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# Use of isothermal heat conduction microcalorimetry to evaluate stability and excipient compatibility of a solid drug

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**Abstract**

Isothermal heat conduction microcalorimetry was used to evaluate chemical stability and excipient compatibility of a solid drug. Calorimetric data were compared with HPLC data in order to determine the origin of the thermal events. For the pure solid drug, heat flow time curves became constantly exothermic after 3–4 days in the temperature range from 60 to 80°C and were due to chemical decomposition. The activation energy calculated by both methods (microcalorimetry and HPLC) was $170 \pm 8$ kJ/mol (mean $\pm$ S.D.). A plot of the evolved heat $Q$ versus the amount of degraded drug showed a linear relationship. Binary mixtures and granules led to higher exothermic signals for microcrystalline cellulose (MCC), potato starch and lactose, and indicated lower stability. In the case of MCC and lactose, physical processes were superimposed and made the interpretation of the heat flow data difficult. In the case of the other systems the exothermic heat flow was in the same range as for the pure solid drug. Neither was physicochemical interaction detected, nor was the chemical decomposition accelerated by the excipients. By combining calorimetric and HPLC data the prediction of final shelf-life at room temperature was estimated. 

*Keywords:* Isothermal microcalorimetry; HPLC assays; Drug stability; Excipient compatibility; Solid state

## 1. Introduction

Stability and compatibility testing is of great importance during the development of drug products. Conventional stability testing includes prolonged storage at elevated temperatures and deter-

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mination of the undegraded or degraded fraction of drug as a function of time. The degradation rate under ambient conditions may then be estimated by extrapolation of the elevated temperature data using the Arrhenius equation. Present techniques are time consuming and, moreover, suffer from the uncertainty of the final shelf-life prediction due to temperature dependent inconsistencies in the Arrhenius relationship. Consequently it would be desirable to have a rapid and less complicated method to perform stability testing.

Chemical and physical processes are due to changes in free energy and the decomposition of a drug is usually accompanied by an evolution of heat (exothermic process). Accordingly, another approach to do stability testing is by isothermal microcalorimetry, an analytical method allowing determination of minute amounts of evolved or absorbed heat. In general, calorimetry produces two types of data: heat output $Q$ in J (thermodynamic data) and heat flow $\Phi = dQ/dt$ in W (kinetic data). For an exothermic process the heat flow value is positive ($\Phi > 0$), for an endothermic process the heat flow value is negative ($\Phi < 0$). An essential difference with conventional techniques is that a variable of a process is examined, whereas for chromatographic and spectroscopic methods a variable of a state is analysed. Thus an advantage for isothermal calorimetry is that there is no need to wait until the desired state is achieved, because the process which gets to this state is directly analysed. A further difference is the non-specifity of the method. All chemical and physical processes can contribute to heat flow signals. This may be considered disadvantageous since the interpretation with respect to the chemical decomposition of a drug is more difficult, on the other hand thermal events in pharmaceutical systems indicate that a process is occurring that may ultimately adversely influence the quality of the final drug product. Consequently, it is necessary to investigate the origin of the thermal events by additional specific assays.

Several authors have shown the applicability of the method (Angberg et al., 1988, 1990, 1993; Hansen et al., 1989; Pikal and Dellerman, 1989; Oliyai and Lindenbaum, 1991; Tan et al., 1992; Willson et al., 1995), however predominantly unstable drugs in solution systems have been investigated. The objective of the present study is to evaluate the stability and excipient compatibility of a solid drug. In particular, the question of interest is the origin of the thermal events.

## 2. Theory

From the reaction scheme $A + B \rightarrow C + D$ a general kinetic equation can be deduced, where $m$ and $n$ are constants characteristic of the reaction mechanism (Ng, 1975) and $k$ is the rate constant:

$$-\frac{dc(A)}{dt} = -\frac{dc(B)}{dt} = \frac{dc(C)}{dt} = \frac{dc(D)}{dt} = k[c(A)]^m[c(B)]^n \quad (1)$$

Since $c(A) = c_0(A) - c(C)$ and $c(B) = c_0(B) - c(C)$, this equation can be expressed as

$$\frac{dc(C)}{dt} = k[c_0(A) - c(C)]^m[c_0(B) - c(C)]^n \quad (1a)$$

where $c(C)$ may denote the concentration of the decomposition product of a drug. In order to simplify this and following equations $c(C)$ was substituted by $x$,

$$\frac{dx}{dt} = k[c_0(A) - x]^m[c_0(B) - x]^n \quad (2)$$

where $dx/dt$ is a function of $x$ depending on five parameters ($k$, $c_0(A)$, $m$, $c_0(B)$ and $n$), that are in most cases of unknown value. $c_0(A)$ may denote the initial concentration of reacting drug, which is not necessarily the total amount of drug present in the sample, since only a fraction of the drug may undergo decomposition.

As the estimation of these five parameters is not possible from the determination of $dx/dt$ and $x$ the following simplified model equation may be used:

$$\frac{dx}{dt} = k^*[c_0(A) - x]^v \quad (3)$$

where $k^*$ and $v$ are functions of the other parameters. Eq. (3) is a suitable basis to describe the kinetic of a chemical reaction, i.e. a drug decomposition.

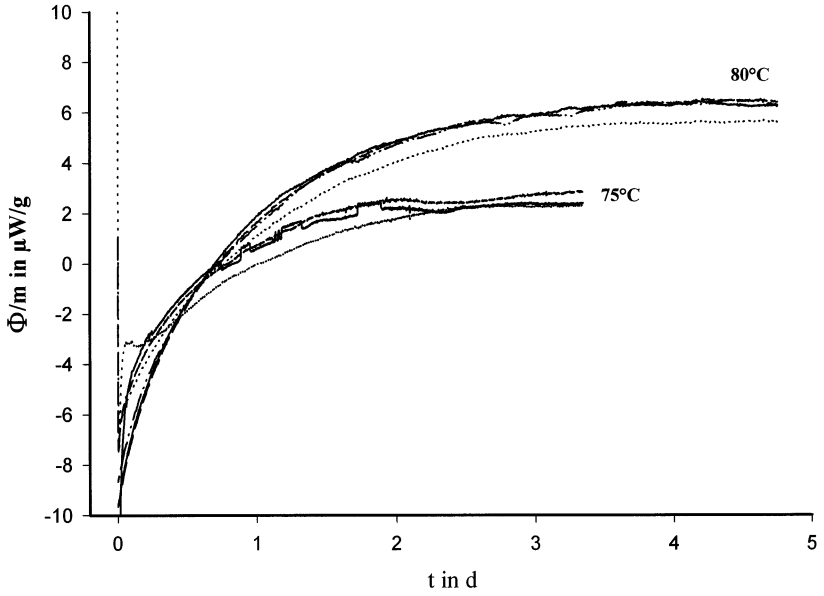


Fig. 1. Heat flow time curves of S 95 5740 in the solid state at 80°C ($n = 4$) and 75°C ($n = 3$). During the first 20 h endothermic processes ($\Phi < 0$) prevail. After 3–4 days heat flows are exothermic ($\Phi > 0$) and fairly constant.

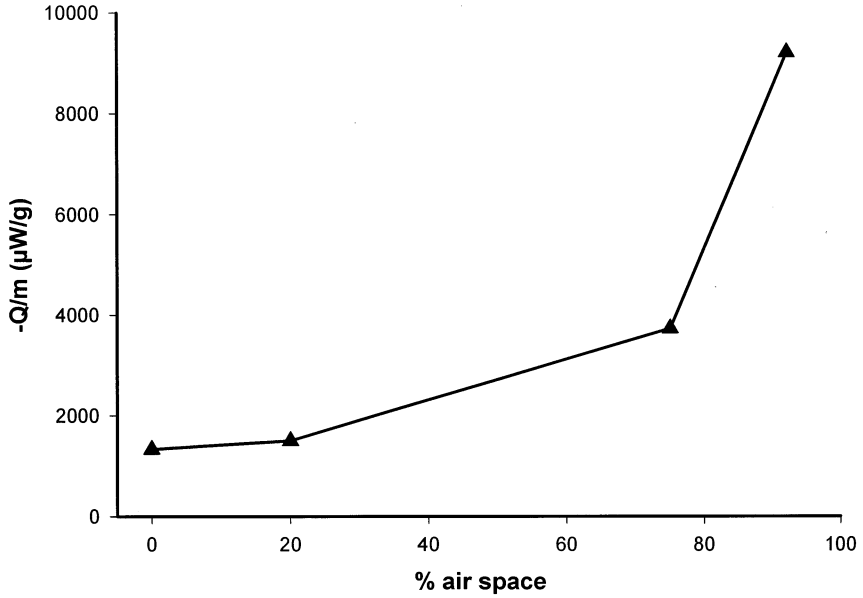


Fig. 2. Plot of the endothermic heat versus the air space within the sample vial at 80°C for S 95 5740.

The decomposition of a drug is usually combined with an exothermic enthalpy of reaction $\Delta_R H$, which is the sum of the endothermic bond breaking and the exothermic bond forming reaction.

The amount of evolved heat, $Q$, is directly proportional to the concentration of the decomposition product, $x$, and thus the heat flow is directly proportional to the decomposition rate $dx/dt$ (constant of proportionality is $\Delta_R H$):

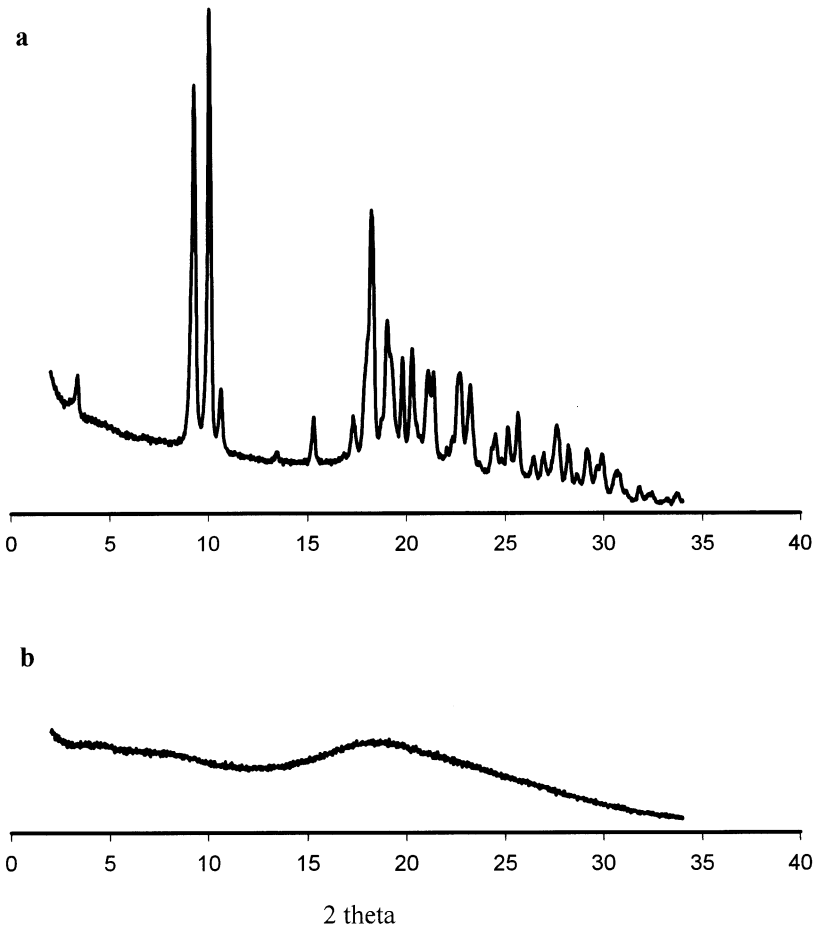


Fig. 3. X-ray powder diffraction patterns for (a) untreated S 95 5740 and (b) S 95 5740 after incubation at 80°C for 4 days.

$$Q = \Delta_R H x \tag{4}$$

$$\Phi = \frac{dQ}{dt} = \Delta_R H \frac{dx}{dt} \tag{5}$$

Substitution of Eq. (4) and Eq. (5) into Eq. (3) yields $\Phi$ as a function of $Q$, as given by Eq. (6):

$$\Phi = \Delta_R H k^* \left[ c_0(A) - \frac{Q}{\Delta_R H} \right]^v \tag{6}$$

Provided that $d\Phi/dQ$ is sufficiently high, information about $\Delta_R H$, $k^*$ and $v$ may be obtained by plotting $\phi$ versus $Q$ and applying a non-linear regression procedure on this data.

If $v = 0$, a zero order reaction is obtained, and a plot of $\Phi$ versus $Q$ yields a constant:

$$\Phi = \Delta_R H k^* = \text{constant} \tag{7}$$

if $v = 1$, a first order reaction is obtained, and $\Phi$ will decrease linearly as a function of $Q$:

$$\Phi = \Delta_R H k^* c_0(A) - k^* Q \tag{8}$$

a second order reaction is obtained from Eq. (6) when $v = 2$,

$$\Phi = \Delta_R H k^* c_0^2(A) - 2k^* c_0(A) Q + \frac{k^*}{\Delta_R H} Q^2 \tag{9}$$

The temperature dependence of the heat flow can be derived from the Arrhenius equation

$$k^* = C \cdot \exp\left( - \frac{E_A}{RT} \right) \tag{10}$$

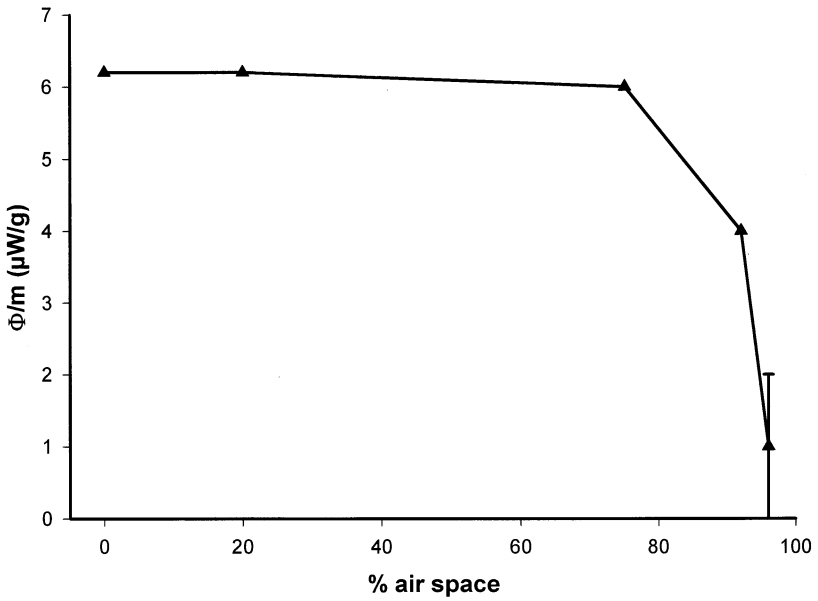


Fig. 4. Plot of the exothermic heat flow caused by chemical decomposition versus the air space within the sample vial at 80°C for S 95 5740.

where $C$ is a constant, $E_A$ is the activation energy, $R$ is the gas constant and $T$ is the absolute temperature. Entering $\Phi_0$ (the initial heat flow) and thus $Q = 0$ into Eq. (6) yields

$$\Phi_0 = \Delta_R H k^* c_0^v \tag{11}$$

and substitution of Eq. (10) into Eq. (11) yields

$$\Phi_0 = \Delta_R H c_0^v C \exp\left( - \frac{E_A}{RT} \right) \tag{12}$$

which can also be expressed as

$$\ln \Phi_0 = \ln (\Delta_R H c_0^v C) - \frac{E_A}{RT} \tag{13}$$

Hence a plot of $\ln \Phi_0$ versus the reciprocal of the absolute temperature $T^{-1}$ ($K^{-1}$) may result in a linear relationship with the slope of $-E_A/R$.

## 3. Materials and methods

### 3.1. Materials

The HMR compound S 95 5740, (*S*)-(3-(2-(4-(*S*)-(4-(amino-imino-methyl)-phenyl)-4-methyl-2,5 - dioxo - imidazolidin - 1 - yl) - acetylamino)) - 3-phenyl-propionic acid ethylester, acetate, in the solid state was used as a model drug, which undergoes hydrolysis. As excipients potato starch (Caesar and Loretz, Hilden, Germany), α-lactose-monohydrate (Meggle, Reitmehring, Germany), microcrystalline cellulose (MCC, Avicel PH101; Pharma Transsanaq, Basel, Switzerland), talcum (Bassermann, Mannheim, Germany), calcium hydrogene phosphate anhydrous extra fine powder (Merck, Darmstadt, Germany) and colloidal silica (Aerosil 200; Degussa, Frankfurt, Germany) were used. For the HPLC assays, acetonitrile (Merck, Darmstadt, Germany, HPLC grade) and ammonium acetate (Fluka Chemie, Neu-Ulm, Germany) were used.

### 3.2. Preparation of samples

Binary physical mixtures were prepared by mixing equal weights of S 95 5740 with each of the aforementioned excipients using a mortar with pestle for approximately 10 min. Granules were prepared by compressing the mixtures on an excenter press (EK 0 Korsch, Berlin, Germany) to biplan tablets (∅ 10 mm) and slugging them through a 1-mm sieve.

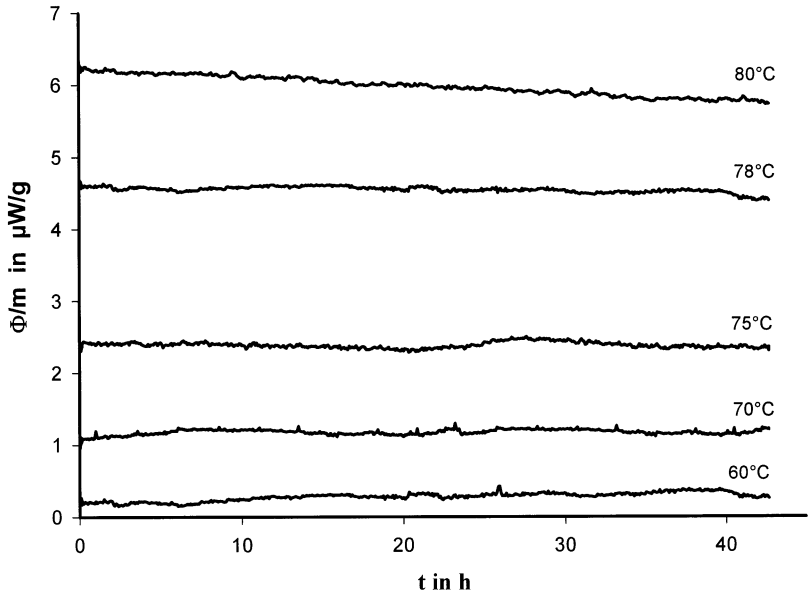


Fig. 5. Exothermic heat flow time curves of S 95 5740 after completion of endothermic events in the temperature range between 60° and 80°C.

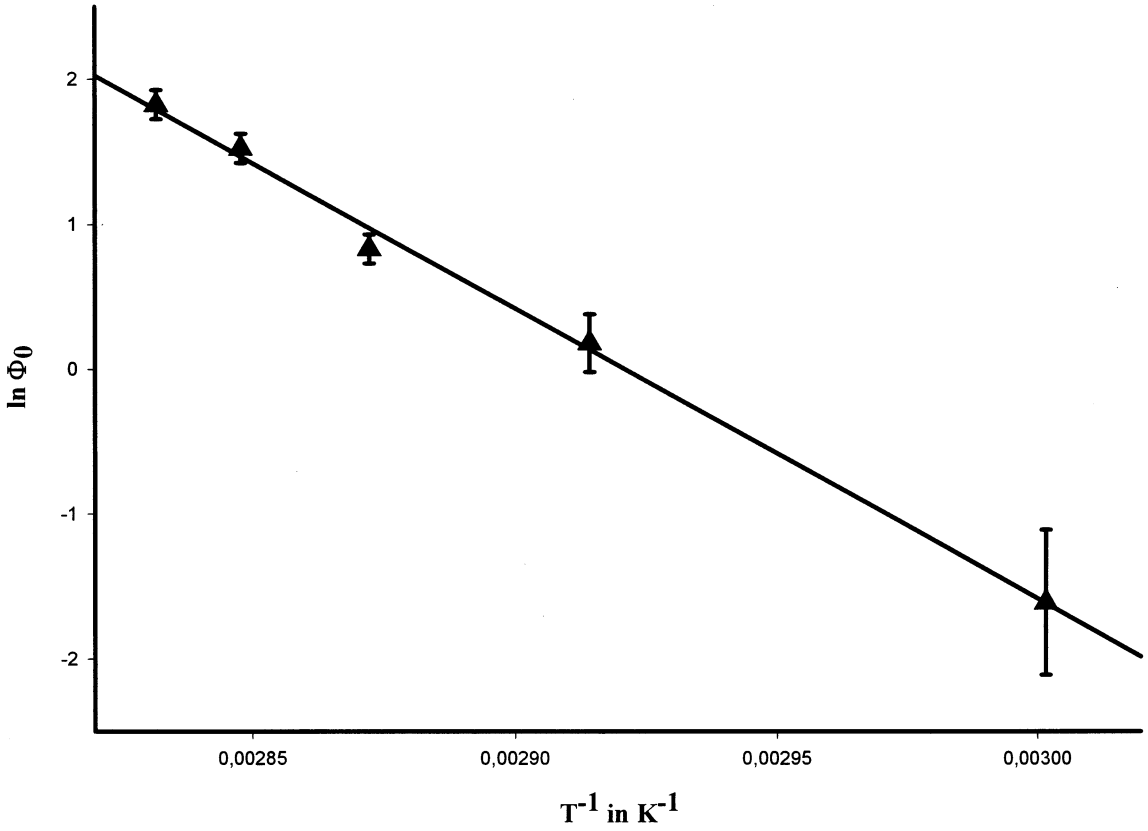


Fig. 6. Arrhenius plot for decomposition of S 95 5740 determined by microcalorimetry. The initial heat flow is obtained by extrapolation. Error bars represent standard deviation for the mean of four determinations of the extrapolated initial heat flow; $y = 58.5 - 20000x$, $R^2 = 0.996$; The activation energy calculated from the slope amounted to $166 \pm 6$ (S.E.) kJ/mol.

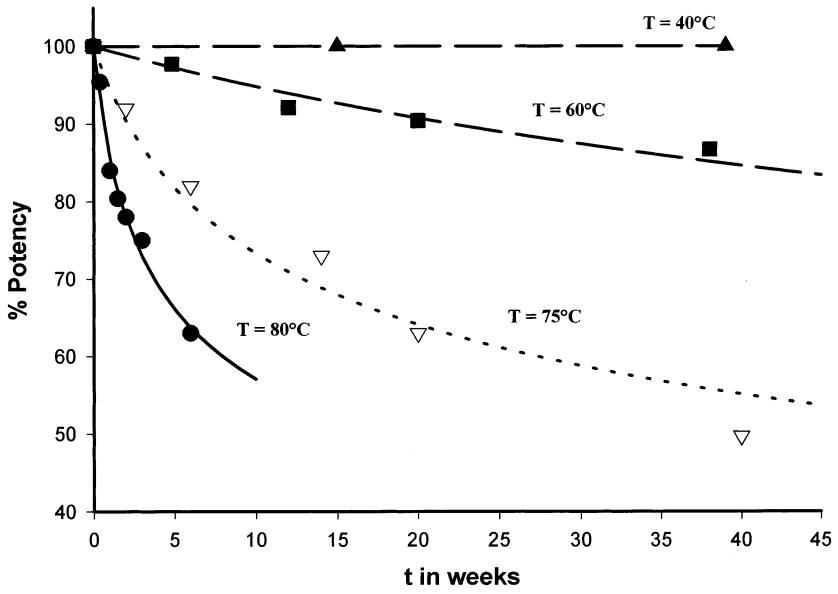


Fig. 7. Drug decomposition for S 95 5740 in the solid state determined by HPLC assays. The lines are obtained by non-linear regression. The model function used is $-\mathrm{d}c/\mathrm{d}t = k^* c^v$. Parameters, $k^*$, $v$, are given in Table 1.

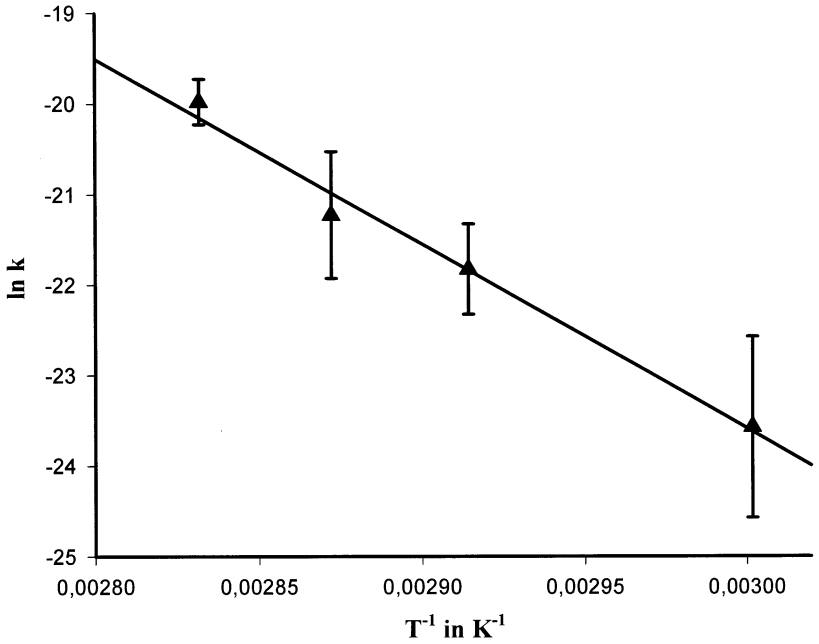


Fig. 8. Arrhenius plot for decomposition of S 95 5740 determined by HPLC. Error bars represent the standard error of $\ln k$ determined by non-linear regression. $y = 37.6 - 20409x$, $R^2 = 0.986$; the activation energy was calculated by the slope ($170 \pm 8$ (S.E.) kJ/mol).

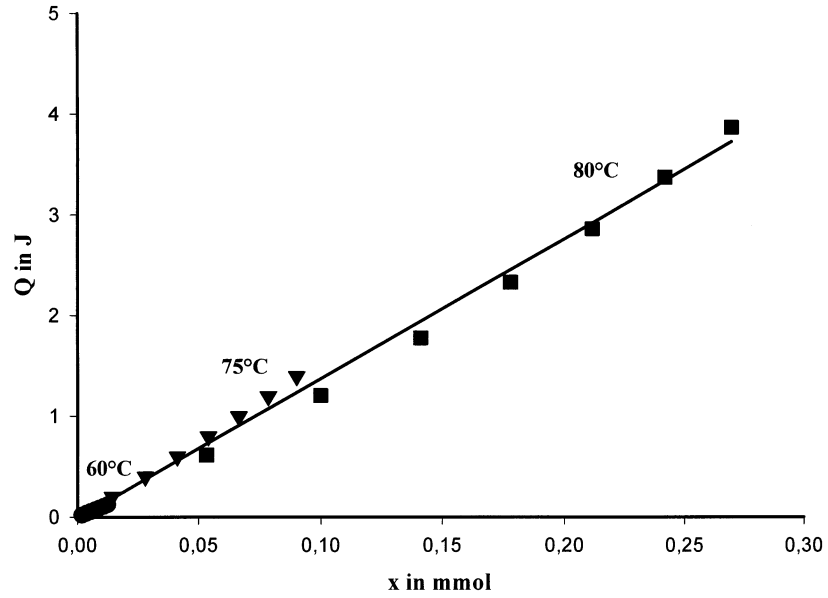


Fig. 9. Evolved heat plotted versus the amount of degraded drug (S 95 5740 in the solid state) for the temperatures 80, 75 and 60°C. The regression line is obtained using all data on plot: $y = 14x$, $R^2 = 0.995$. The slope represents the enthalpy change, 14 kJ/mol.

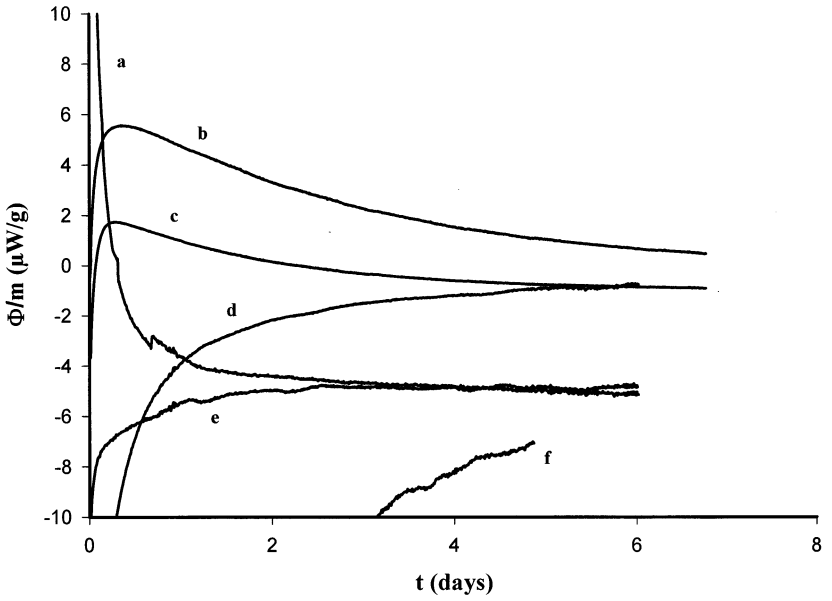


Fig. 10. Heat flow time curves of excipients at 80°C. (a) Potato-starch; (b) lactose; (c) calcium hydrogene phosphate; (d) talcum; (e) MCC; (f) colloidal silica.

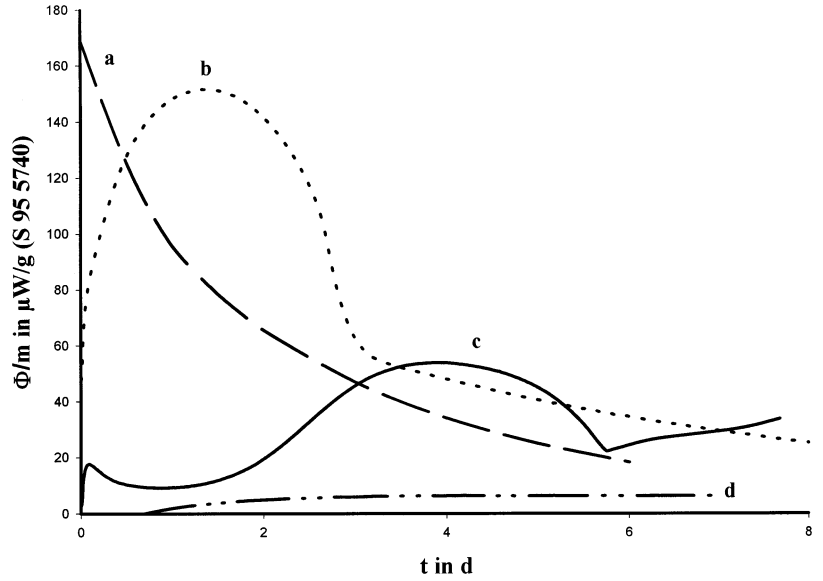


Fig. 11. Heat flow time curves of binary mixtures 1:1 at 80°C. (a) S 95 5740/potato starch; (b) S 95 5740/MCC; (c) S 95 5740/lactose; (d) S 95 5740, S 95 5740/talcum, S 95 5740/$CaHPO_4$, S 95 5740/colloidal silica.

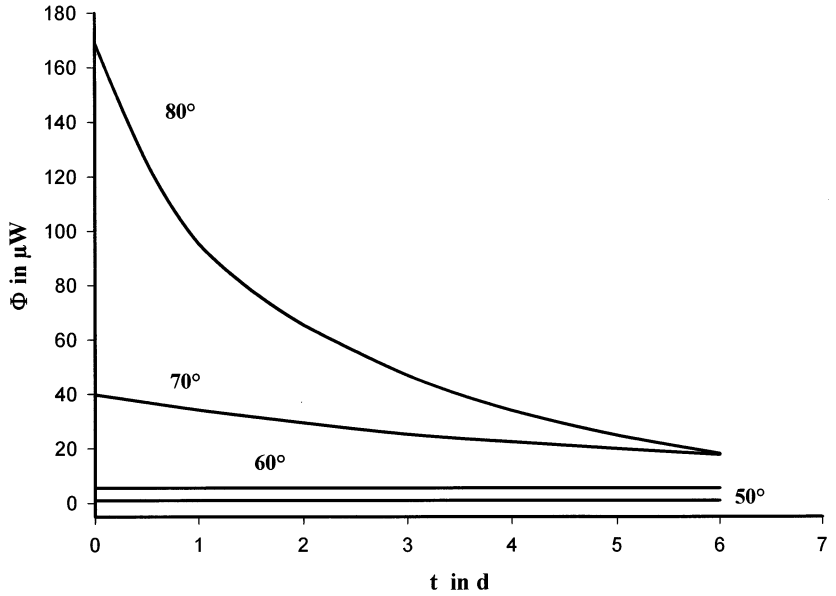


Fig. 12. Heat flow time curves of S 95 5740/starch mixture 1:1. Endothermic events in the initial phase are not shown. Curves are extrapolated to $t_0$.

### 3.3. Isothermal heat-conduction microcalorimetry

The calorimeter used in these studies was the 2277 Thermal Activity Monitor (TAM) (Thermometric, Sweden). The design principle was previously described in detail (Suurkuusk and Wadsö, 1982; Angberg et al., 1988). The system consisted of a 25-l water bath with a temperature constance of $< \pm 2 \times 10^{-4}$ K. Four calorimeter units were installed and ran simultaneously. Each unit could

Table 1
Stability data of S 95 5740 determined by HPLC assays

| | $v$ | $k_{80}$ | $k_{75}$ | $k_{70}$ | $k_{60}$ | $k_{50}$ | $k_{40}$ | $E_A$ | $k_{25est}$ | % dg/a |
|---|---|---|---|---|---|---|---|---|---|---|
| S 95 | 5 | 2.1e-9 | 6.1e-10 | 3.3e-10 | 5.8e-11 | – | – | 170 | 1.6e-14 | 0.01 |
| S 95/starch | 2 | 3.3e-3 | – | 6.5e-4 | 1.1e-4 | – | 3.3e-6 | 159 | 1.5e-7 | 0.5 |
| S 95/starch gran | 2 | 2.8e-3 | – | 6.6e-4 | 1.3e-4 | – | – | 147 | 2.3e-7 | 0.8 |
| S 95/MCC | 2 | 1.6e-3 | – | 2.1e-4 | 3.2e-5 | 3.6e-6 | – | 191 | 9.2e-9 | 0.03 |
| S 95/MCC gran | 2 | 1.6e-3 | – | 2.2e-4 | 3.6e-5 | – | – | 185 | 1.3e-8 | 0.05 |
| S95/Mg-stearate | 5 | 9.5e-9 | – | 1.7e-9 | 5.4e-10 | 5.0e-11 | – | 160 | 2.7e-13 | 0.14 |
| S 95/$CaHPO_4$ | 5 | 2.4e-9 | – | 3.7e-10 | 3.0e-11 | 1.0e-11 | – | 179 | 2.6e-14 | 0.01 |
| S 95/lactose | 0 | 1.56 | – | 0.086 | 0.024 | 0.003 | – | 189 | 7.1e-6 | 0.003 |
| S 95/lactose gran | 0 | 3.91 | – | 0.70 | 0.092 | – | – | 183 | 4.0e-5 | 0.015 |
| S 95/talcum | 5 | 1.9e-9 | – | 4.4e-10 | 4.9e-11 | – | – | 179 | 3.0e-14 | 0.02 |

$v$ and $k^*$ are obtained by non-linear regression procedure. $E_A$ (kJ/mol) is calculated from the Arrhenius-plot ($\ln k$ vs $1/T$). $k_{25est}$ is estimated by extrapolation. % dg/a constitutes the estimated annual degradation at 25°C. The error of $k^*$ and $E_A$ may be up to 20% due to temperature fluctuation of $\pm 2$°C, in the temperature ovens.

register the difference in heat flow ($\Phi$ in $\mu$W) respectively in heat output ($Q$ in J) between a sample and a reference as a function of time. The sensitivity of the system reached 0.1 $\mu$W. The short-term baseline noise was $\pm 0.05$ $\mu$W, baseline-drift was $< 0.2$ $\mu$W/24 h. In the present study, 3-ml glass vials were used that were tightly sealed with a teflon-coated butyl rubber disc and an aluminium cap. The volume of the powder sample in the vial was above 80% for limiting the air space below 20%. The samples were assayed in quadruplet in the temperature range between 60 and 80°C. In addition, different air spaces were employed by placing several amounts of powder in the vial in order to examine their influence on endothermic processes: 1.25 g S 95 5740 ($\equiv$ 0% air space), 1 g ($\equiv$ 20% air space), 0.3 g ($\equiv$ 75% air space), 0.1 g ($\equiv$ 92% air space). Before lowering the vessels in the measurement position, which was in the middle of the water bath, they had to reach the corresponding temperature. For that the vessels were left in the equilibrium position for 1 h. After that they were slowly lowered in the measurement position between two thermopiles through which the heat was transported and detected. Empty glass vials were used as reference to ensure thermal inertness. The monitoring of the heat flow signal was then started by the computer program DIGITAM (Thermometric, Sweden) and this time point was referred to as $t = 1$ h. Before each experiment an electrical calibration of 10 or 100 $\mu$W respectively was performed depending on the expected heat.

### 3.4. HPLC

The systems studied were also examined by HPLC after storage in controlled temperature ovens. The samples were placed in 0.3-ml glass vials that were equally tightly sealed with teflon coated butyl rubber discs and aluminium caps. The volume of the powder sample in the vial was also above 80% as in the me glass vials used for the calorimetric assays. The drug was stored at 80, 75, 70, 60 and 40°C. The mixtures and granules were stored at 80, 70, 60, 50 and 40°C. The vials were removed after different time intervals and stored at 5°C until the HPLC analysis was performed. The HPLC assays were carried out using a Merck-Hitachi chromatograph (L-6220 Intelligent Pump, AS 2000 A Autosampler, L-4500 Diode Array Detector, D-6000 A Interface, Merck-Hitachi, Darmstadt, Germany). A $C_{18}$ reversed phase column (LiChrospher 60 Select B RP 18, $125 \times 4$ mm, 5 $\mu$m; Merck, Darmstadt Germany) and a guard column (LiChrospher 60 RP-select B, 5 $\mu$m; Merck, Darmstadt, Germany) were used. The mobile phase consisted of two solutions; solution A: aqueous ammonium acetate solution 0.1%; solution B: 80% (v/v) acetonitrile, 20% (v/v) aqueous ammonium acetate solution 0.1%. Solution A + solution B (90 + 10) were used

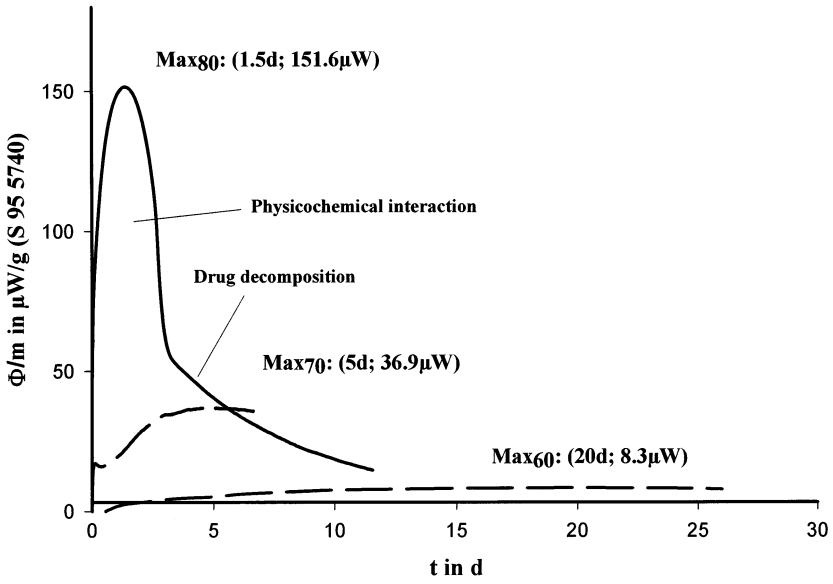


Fig. 13. Heat flow time curves of S 95 5740/MCC mixture 1:1 at 80, 70 and 60°C. A physicochemical interaction yields an exothermic peak, which lasted for 3 days at 80°C, 10 days at 70°C and approximately 50 days at 60°C. After that peak the drug decomposition yields a constantly decreasing heat flow, that is shown for 80°C.

in the time intervals 0–5 min and 16–20 min and solution A + solution B (50 + 50) in the time interval 6–15 min at a constant flow rate of 1 ml/min. The peak obtained by UV detection at 230 nm was well separated from those of the decomposition products and was used for quantitative determination using pure drug as external standard. Calculation of the peak area was performed online by a computer program (DAD system manager Merck-Hitachi model D-6500) connected to the UV detector. The samples were weighed into 25-ml volumetric flasks and filled up with solution B. From this solution 25 $\mu$l was injected. The assay accuracy was better than $\pm 1\%$ (S.E.M.) for the pure drug and better than $\pm 5\%$ (S.E.M.) for the binary systems.

### 3.5. HPLC data treatment

Stability data treatment was performed by the Sigma-Plot graph fitting package (SigmaPlot version 3.0, Jandel Scientific Software, Erkrath, Germany). Eq. (3) in the modified form $-\frac{dc(A)}{dt} = k^*[c(A)]^v$ was applied as a model function, and then a non-linear regression procedure using the Marquardt-Levenberg algorithm (Marquardt, 1963) was carried out to estimate the values of $k^*$ and $v$. The natural logarithm of $k^*$ was then plotted versus the reciprocal of the absolute temperature $T^{-1}$ ($K^{-1}$) to determine the activation energy in order to predict the room temperature stability.

### 3.6. X-ray powder diffraction

X-ray powder diffraction was determined before and after calorimetric runs at room temperature. A STOE Transmission X-ray powder diffractometer (STOE and CIE, Darmstadt, Germany) was used combining a focused $K\alpha_1$ incident beam from a Germanium monochromator with linear and curved position sensitive detectors (PSDs). The samples were scanned in steps of 0.02° from 0 to 35° ($2\theta$).

Table 2
Temperature- and time-dependence of the physicochemical interaction between S 95 5740 and MCC

| $T$ (°C) | $T^{-1}$ ($K^{-1}*10^{-3}$) | $\Phi_{max}$ ($\mu$W/g) | ln $\Phi_{max}$ | $t_{max}$ (days) | ln $t$ | $Q_{spec}$ (J/g) |
|---|---|---|---|---|---|---|
| 80 | 2.83 | 151.6 | 5.02 | 1.5 | 0.41 | 4.1 |
| 70 | 2.91 | 36.9 | 3.61 | 5 | 1.61 | 5.2 |
| 60 | 3.00 | 8.3 | 1.90 | 20 | 3.00 | 4.6 |

## 4. Results and discussion

The heat flow time curves were reproducible within normal methodical and statistical fluctuation limits. During the first 20 h endothermic processes prevailed. These processes were due to physical events (see below). After 3–4 days constant exothermic heat flows were obtained which were confirmed by HPLC data to be due to chemical degradation by hydrolysis, $\Phi_{75°} = 2.3 \pm 0.17$ $\mu$W/g (mean $\pm$ S.D., $n = 4$); $\Phi_{80°} = 6.2 \pm 0.36$ $\mu$W/g (mean $\pm$ S.D., $n = 4$) (Fig. 1). Since the heat flow values were low and fairly constant, no estimation of the rate law was possible. The heat flow at 80°C decreased very slightly after 5 days. The extent of the endothermic processes was obtained by extrapolation of the constant exothermic heat flow to $t_0$ and subtraction from the total heat flow.

### 4.1. Influence of the air space in the sample on endothermic processes

As endothermic processes can be due to drying and since S 95 5740 contains approximately 3% water, the endothermic events were examined with respect to the air space present in the vials. For this purpose, the derived endothermic specific heats $\Phi/m$ were plotted against the volume of the air space (Fig. 2). The endothermic heat increased with increasing air space. Hence it was obvious that drying processes occurred during the first days. Since an endothermic event also occurred at 0% air space a further additional process was apparent. X-ray diffraction patterns showed that the drug lost its crystallinity within 4 days at 80°C (Fig. 3). This might be the cause of this endothermic event, but also moisture redistribution within the powder could contribute to the endothermic signal.

Table 3
Enthalpy change of the decomposition of S 95 5740 in various mixtures (see text) calculated from a plot of the evolved heat versus the amount of degraded drug

| | $\Delta_R H$ (kJ/mol) |
|---|---|
| S 95 5740 | 15 |
| S 95 5740/starch | 25 |
| S 95 5740/MCC | 22[a] |
| S 95 5740/talcum | 19 |
| S 95 5740/$CaHPO_4$ | 16 |

[a] Only the heat flow of drug decomposition is taken into consideration.

Concerning the exothermic heat flow of chemical degradation, which was obtained from the constant heat flow values after completion of the endothermic events, it was obvious that chemical hydrolysis decreased significantly if the air space was higher than 75% (Fig. 4). This was in accordance with the time course and the magnitude of the heat of drying: because of drying the water content in the powder decreased. This decrease was higher with larger air spaces and accordingly the chemical degradation rate was reduced. Consequently, the method of storage and in particular the existence and volume of the air space in the sample vessel has an important impact on the interpretation of the stability data.

### 4.2. Temperature dependence of the exothermic heat flow and comparison with HPLC data

Heat flow time curves after completion of endothermic events are shown in Fig. 5 in the 60–80°C temperature range. Below 60°C no heat flow signal was detectable. Applying Eq. (13) to these values, a plot of ln $\Phi_0$ versus $1/T$ yielded a straight line: $\ln \Phi_0 = 58.5 - 20000\ 1/T$ with a

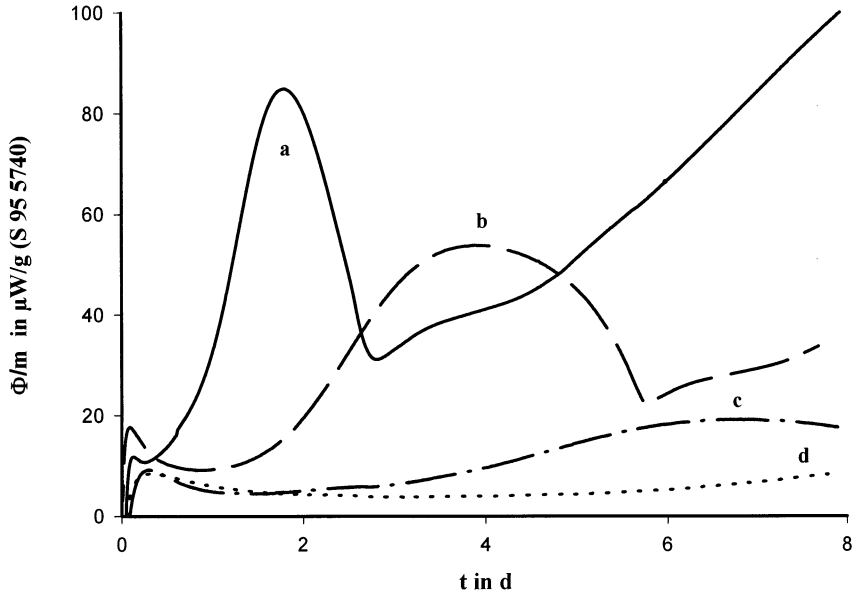


Fig. 14. Heat flow time curves of S 95 5740/lactose at 80° and 70°C. (a) Granules 1:1 80°C; (b) mixture 1:1 80°C; (c) granules 1:1 70°C; (d) mixture 1:1 70°C.

slope of $-E_A/R$ (Fig. 6). The activation energy calculated from the slope was $166 \pm 6$ kJ/mol and was in agreement with the activation energy calculated by the HPLC data ($170 \pm 8$ kJ/mol) (Figs. 7 and 8). A plot of the evolved heat $Q$ versus the amount of degraded drug in mmol (HPLC data) showed a linear relationship and revealed that the heat flow signals were due to chemical decomposition. The slope of the line constitutes the enthalpy of reaction which amounted to 14 kJ/mol (Fig. 9).

### 4.3. Heat flow of excipients

Thermal events in multiple component systems can either be due to the single components or due to interactions between two or more components. In order to evaluate the heat flow of heterogeneous systems, e.g. powder mixtures or dosage forms like granules or tablets, it is necessary to examine the heat flow of each single component. In the present study heat flow time curves of each of the aforementioned excipients were monitored between 50 and 80°C. Fig. 10 shows heat flow time curves at 80°C: talcum, colloidal silica and microcrystalline cellulose showed endothermic heat flows that might be caused by moisture redistribution. Lactose showed a permanent exothermic heat flow and calcium hydrogene phosphate exhibited an exothermic heat flow within the first 2 days and after that an endothermic heat flow. The values did not exceed 5 $\mu$W/g. The heat flow time curve of potato starch was apparently caused by two processes: a high exothermic heat flow in the initial phase which changed to an endothermic after 8 h to become a constant signal of $-5\mu$W/g. As the water content in the starch was approximately 10%, the signal was likely to be either caused by the starch forming a paste or by water redistribution processes.

The thermal events of the pure excipients were low, but have to be considered, since they diminish the sensitivity towards detection of low amounts of drug decomposition in heterogeneous systems. In further investigations with the binary systems, the heat flow caused by the pure excipients was substracted from that of the binary systems, assuming that these thermal events attributable to the excipients alone also occur within heterogeneous systems.

### 4.4. Compatibility with the excipients

Fig. 11 shows heat flow time curves of physical mixtures (1:1) of drug with the excipients at 80°C. The heat flow of the mixtures with talcum, $CaHPO_4$, and colloidal silica (Aerosil 200) was in the same range as the heat flow of the pure solid drug. In contrast, the mixtures with lactose, microcrystalline cellulose and potato starch showed much higher heat flow signals.

For the system S 95 5740/potato starch the heat flow time curve could be described by a second order reaction (Eq. (9)) (Fig. 12). This result was in agreement with the rate law determined by HPLC data (Eq. (3)) for $v = 2$ (Table 1). The initial heat flow $\Phi_0$ showed the same temperature dependence as the pure drug. Also, the activation energy calculated by both methods, microcalorimetry as well as HPLC, was the same for this mixture and the pure drug and amounted to 160 kJ/mol. Furthermore, a linear relationship between the evolved heat $Q$ and the amount of degraded drug was evident. Therefore, it can be concluded that the heat flow time curves in this binary system were due to chemical degradation of the pure drug alone. The decomposition at room temperature was estimated at 0.5% per year and the decomposition at 40°C at 10% per year.

For the system S 95 5740/MCC the heat flow at 80°C initially increased to a maximum of 152 $\mu$W/g S 95 5740 after 1.5 days, then fell sharply to 60 $\mu$W/g S 95 5740 after 3.5 days and finally decreased slowly. The HPLC data confirmed that two superimposed processes occurred. One is the chemical decomposition of the drug that yielded a constantly descending heat flow and the other is a physico-chemical interaction that yielded an exothermic peak lasting for 3 days at 80°C, 10 days at 70°C and approximately 50 days at 60°C (Fig. 13). The total heat ($\approx 4.6$ J/g) of this physico-chemical interaction did not change with the different temperatures. Table 2 shows the temperature and time dependence of this process. This physico-chemical interaction also occurred when the drug and the excipient were separately filled into the sample vial and not mixed. However, when dried MCC was used, this physico-chemical interaction did not take place. Consequently, this interaction can be attributed to water redistribution from the MCC to the drug.

For the system S 95 5740/lactose, an exothermic peak also was apparent with $\Phi_{max} = 54$ $\mu$W/g (S 95 5740), $t_{max} = 4$ days, and $Q = 7.7$ J/g. After completion of this peak at 6 days, the heat flow increased constantly. This exothermic peak again can be attributed to water redistribution from the lactose to the drug. The increasing heat flow indicated an autocatalytic event that cannot be explained by chemical decomposition of the drug. On the one hand the evolved heat was too high ($> 65$ kJ/mol), on the other hand HPLC data revealed that the chemical decomposition occurred with a constant reaction rate (zero-order reaction). The autocatalytic event that was also apparent by a brown coloration was probably caused by a chemical reaction between lactose and the drug or the decomposition product.

For the mixtures of talcum, calcium hydrogene phosphate and colloidal silica, respectively, with the drug the heat flow became constantly exothermic after 3–4 days and was due to chemical decomposition of the drug. Neither a physico-chemical interaction between the drug and the excipients was detectable, nor was the chemical decomposition accelerated by the excipients. This was in agreement with the HPLC data. Table 3 shows the enthalpy change calculated from a plot of the evolved heat versus the amount of degraded drug.

### 4.5. Influence of compression on heat flow and decomposition

Dry granules were examined by the same procedure as the mixtures in order to determine the influence of compression on the aforementioned physical or chemical processes. With the systems S 95 5740/potato starch, S 95 5740/MCC and S 95 5740/talcum the heat flow time curves and decomposition rates of the granules showed the same time course as with the mixtures. In the case of the system S 95 5740/lactose, however, a significant difference was apparent (Fig. 14). With the granules the physicochemical interaction as well as the chemical decomposition were accelerated. This acceleration might be explained by an in-

crease of contact area between drug and excipient resulting from the compression. For the other systems the compression did not influence the chemical decomposition.

## 5. Conclusion

This investigation demonstrates the application of isothermal heat-conduction microcalorimetry in pharmaceutical stability and excipient compatibility studies. A general advantage of the method is that no further preparation of the sample is necessary, and, consequently, formulated dosage forms can be directly investigated. Moreover, the technique is non-invasive and the samples can be used for further assays.

The results of this study clearly show that chemical decomposition of a drug exhibits heat flow time curves that are detectable by microcalorimetry after a few days. However, it is important to confirm the calorimetric data by other analytical assay. Calorimetry is a non-specific technique and thus not all signals correspond to chemical decomposition of the investigated drug. The thermal events in complex systems (e.g. solid dosage forms) can be due to processes occurring in parallel such as moisture redistribution, drying, changes in crystallinity, melting, etc. This study shows that these physical events occur especially in the initial phase. Hence monitoring a signal over at least 1 week is recommended in order to determine the origin of the thermal event. The heat flow of excipients at elevated temperatures is low, but nevertheless diminishes the sensitivity to determine drug decomposition in heterogeneous systems.

Experimental temperatures close to ambient could not be employed in this study, since the enthalpy change was not sufficiently large. To determine drug decomposition, the sensitivity depends on the enthalpy change, the reaction rate and the amount of reacting sample. For most drug decompositions, microcalorimetry is not sensitive enough to detect heat flow signals at room temperature. In order to predict the final shelf-life at room temperature at least one HPLC assay is necessary as in most cases the value of the enthalpy change is unknown and cannot be estimated from low heat flow values alone.

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