Journal of Thermal Analysis, Vol. 33. (1988) 37–45

APPLIED CHEMICAL THERMODYNAMICS AND KINETICS ON PHARMACEUTICAL COMPOUNDS

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The important role of thermoanalytical methods in the field of pharmaceutical and galenic research is outlined. The thermodynamic stability of polymorphic forms of a substance is discussed.

The development of a pharmaceutical compound or a dosage form is a long-range task affording normally a period of more than ten years. Many research and development steps are necessary from the first step the synthesis of a pharmaceutical compound for which a certain therapeutic effect can be expected to the final step of the galenic formulation.

A second development pathway gains to-day a marked importance in creating new dosage forms for already known pharmaceutical compounds. The whole field of the galenic development changed in the last years to a major research and development task. Of course the question may be put foreward what are the rational facts causing such a shift of emphasis. First of all many

John Wiley & Sons, Limited, Chichester
Akadémiai Kiadó, Budapest

objectives of research are not completely new, however, basic ideas are often not properly defined and as a consequence a realization is impossible. The basis of pharmaceutical research was formulated by Ehrlich, Nobel prize winner for medicine in 1908. He stated with "Corpera non agunt nisi fixata" or translated "substances act only when they are linked" the first definition of the receptor theory [1]. The impact of this theory at the time of Ehrlich was very limited. It was not until the 1960's that the observation of the decrease of the blood sugar level by the action of the insulin could be attributed to an insulin-receptor-complex formation.

A concept for the application of pharmaceutical compounds namely the so-called site-specific drug delivery has been generated on the basis of the receptor theory. The goal of this pharmaceutical approach is: to create a pharmaceutical formulation in such a way, to get in the human body a single binding process of the active molecules on a selected receptor site. The benefits of such a drug delivery are an extremely high efficacy of the active substance and also a minimalization of adverse reactions. The achievement of such an ideal site-specific drug delivery is certainely a question of a broad future research.

In reality any binding of the active molecule at the receptor site is only the final step of the administration. Depending on the dosage form and also on the up-take pathway for a given drug many different physical and physico-chemical processes are involved such as dissolution, diffusion and flow transport, distribution between different body compartments, complex formation and adsorption. Furthermore processes of chemical degradation and binding on unspecific sites are also occurring. All these different processes of drug delivery are depending on the active molecule and furthermore may be influenced by a given dosage form and also by the selected administration pathway.

Not only the many different chemical and physical possibilities of the administration of a pharmaceutical compound must be considered carefully, but also the chemical production and galenic formulation as well as the conditions during these procedures. On the other hand the storage and transport conditions are also important. The development of a pharmaceutical compound and of the appropriate galenic formulation is by all these facts a highly sophisticated task involving a great many of analytical, chemical and physico-chemical methods. Chemical thermodynamics and kinetics with all applied thermoanalytical methods play an important role in different aspects of the development tasks for a pharmaceutical compound as well as for a dosage form. The possible applications of all these thermoanalytical methods in the area of pharmaceutical and galenic research and development

work are far from being exhausted. Broader applications of the existing instrumentation especially in the research area with calorimetry and in process control with the classical thermoanalytical methods could be introduced in the near future. On the other hand more sophisticated instruments especially in the fields of calorimetry and also new instruments which enable simultaneous measurements may give new opportunities.

The unspecificity of the classical thermoanalytical methods measuring a mass or a heat change as a function of temperature is often a handicap, however, in certain cases also of a high utility. Thermoanalytical instruments using a substance specific measuring principle or which combine an unspecific measurement with a second procedure will gain broader fields of application. To give examples: Harel, Adamson *et al.* [2], Cooper [3], and Wadsö are engaged in the development of the photocalorimetry and Rordorf [4, 5] developed in the area of thermochemistry several methods which allow the determination of a substance specific dependent variable. One of these methods by Rordorf is the following one: "A scanned flow tube pyrolysis method with on-line MS detection in the temperature region from 100 to 1200°".

The list of such examples from institutes and industry could be enlarged without difficulties. There are many indications existing of a strong development of non-classical thermoanalytical methods even also to commercially available instruments. The prediction made 1976 of the importance and the introduction of thermoanalitytical methods in a wider sense seems to become reality [6].

Thermoanalytical applications to pharmaceutical compounds and formulations are summarized in Table 1.

Only one subject concerning thermoanalytical investigations on pharmaceutical compounds shall be outlined here. The thermodynamic stability of polymorphic forms of a substance is discussed in detail. The stability of a crystal modification is normally tested at certain selected temperatures or with a DSC or DTA instrument in the scanning mode over an appropriate temperature region. Such a transition is occuring normally rather fast in the melting region of the instable crystal modification. The elucidation of DSC or DTA curves for such a change of modification is preferably performed by X-ray diffraction or infrared-spectroscopy.

The existence of an instable crystal modification at room temperature can even last for many years. The reason for such a finding is a rate determining step which is an extremely slow solid state rearrangement of the molecules.

Table 1

Field of application	Instrument	Task
• Synthesis and research	• DSC, DTA • TG • solution and titration calorimeter • isothermal calorimeter	• characterization of • pharmaceutical compounds
• Chemical and physical production steps	• DSC, DTA • TG • heat flow calorimeter • solution calorimeter • combustion calorimeter • vapor pressure instruments • thermochemical instruments	• characterization of intermediates and products • process development • process safety • in process control • quality control
• Galenic production	• DSC, DTA • TG • solution calorimeter • isothermal calorimeter	• characterization of polymers and auxiliary materials • chemical and physical stability of formulations

In contrary, the molecules of the liquid phase present in the melting region of the instable crystal modification tend to crystallize spontaneously into a more stable form especially if the corresponding nuclei are present. The stability of a crystalline pharmaceutical compound should be known in any case at room temperature and in addition also in the temperature region of the crystallization step during the chemical production and also for the possible temperatures during the galenic production.

The open questions in pharmaceutical applications are:

- How many crystal modifications are existing for a given pharmaceutical compound?
- Which are the stability regions of polymorphic forms as a function of temperature and pressure?

Further complications may arise, if the active substance forms one or even several hydrates or solvates and if the amorphous form of an active substance is also involved.

Our stability considerations shall be limited to the temperature as the parameter. A polymorphic transformation will occur at a given temperature with a certain rate depending on thermodynamic and kinetic facts, and also depending on preconditions of the substance with the given physical and chemical purity. Such a temperature for which a tranformation is observed may be far outside the temperature region of pharmaceutical interest.

Therefore an extrapolation of the stability data obtained by thermoanalytical methods for a given polymorphic form mainly to lower temperature values has to be made. However, only stability data which are transferable to a thermodynamic function or in other words into equations for equilibrium conditions may be extrapolated to other temperatures. The stability of crystal modifications is normally determined over large temperature regions from vapor pressure or solubility curves and also from Gibbs functions. The latter are calculated with the melting points, the enthalpies of fusion and eventually the heat capacities of the polymorphic phases and the liquid phase of the given substance.

The calculation of Gibbs functions shall be outlined in some detail [7, 8]. A substance consisting of two crystal modifications designated as α and β, respectively, is assumed. The stability region on a thermodynamic basis can be determined with the Gibbs free energy functions. The difference of the Gibbs functions between the crystalline state and the liquid or supercooled state is defined as

$$\Delta G_{s,i}\,(T) = G_{s,i}\,(T) - G_{lq}\,(T) \qquad i = \alpha,\beta \tag{1}$$

The liquid and supercooled phases of the given substance is regarded as reference state.

The Gibbs function in the thermodynamic expression is

$$\Delta G_{s,i} = \Delta H_{s,i} - T\Delta S_{s,i} \tag{2}$$

Several levels of approximation shall be further discussed. The first approximation assumes enthalpies of fusion $\Delta_{\mathrm{fus}}\,H_{\alpha}$ and $\Delta_{\mathrm{fus}}H_{\beta}$ which are independent in temperature.

The enthalpies and entropies of fusion are therefore

$$\Delta H_{s,i} = -\,\Delta_{\mathrm{fus}}\,H_i \tag{3}$$

$$\Delta S_{s,i} = -\,\frac{\Delta_{\mathrm{fus}}\,H_i}{T_{\mathrm{fus},i}} \tag{4}$$

Inserting Eqs (3) and (4) into (2) yields to

$$\Delta G_{s,i} = -\,\Delta_{\mathrm{fus}}\,H_i\,(1-\frac{T}{T_{\mathrm{fus},i}}) \tag{5}$$

In this approximation the Gibbs free energy functions of the two crystal modifications α and β are linear in temperature and a calculation from data is rather easy.
The transition point, namely the temperature $T_{\alpha\beta}$ for which the two Gibbs functions are equal is given by

$$T_{\alpha\beta} = \frac{\Delta_{\text{fus}} H_\alpha - \Delta_{\text{fus}} H_\beta}{\frac{\Delta_{\text{fus}} H_\alpha}{T_{\text{fus},\,\alpha}} - \frac{\Delta_{\text{fus}} H_\beta}{T_{\text{fus},\,\beta}}} \tag{6}$$

The chosen approximation of the Gibbs functions as a linear function in temperature is valid over small temperature ranges only. Extrapolation over an extended range is only satisfactory with enthalpy functions of known temperature dependence. Introduction of the following equations take this fact into consideration

$$\Delta H_{s,i} = H_{s,i}\,(T) - H_{lq}\,(T) = -\Delta_{\text{fus}} H_i - \int_T^{T_{\text{fus},i}} \Delta C_{p,i}\,\mathrm{d}T \tag{7}$$

$$\Delta S_{s,i} = S_{s,i}\,(T) - S_{lq}\,(T) = -\frac{\Delta_{\text{fus}} H_i}{T_{\text{fus},i}} - \int_T^{T_{\text{fus},i}} \frac{\Delta C_{p,i}}{T}\,\mathrm{d}T \tag{8}$$

The heat capacity of the solid and the liquid phases can be expressed by different power series in temperature. Usually the following approximation is used

$$\Delta C_{p,i} = C_{p,s,i} - C_{p,lq} = \sum_{j=o}^{n} \Delta a_{i,j}\, T^j \tag{9}$$

with

$$\Delta a_{i,j} = a_{s,i,j} - a_{lq,j} \qquad \begin{matrix} i = \alpha,\beta \\ j = o,\ldots,n \end{matrix} \tag{10}$$

Combination of Eqs (2), (7), (8) and (9) yields to the Gibbs functions

$$\Delta G_{s,i} = -\Delta_{\text{fus}} H_i \left(1 - \frac{T}{T_{\text{fus},i}}\right) - \Delta a_{i,o}\left[T_{\text{fus},i} - T\left(1 + \ln \frac{T_{\text{fus},i}}{T}\right)\right]$$

$$-\sum_{j=i}^{n} \frac{\Delta a_{i,j}}{j(j+1)} [T^{j+1} + j \cdot T_{\mathrm{fus},i}^{J+1} - (j+1)\, T \cdot T_{\mathrm{fus},i}^{J}] \qquad (11)$$

In practical applications and with data of the accuracy of normal thermoanalytical equipment one would preferably follow the procedure: use as a zero order approximation the linear Gibbs functions according to Eq. (5) and as a second approach in addition to the melting points and the enthalpies of fusion the data for the heat capacities with the following approximation

$$\Delta C_{p,i} = \Delta a_{i,o} + \Delta a_{i,1} T \qquad (12)$$

The Gibbs functions for this latter approximation take the form

$$\Delta G_{s,i} = -\Delta_{\mathrm{fus}} H_i \left(1 - \frac{T}{T_{\mathrm{fus},i}}\right) - \Delta a_{i,o} \left[T_{\mathrm{fus},i} - T \left(1 + \ln \frac{T_{\mathrm{fus},i}}{T}\right)\right] - \frac{\Delta a_{i,1}}{2} (T - T_{\mathrm{fus},i})^2 \qquad (13)$$

The Gibbs free energy functions can also be determined with partial pressures or solubility measurements. These functions are with the assumption of a perfect gas

$$\Delta G_{s,i}(T) = RT(\ln p_i - \ln p_{lq}) = RT \cdot \ln \frac{P_i}{P_{lq}} \qquad (14)$$

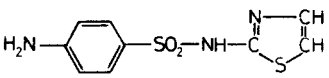
where p_i and p_{lq} are the partial pressures of the crystal modifications and of the liquid phase at the same temperature. In case of ideal solutions the partial pressures in the Eq. (14) must be replaced with solubilities, expressed as mole fractions. In non-ideal solutions the activities have to be introduced. The activity ratio of two crystal modifications of the same substance at a given temperature as the ratio of partial pressures and solubilites, respectively, is under approximation straightforward calculated from Gibbs functions obtained by thermoanalytical data

$$\frac{P_\alpha}{P_\beta} = e^{\frac{\Delta G_{s,\alpha} - \Delta G_{s,\beta}}{RT}} \qquad (15)$$

Experimental

The Gibbs free energy functions for the three known crystal modifications of sulphatriazole were determined for all three forms with the most simple linear function and for two modifications also by measurements of the heat capacities with the Gibbs function according to Eq. (13). The thermoanalytical data are presented in Table 2.

Table 2 Sulphathiazole



Phase or Modification	Melting point	Molar heat of fusion	Constants for the molar heat capacity	
	$T_{fus,i}$ in K	$\Delta_{fus}H_i$ in kJ mol^{-1}	$a_{s,i,o}$ in Jmol^{-1}K^{-1}	$a_{s,i,1}$ Jmol^{-1}K^{-2}
α	473.3±0.4	28.89±0.25	16.8±6.1	0.812±0.09
β	445.8±1.2	33.31±0.63	55.7±56.1	0.732±0.134
γ	468.3±1.2	23.92±0.50	–	–
			$a_{lq,0}$	$a_{lq,1}$
liquid	–	–	226.4±13.4	0.598±0.025

The transition point $T_{\alpha\beta}$ for sulphathiazole is according to literature and to our own measurements:

$T_{\alpha\beta}$ in K

- rate of solubility [9] 367±3
- this work Eq. (6) 324
- this work Eq. (13) 370±11

The rate of solubility, evaluated by an approximation of Nernst, gives a value for $T_{\alpha\beta}$ which is in good agreement with our value according to Eq. (13). The α-modification is the stable form between 368 and 473 K. Below 368 K and therefore also at room temperature the β-modifications is the stable one. The partial pressure ratio of these two crystal modification of sulphathiazol at 25° is calculated with the Gibbs free energy values according to Eq. (13)

$$P_\alpha/P_\beta = 1.9\pm0.3.$$

Therefore also the solubility of the α-modification at ,25° is about 90% higher in all solvents compared to the solubility of the β-modification.

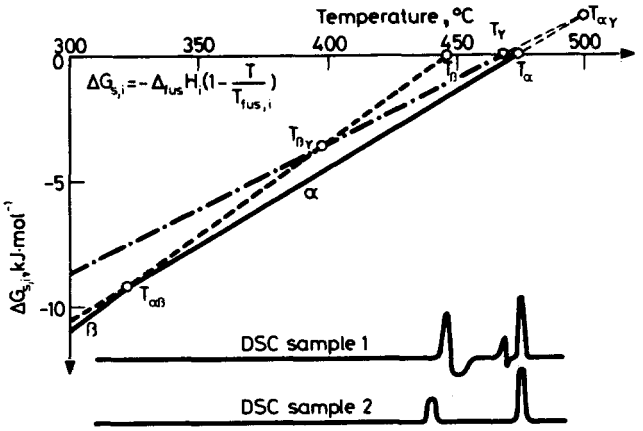


Fig. 1 Thermodynamics: Gibbs function of sulphathiazole $i = \alpha, \beta, \gamma$
Kinetics: DSC curves at two samples of sulphathiazole with T = 8 K min^{-1}

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Zusammenfassung – Es wird die wichtige Rolle thermoanalytischer Methoden auf dem Gebiet der pharmazeutischen und galenischen Forschung betont und die thermodynamische Stabilität polymorpher Formen von Substanzen besprochen.

РЕЗЮМЕ — В общих чертах описана важная роль термоаналитических методов в исследовании фармацевтических и природных веществ. Обсуждена термодинамическая устойчивость полиморфных форм вещества.