with a Perkin-Elmer Diamond thermobalance, in the temperature range of 25–500°C, under a dynamic atmosphere of nitrogen at a flow rate of 50 mL min⁻¹. Samples with the mass in the range of 7 to 20 mg were put into platinum crucibles, at a heating rate, β, of 2.5, 5, 7 and 10°C min⁻¹.

DSC curves were recorded with a Netzsch differential scanning calorimeter, model DSC–204, using aluminium
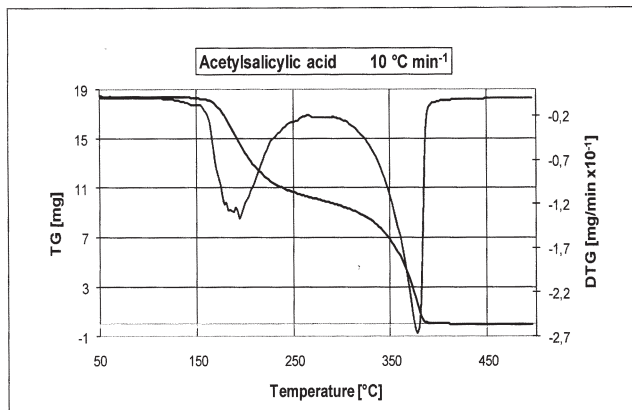
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Fig.2. TG and DTG thermal curves of the acetylsalicylic acid active substance

Fig.3. TG and DTG thermal curves of the acetylsalicylic acid tablets

crucibles with samples of 2 mg, in a dynamic nitrogen atmosphere, with a constant flow of 50 ml min^{-1} and a heating rate of 10°C min^{-1}, up to a temperature of 600°C.

Results and discussions
Thermal behaviour

Some of the thermal curves of the two substances, obtained under dynamic temperature conditions are presented in figures 2,3 and 5,6.

From the curves TG/DTG presented in fig.2–3 it comes out that the active substance as the tablets present two stages of decomposition, distinct or relatively distinct (for M). So, the active substance presents a first stage of decomposition, of endothermic nature, in the 160-260°C temperature range with $T_{max} = 185$°C, while the second stage, of slight exothermic nature, takes place in the 295-390°C temperature range with $T_{max} = 378$°C (fig.2.).

The first (complex) process is the elimination of the acetic acid and the formation of the salicylic acid.

The second (complex) process corresponds to elimination of CO_2 and the formation of the phenol. The elimination of CO_2 begins in the first process (the experimental lost mass ≈44% > the calculated one =34%).

Finally the phenol is decomposed and the carbonated residuum suffers a complete burning, together with a slight endothermic effect. The mentioned products were detected by FT–IR spectroscopy. Also, the curves TG / DTG of the the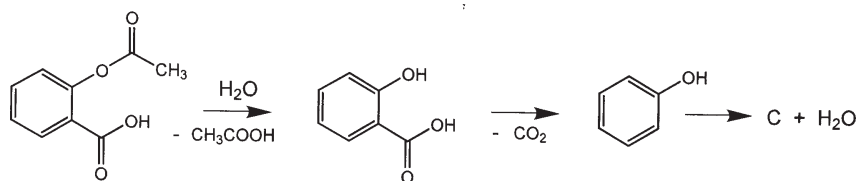rmal decomposition of the salicylic acid confirm the formation of this acid in the first moment of the decomposition process. Corresponding to the presented processes, one can write the chemical reactions which are presented in figure 4.

Also, the curves TG/DTG of the thermal decomposition of the salicylic acid confirm the formation of this acid in the first moment of the aspirins' decomposition (fig.5.)

In the same way, the tablets present a first stage of decomposition of endothermic nature, in the 150-220°C temperature range, with $T_{max} = 180$°C (fig.3.) followed immediately, in a larger temperature range, 220-315°C, by an exothermic decomposition process, at $T_{max} = 253$°C. Next, a third exothermic process follows, in 315-400°C temperature range at $T_{max} = 355$°C. The appearing of the intermediate stage in the case of aspirin tablets, together with an exothermic effect, is due to the decomposition of excipients from tablets.

The DSC curves of AS and M show the same manner of decomposition. So, on the DSC curves (fig.6 and 7) it can be distinguished an endothermic transition stage, without loss of mass on the TG curves, which corresponds to the melting process (143.9°C for AS and 133.4°C for M).

The melting point obtained from the DSC curve (133.4°C) is similar to the values mentioned in speciality literature (134-135°C) [17–18]. This indicates a high purity of the aspirin tablets.

The difference between the thermal decomposition ranges (inclusive the melting points) of the active substance and tablets is due to the possible interactions of the active

Fig.4. The decomposition scheme of the acetylsalicylic acid

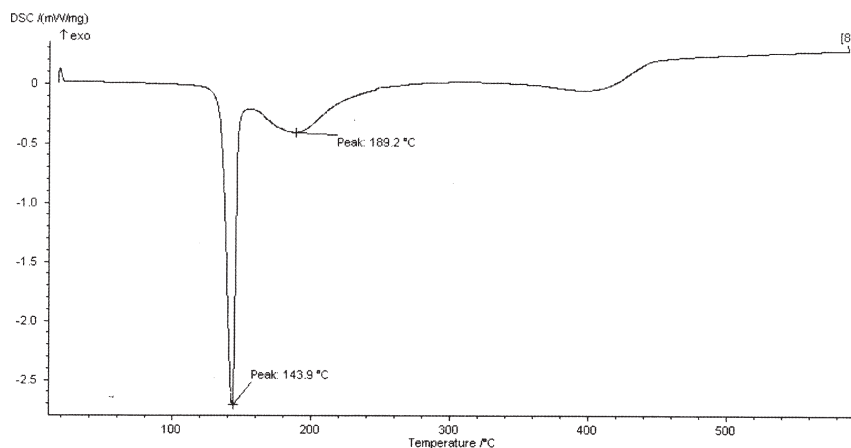Fig.5. TG and DTG thermal curves of the salicylic acid

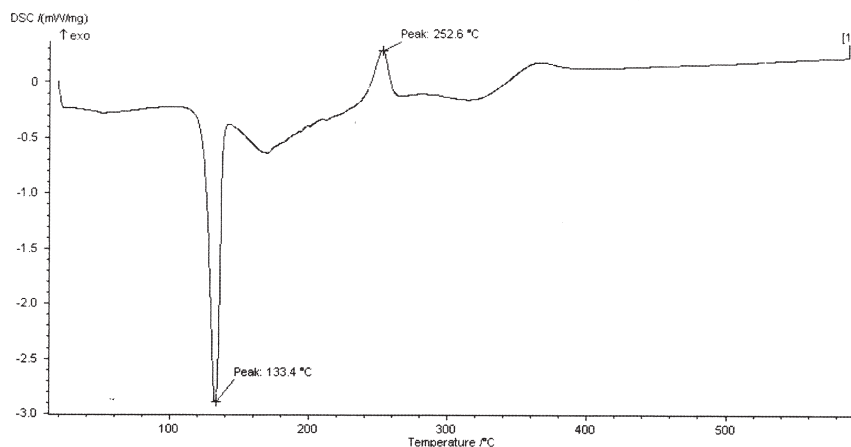Fig.6. The DSC thermal curve of the acetylsalicylic acid active substance

Fig.7. The DSC thermal curve of the acetylsalicylic acid tablets

substance with the excipients, an aspect which is more and more mentioned in the speciality literature [19–21]. As it could be seen, these possible interactions lead to the reducing of the decomposition temperatures. So, the AS presents a better thermal stability than the M, especially in the second stage of decomposition, as well as the temperature range between the two stages.

Kinetic analysis

The thermal stability of the acetylsalicylic acid-active substance was also characterized through the kinetics study effectuated, in non-isothermal conditions.

The kinetic parameters, the constant rate (k), the activation energy (E), the pre-exponential factor (A) and the reaction order (n) were obtained from the TG curves by using the differential-isoconversional Friedman method [22] and the non-parametric kinetics (NPK) method [23–24], that are characteristic to the non–isothermal regime.

It is well known that kinetic analysis of decomposition process can be represented by the equation:

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

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

For non–isothermal conditions $d\alpha/dt$ in equation 1 is replaced with $\beta \cdot d\alpha/dT$, where β is the heating rate, giving:

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

From the generally accepted equation of the non–isothermal kinetics (2), the equation corresponding to the Friedman's differential isoconversional method, was obtained:

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

For α = constant and using various heating rates, the plot $ln[\beta \cdot d\alpha/dT)]$ *vs. (1/T)* is linear. From the slope and the intercept of the straight line, the value of activation energy (E) and product $[A \cdot f(\alpha)]$ were obtained.

The values of the activating energy (E) obtained according to equation (3) for four heating rates at different reaction degrees have been represented graphically depending on α (fig.8.).
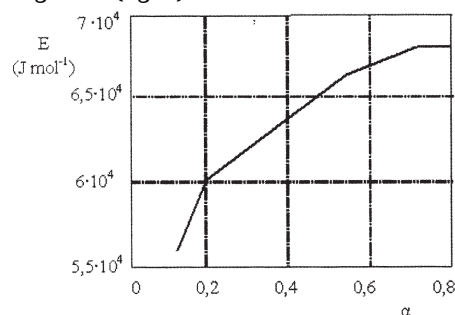

Fig.8. Dependence of E on α, using the Friedman isoconversional method

A significant variation of E *vs.* α is observed, indicating the existence of a multistage decomposition process as the thermal curves indicates too. This dependence is probably due to the change of the reaction mechanism in the non–isothermal conditions used.

Table 1
KINETIC PARAMETERS BY NPK METHOD

Acetylsalicylic acid AS	Stage	λ / %	E/ kJ mol^{-1}	ln A/ min^{-1}	n (ec. S–B)	m (ec. S–B)
	I	69.2	24.7±0.9	5.44±0.14	2	3/2
	II	28.3	58.3±2.4	13.59±0.34	2	2/3

In that case, for calculating the kinetic parameters it is indicated to use the non-parametric kinetics (NPK) method, a relatively recent well documented method. The main characteristic of this method is its ability to give information about kinetics reaction without presumptions regarding the dependence of the reaction rate on the conversion degree or temperature.

NPK method permits the separation of two or more stages of a complex process, based on the following reasoning:

– the experimental data are represented in a 3D space $(d\alpha/dt, \alpha, T)$;

– these data are interpolated to generate a continuous surface corresponding to an equation:

$$\frac{d\alpha}{dT} = f(T) \cdot g(\alpha) \tag{4}$$

– the continuous surface of the reaction rate is discretized as a ixj matrix M:

$$M = \{m_{ij}\} = \{f(T_i) \cdot g(\alpha_j)\} \tag{5}$$

– using the singular value decomposition (SVD) algorithm, the matrix M is decomposed according to equation (6):

$$M = U(diagS)V^T \tag{6}$$

and S is the vector of singular value;

– the first columns of U and V matrix, respectively u_1 and v_1 are analyzed for determining the kinetic model, i.e.:

$$u_1 = g(\alpha) \tag{7}$$

respectively, the temperature dependence, i.e.:

$$v_1 = f(T) \tag{8}$$

For temperature dependence, the classical Arrhenius equation is selected and for the kinetic model we suggest the Šesták–Berggren equation of two–parameters model [25]:

$$g(\alpha) = \alpha^m \cdot (1-\alpha)^n \tag{9}$$

where:

n - reaction order

m is a parameter which together with n characterize the mathematical expression of the kinetic model.

If the decomposition reaction is a two step process, the matrix M became:

$$M = M_1 + M_2 = U_1(diagS_1)V_1^T + U_2(diagS_2)V_2^T \tag{10}$$

and the contribution of each step to the entire process is expressed by the explained variance λ, so that $\lambda_1 + \lambda_2 = 100\%$.

With these conditions, the following data can be obtained: E, A, m, n.

The results obtained by using the NPK methods are represented in table 1.

By inspecting the data in table 1 it is evidently the existence of two distinct reaction steps ($\lambda > 15\%$), that appear during the thermal decomposition process. The significance of each step for the whole process is different but it is not to be neglected.

The first step, predominant, is in connection with significant lower thermal stability (the lowest value of the activation energy). The value of $m \neq 0$ indicates a contribution of the nucleation process on the kinetic law, followed by the linear increase of the agents of nucleation (inclusive the explosive reactions: $n > 1$).

Conclusions

There was performed a thermal study (thermal behaviour and kinetic determinations) under non-isothermal conditions for the acetylsalicylic acid and their pharmaceutical form.

The decomposition took place in a nitrogen dynamic atmosphere, so there were no secondary oxidation processes. So, the decomposition was due only to the thermal "sensibility" of the molecular structure.

By comparing the thermal curves and the temperature ranges of the two thermal decomposition processes, it is obtained a better thermal stability of the aspirin active substance than of the aspirin tablets, especially in the second decomposition stage. This is shown by rather smaller decomposition temperatures in the case of aspirin tablets and by rather larger decomposition ranges. The reason of this behaviour is the possible interaction of the excipients with the active substance.

Two different methods were used to process the experimental data.

The differential-isoconversional Friedman method gives an activation energy's dependence on the conversion degree, which indicates a complex decomposition process of the acetylsalicylic acid.

By applying the NPK method it has been achieved a separation between the conversion influences, respective of the temperature influence on the reaction speed. The NPK method also permits the separation of the two stages of reaction and determines for each of them the conversion function and the kinetics parameters.

Only the NPK method is capable to offer a less speculative way of discussions regarding the decomposition process because this method uses a larger number of points and a wider range of temperatures unless classical methods which use only few points (usually three or four, corresponding to the maximum of the thermoanalytical curves).

Comparing with the classical methods, the NPK method is not restricted to the mathematical equations of the kinetic models.

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