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New screening method for the determination of stability of pharmaceuticals

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Abstract

A rapid method for obtaining the parameters describing the lengths of oxidation induction periods from non-isothermal differential scanning calorimetry measurements, based on the dependence of onset temperature of the oxidation peak on heating rate, is presented. The method has been applied for screening the stability of a set of three pharmaceuticals. The order of stabilities of the compounds obtained by the method coincides with the order determined by classical stability tests.

Keywords: Induction period; Non-isothermal and isotermal kinetics; DSC; Pharmaceuticals; Oxidation stability

1. Introduction

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of pharma products. Stability assessment started with studies on the substance to determine degradation products and degradation pathway. Stability studies can influence the specification, limits and control methods for drug. In the ICH Harmonized Tripartite Guidelines on Stability Testing of New Drug Substances and Products (ICH Harmonized Tripartite Guideline) fundamental recommendations are summarized. According to the ICH guideline, long term (12 months) and accelerated stability studies (least 6 months) have to be carried out.

Thermal analysis is a routine method for the analysis of drugs and substances of pharmacological interest. Differential scanning calorimetry (DSC) is one of the thermoanalytical techniques which can be used to provide information on the melting behaviour, heat of fusion, purity, polymorphism, pseudo-polymorphism, glass transition, compatibility, crystallization and chemical reactions of drugs such as stability and kinetics of decomposition (Schwarz and de Buhr, 1998; Höhne et al., 1996). Influence of selected experimental parameters on the results of DSC measurements has been discussed in detail recently (Roy et al., 2002). The use of thermoanalytical techniques for the study of the stability of drugs has been lately demonstrated in a number of papers (Burnham et al., 2000; Rodante et al., 2001; Rodante et al., 2002a,b).

Recently, in our laboratory we developed a method for the determination of stability of materials. The main idea is that many processes exhibit an induction period (IP), in other words, the stage preceding

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the main process, where seemingly no chemical or physical action takes place. After the termination of induction period, the quality of the tested sample often dramatically changes. The oxidation in solid state belongs to this group. In our previous papers the induction periods of rubber compounds vulcanization (Šimon and Kučma, 1999), oxidation of edible oils (Šimon et al., 2000) and oxidation of polyolefines (Šimon and Kolman, 2001) under non-isothermal conditions have been studied. In this paper the method for obtaining the kinetic parameters of induction periods from the onset temperatures of non-isothermal DSC peaks with a linear increase of temperature is outlined. The method is applied for screening the stability of pharmaceuticals on a set of three compounds.

2. Theoretical part

For any mechanism, the rate of reaction can be described by the general rate equation (Höhne et al., 1996)

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = kf(\alpha) \tag{1}$$

where α is the conversion of the reaction and $f(\alpha)$ is the conversion function. The temperature dependence of the rate constant k is usually expressed by the Arrhenius equation

$$k = A_k \exp\left[-\frac{E_\mathrm{a}}{RT}\right] \tag{2}$$

where A_k is the preexponential factor, E_a is the activation energy, T is absolute temperature and R stands for the gas constant.

Since Eq. (1) is general, we assume that it describes also the kinetics of the reactions occurring during IP. Existence of these reactions is not detected by the experimental technique used; however, they have to take place as a preparatory stage preceding the main oxidation process. Combination of Eqs. (1) and (2), after the separation of variables, gives the result:

$$\int_0^{\alpha_i} \frac{\mathrm{d}\alpha}{f(\alpha)} = \int_0^{t_i} A_k \exp\left[-\frac{E_\mathrm{a}}{RT}\right] \mathrm{d}t \tag{3}$$

The conversion α_i in Eq. (3) is the conversion of the reactions occurring during IP corresponding to the end of IP, i.e. to the start of the main process detected by the apparatus, and t_i is the length of IP. Further it is assumed that the conversion α_i is the same for any temperature. Then, after integration of the left side of Eq. (3) one can get:

$$F(\alpha_i) - F(0) = \int_0^{t_i} A_k \exp\left[-\frac{E_\mathrm{a}}{RT}\right] \mathrm{d}t \tag{4}$$

Since the conversion α_i corresponding to the end of IP is assumed to be independent of temperature, also the value of the integrated function $F(\alpha)$ at the point α_i, $F(\alpha_i)$, is constant. Therefore, Eq. (4) can be rewritten as:

$$1 = \int_0^{t_i} \frac{\mathrm{d}t}{A \exp[B/T]} \tag{5}$$

where the constants A and B are given as:

$$A = \frac{A}{F(\alpha_i) - F(0)}, \quad B = \frac{E}{R} \tag{6}$$

The physical meaning of the denominator in Eq. (5) can be simply demonstrated for a special case of isothermal processes where the denominator is a constant equal to the induction period at the given temperature. Thus, the temperature dependence of IP can be expressed as

$$t_i = A \exp\left[\frac{B}{T}\right] \tag{7}$$

For the linear increase of temperature in DSC measurements, the furnace temperature can be expressed as

$$T_\mathrm{f} = T_0 + \beta t \tag{8}$$

where T_f is the furnace temperature, T_0 is the starting temperature of the measurement and β stands for the heating rate. If one assumes that the temperature of the sample equals that of the furnace, combination of Eqs. (5) and (8) gives the result (Šimon and Kolman, 2001)

$$\beta = \int_0^{T_i} \frac{\mathrm{d}T}{A \exp[B/T]} \tag{9}$$

where T_i is the temperature of the end of induction period, i.e. the onset temperature of the oxidation peak. The starting temperature in Eq. (9) is set as $T = 0\,\mathrm{K}$ since the reaction rate at the starting temperature is negligible. When deriving Eqs. (3) and (4), the assumption is implied that the conversion function $f(\alpha)$

holds during the induction period which means that no change of the reaction mechanism occurs. As Eq. (9) indicates, when increasing the rate of heating, the onset temperature also increases.

3. Experimental part

3.1. Materials

Three representative samples of various analgesic activity compounds 1–3 were selected from pilot batches. Compounds combine a substituted aromatic system and amino alkyl moieties. They exist as solid hydrochloric acid salts at room temperature with a melting point in excess of 160 °C. Various pilot scale batches for compounds 1, 2 or 3, respectively, exhibit the same thermal behaviour.

Differential scanning calorimeter Shimadzu DSC-60 was used for the oxidation stability measurements. The temperature scale was calibrated using the standards In, Sn and Zn. The enthalpic scale was calibrated to the enthalpy of In fusion. Samples of 3–4 mg were placed in open standard aluminium pans, air was used as a purge gas forming also the oxidation atmosphere. In the records, exothermal peaks are oriented upwards. The records were corrected for the baseline. The standard deviation of a single measurement of the oxidation onset temperature, determined from three measurements, was less than 1.5 K for all scans.

4. Results and discussion

Both the isothermal and non-isothermal DSC measurements have been carried out. For isothermal measurements in the temperature region 120–220 °C, no oxidation peaks were detectable. The record departed from the baseline very slowly so that the onset of oxidation could not be read unambiguously. On the other hand, the onset temperature of oxidation was very clearly and sharply detectable from non-isothermal measurements. As it can be seen from Fig. 1, the endothermic decrease of the baseline is observed, obviously due to sublimation of the samples. Then, the sample ignites which is accompanied with a rapid heat evolution. Oxidation then proceeds in several stages. The point of the steep increase of the DSC record due to oxidation is taken as the onset temperature of oxidation.

The parameters A and B in Eq. (9) have been obtained by minimizing the sum of squares between experimental and theoretical values of onset temperature for various heating rates by the simplex method (Nelder and Mead, 1965). The theoretical values of onset temperature are given by Eq. (9). The integration indicated in Eq. (9) has been carried out by the

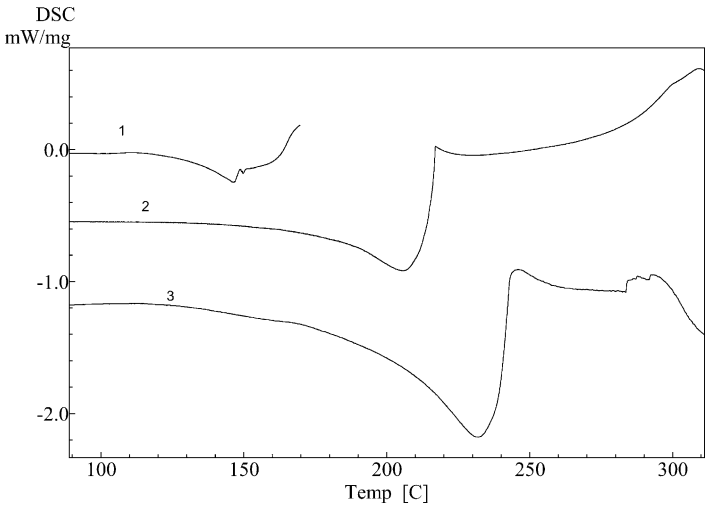

Fig. 1. DSC records of the oxidation for the set of compounds, heating rate 1 K/min.

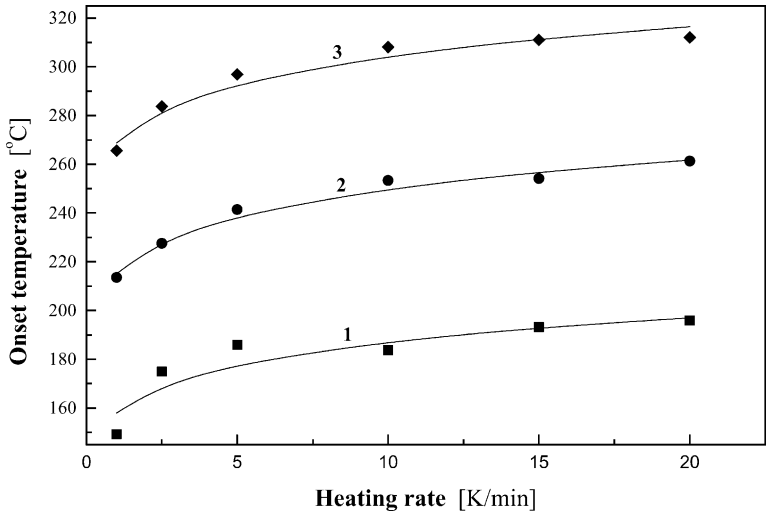

Fig. 2. Comparison of experimental (squares, circles, diamonds) and theoretical (lines) values of the oxidation onset temperatures for various heating rates.

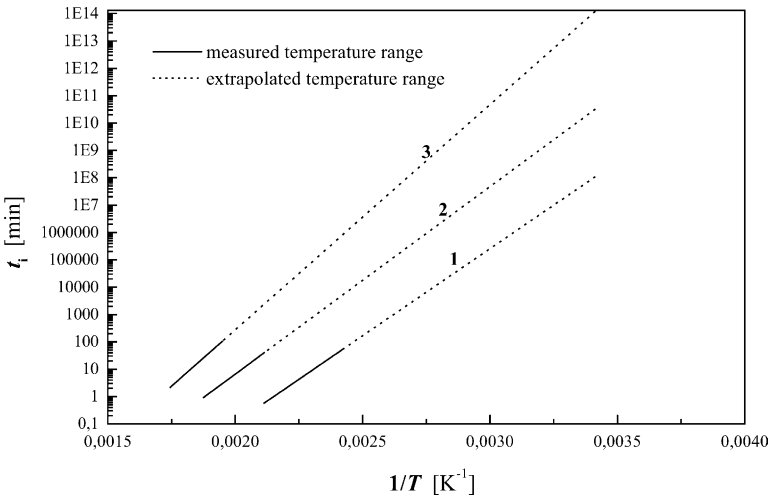

Fig. 3. Induction times of oxidation for individual compounds calculated by Eq. (7).

Simpson method. The standard deviations of A and B were calculated assuming a quadratic surface near the minimum (Nelder and Mead, 1965). The agreement between experimental and calculated values of onset temperatures for various heating rates is shown in Figs. 2 and 3. The resulting values of A and B are listed in Table 1.

The range of temperatures for the DSC accelerated test differs greatly from the temperatures where the stability should be assessed. The classical tests were

Table 1
Parameters A and B describing the length of induction period using Eq. (7) for the compounds under study

Sample	A (min)	$B \times 10^{-3}$ (K)
Compound 1	$(2.03 \pm 0.27) \times 10^{-14}$	14.7 ± 0.3
Compound 2	$(1.28 \pm 0.21) \times 10^{-13}$	15.8 ± 0.2
Compound 3	$(9.17 \pm 2.04) \times 10^{-15}$	19.0 ± 0.3

carried out at 25 °C, the accelerated DSC tests within 160–320 °C. In the accelerated tests, the end of the induction period of the oxidation coincides with the start of thermooxidative degradation. If the values of induction periods are calculated from the data of Table 1 using Eq. (7) for 25 °C, the resulting lengths of induction periods are 10, 25,000 and 8.3×10^7 years, respectively, for the compounds 1, 2 and 3. Hence, the values obtained by extrapolation outside the temperature range where the process occurred seem to be quite unrealistic. Elevated temperatures may introduce new types of reactions that do not reflect perfectly the situation at room temperature. This means that the function $f(\alpha)$ in Eq. (1) varies with temperature. A considerably more reasonable picture can be obtained if the ratios of the lengths of induction periods are considered. From the above figures it follows that the compounds 2 and 3 are by about three and six orders of magnitude, respectively, more stable than the compound 1. The order of thermooxidation stabilities is thus compound 1 < compound 2 < compound 3. Table 2 shows that the same order of stabilities was found by the classical method. The accelerated DSC tests cannot thus replace the classical stability program that implies long-time observations. It can provide, however, early alert to problems occurring at high temperatures and indicate the most favourable directions to pursue a successful formulation (Rodante et al., 2002b). The procedure presented here could thus be useful for a rapid screening of pharmaceuticals stability where the order of stabilities could be predicted with a reasonably high level of probability from the DSC accelerated tests. Since the complete DSC accelerated test takes about two working days, the saving of time could reach up to 99% compared to the classical stability tests. The main implicit assumption in the comparison of the stability of drugs employing the DSC accelerated test is that the same structural moieties are responsible both for the high-temperature thermooxidation and for the low-temperature degradation.

The method presented here belongs to the family of integral isoconversional methods. Unlike other

Table 2
Results of the classical stability tests for the compounds under study

Parameter	Limits	Storage time (months)				
		0	3	6	9	12
Compound 1: ambient conditions (25 ± 2 °C, RH 60 ± 5%)						
Appearance	White crystalline powder	Complies	Complies	Complies	Complies	No passed
Optical rotation (°)	−0.05 to 0.05	−0.05	−0.03	−0.04	−0.12	−0.15
Appearance of solution	Clear and colourless solution	Complies	Complies	Complies	Complies	No passed
Loss on drying (%)	2.5–3.5	2.84	2.84	2.82	2.91	2.89
Related substances sum of impurities (%)	NMT 1.0	0.04	0.18	0.58	0.64	0.75
Assay HPLC (%)	98.5–100.5	99.96	100.78	99.35	99.36	99.63
Compound 2: ambient conditions (25 ± 2 °C, RH 60 ± 5%)						
Appearance	White crystalline powder	Complies	Complies	Complies	Complies	Complies
Optical rotation (°)	−0.05 to 0.05	Complies	Complies	Complies	Complies	Complies
Appearance of solution	Clear and colourless solution	Complies	Complies	Complies	Complies	Complies
Loss on drying (%)	NMT 0.5	0.06	0.10	0.06	0.04	0.05
Related substances sum of impurities (%)	NMT 1.0	0.48	0.51	0.59	0.60	0.72
Assay titrimetry (%)	99.5–101.0	99.96	100.78	99.35	99.36	99.63
Compound 3: ambient conditions (25 ± 2 °C, RH 60 ± 5%)						
Appearance	White crystalline powder	Complies	Complies	Complies	Complies	Complies
Optical rotation (°)	−137 to −149	−145	−148	−143	−143	−145
Appearance of solution	Clear and colourless solution	Complies	Complies	Complies	Complies	Complies
Loss on drying (%)	NMT 7.0	4.56	4.73	4.89	5.77	5.43
Related substances sum of impurities (%)	NMT 2.0	0.44	0.39	0.58	0.43	0.48
Assay HPLC (%)	97.0–103.0	100.51	100.09	100.23	99.45	100.27

methods such as KAS and FWO (Sbirazzuoli et al., 1997), this one does not carry the inaccuracies associated with analytical approximations of the temperature integral given in Eq. (9). Further, the method represented by Eq. (9) does not use any transformation of the experimental data nor the mathematical simplification. The parameters A and B describing the length of induction period are determined directly from the comparison of experimental and calculated values of onset oxidation temperatures for a set of heating rates by the non-linear least squares method. The activation parameters are determined from the quantities measured directly, such as temperature and heating rate. The other methods use transformations such as $\ln\beta = f(1/T)$ or $\ln(\beta/T^2) = f(1/T)$. Any transformation of experimental data leads to the deformation of the distribution of errors, heteroskedasticity and a shift in the position of minima of the sum of squares between experimental and calculated values (Šimon et al., 2003). Thus, the other methods using the objective functions with transformed experimental data have to lead to biased values of parameters A and B comparing to the values using directly the source experimental data. The use of unbiased parameters should lead to a more reliable extrapolation of the results obtained at high temperatures to lower temperatures, which are of practical interest.

A DOS version of the program KINPAR for the calculation of the parameters A and B in Eq. (9) is available on request.

5. Conclusions

We believe that the rapid method for obtaining the parameters from non-isothermal differential scanning calorimetry measurements, based on the dependence of onset temperature of the oxidation peak on heating rate, could be suitable to be applied for screening the stability of pharmaceuticals. For a set of three compounds, the order of stabilities obtained by the method coincides with the order determined by classical stability tests. The method provides unbiased parameters describing the length of induction period, which should lead to a more reliable extrapolation of the results obtained at high temperatures to lower temperatures of practical interest.

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References

Burnham, L., Dollimore, D., Alexander, K., 2000. A rising temperature kinetic model to describe complex reaction kinetics of a drug: procainamide hydrochloride. Thermochim. Acta 357/358, 15–22.

Höhne, G., Hemminger, W., Flammersheim, H.J., 1996. Differential Scanning Calorimetry. Springer-Verlag, Berlin, Heidelberg, ISBN 3-540-59012-9.

ICH Harmonized Tripartite Guideline on Stability Testing of New Drug Substances and Products. Accepted by Steering Committee at step 4 of the ICH process on 27 October 1993 in Orlando, Florida (www.ich.org).

Nelder, J.A., Mead, R.A., 1965. A simplex method for function minimization. Comput. J. 7, 308–313.

Rodante, F., Catalani, G., Vecchio, S., 2002a. Kinetic analysis of single or multistep decomposition proceseses. J. Therm. Anal. Cal. 68, 689–713.

Rodante, F., Vecchio, S., Catalani, G., Tomassetti, M., 2001. Application of TA and kinetic study to compatibility and stability problems in some commercial drugs. J. Therm. Anal. Cal. 66, 155–178.

Rodante, F., Vecchio, S., Tomassetti, M., 2002b. Multi-step decomposition processes for some antibiotics. A kinetic study. Thermochim. Acta 394, 7–18.

Roy, S., Riga, A.T., Alexander, K.S., 2002. Experimental design aids the development of a differential scanning calorimetry standard test procedure for pharmaceuticals. Thermochim. Acta 392–393, 399–404.

Sbirazzuoli, N., Girault, Y., Elégant, L., 1997. Simulations for evaluation of kinetic methods in differential scanning calorimetry: part 3—peak maximum evolution methods and isoconversional methods. Thermochim. Acta 293, 25–37.

Schwarz, E., de Buhr, J., 1998. Pharmaceuticals—Collected Applications. Mettler-Toledo, Schwerzenbach.

Šimon, P., Kolman, L'., 2001. DSC study of oxidation induction periods. J. Therm. Anal. Cal. 64, 813–820.

Šimon, P., Kolman, L'., Niklová, I., Schmidt, Š., 2000. Analysis of the induction period of oxidation of edible oils by differential scanning calorimetry. J. Am. Oil Chem. Soc. 77, 639–642.

Šimon, P., Kučma, A., 1999. DSC analysis of the induction period in the vulcanisation of rubber compounds. J. Therm. Anal. Cal. 56, 1107–1113.

Šimon, P., Thomas, P.S., Okuliar, J., Ray, A., 2003. An incremental integral isoconversional method. Determination of activation parameters. J. Therm. Anal. Cal. 72, 867–874.