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Theoretical derivation and practical application of energy/temperature diagrams as an instrument in preformulation studies of polymorphic drug substances

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Abstract

The construction of semiquantitative energy/temperature (E/T) diagrams is discussed on the basis of thermodynamic equations. An E/T diagram describes the temperature dependence of the enthalpy and the Gibbs free energy of polymorphs. Knowledge of the E/T diagram of a compound permits the prediction of relative physicochemical values for polymorphs. Construction and interpretation of E/T diagrams is discussed with reference to the drug substances nimodipine and acemetacin. The predicted data are compared with experimental values.

Keywords: E/T Diagram; Polymorphism; Preformulation; Physical stability; Thermal analysis

1. Introduction

Many substances crystallize in more than one crystal form. This property is called allotropism in elements and polymorphism in compounds. Polymorphism occurs frequently in organic compounds. It has been shown that about 80% of drug substances are polymorphic (Grunenberg, 1992). The polymorphs of a substance are chemically identical but can differ significantly in their physical properties. There can be considerable differences in the solubilities, melting points, densities, X-ray diffraction patterns and molecular spectra. Phase transitions of solids can be thermodynamically reversible or irreversible. Modifications, which transform reversibly without passing the liquid or gaseous phases are called enantiotropic polymorphs. If the modifications are not interconvertible under these conditions, the system is monotropic.

Solubility of drug substances in aqueous media is of particular interest. It is possible that water solubility influences the bioavailability of a drug substance. In pharmaceutical technology the physical properties are also very important. For these reasons particular care must be taken in the production of an active substance to ensure that the same modification is always produced.

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In the investigation of polymorphism many methods are used. The obtained data can be interpreted with thermodynamic equations. It has been pointed out (Burger and Ramberger, 1979b; Burger, 1990) that many examples of erroneous interpretations of the physicochemical properties of polymorphic drug substances have been published. It is useful to treat the data as part of a closed system. The graphical solution derived from these data is the energy/temperature diagram. It was introduced in crystallography by Buerger (1951) without application onto a specific example.

2. Theory

A basic value in thermodynamics is the heat capacity at constant pressure C_p. Each crystalline form has its own specific heat capacity, which is a function of the enthalpy H and the temperature T at constant pressure p:

$$\left(\frac{\delta H}{\delta T}\right)_p = C_p \tag{1}$$

The heat capacity of a solid indicates the energy absorbed by the crystal lattice during heating. Einstein (1907) developed a theoretical approach to the determination of heat capacities of solids at constant volume (C_v). He assumed that each atom in a crystal vibrates about its equilibrium position at a certain frequency v:

$$C_v = 3 \cdot R \cdot \frac{\left(\frac{h \cdot v}{k \cdot T}\right)^2 \cdot e^{\left(-\frac{h \cdot v}{k \cdot T}\right)}}{1 - e^{\left(-\frac{h \cdot v}{k \cdot T}\right)}} \tag{2}$$

where k = Boltzmann constant; R = gas constant; h = Planck's constant; v = frequency of vibration; T = absolute temperature.

This simple mathematical description of the heat capacity is sufficient to understand the following conclusions. Given that solids have only low compressibility, the heat capacity at constant volume is approximately the same as at constant pressure. At absolute zero (T = 0 K) the lattice vibrations of an ideal crystal are zero. It follows from Nernst's formulation of the third law of thermodynamics that the heat capacity of an ideal crystal is zero at 0 Kelvin:

$$\left(\frac{\delta H}{\delta T}\right)_p = C_p = 0 \tag{3}$$

$$dV = 0, T = 0$$

The slope of the function H versus T is 0 at absolute zero (Fig. 1). The heat capacity of a substance is measured experimentally by adding a known amount of energy and recording the resulting rise in temperature. Since both absolute temperature T and enthalpy H, can only take positive values (cf. Eq. (1)), the heat capacity of a crystalline substance increases with increasing temperature (Fig. 1).

If two modifications of a substance coexist at a given temperature, it follows from Eq. (2) that the H isobars of the two modifications diverge. The distance between the H isobars is the integration constant ΔH_t. This can be obtained by integrating Eq. (4):

$$dH = \int_{T_1}^{T_2} C_p \, dT \tag{4}$$

If a polymorph transforms thermally into another, appropriate methods (e.g., DSC) can be used to determine the transition enthalpy ΔH_t experimentally (Fig. 2). At absolute zero a liquid has more energy than the crystalline forms. Therefore, the H isobar of a liquid is positioned above

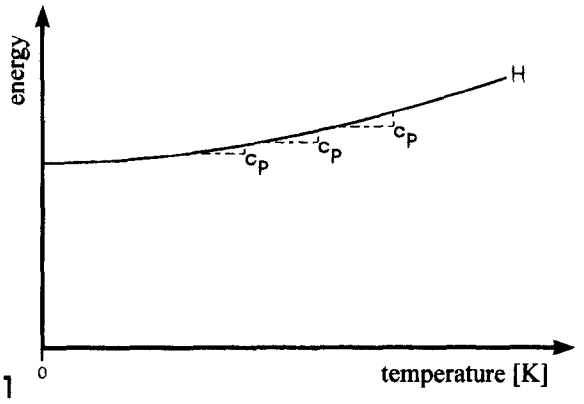

Fig. 1. Fundamental course of an E/T diagram H-isobar constructed with the aid of heat capacity (C_p) determination.

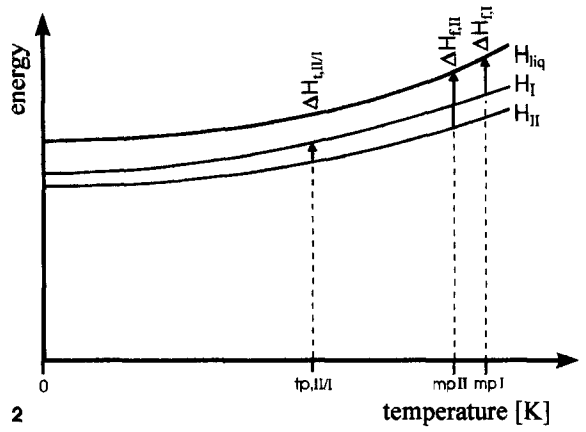

Fig. 2. Fundamental course of the H-isobars of enantiotropically related Mod.I and II (t_p, transition point; $\Delta H_{t,II/I}$, heat of transition) relative to the liquid phase (mp, melting point; ΔH_f, heat of fusion).

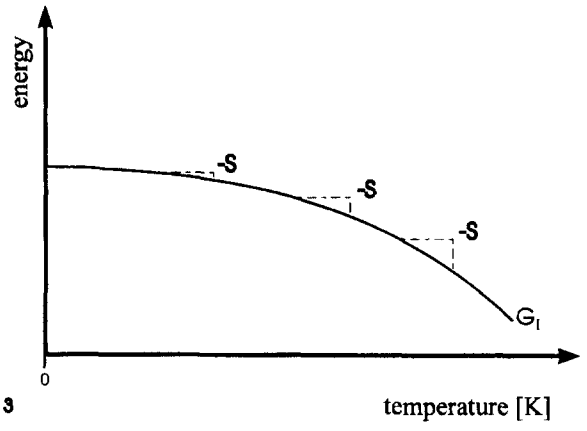

Fig. 3. Fundamental course of a G-isobar of an E/T diagram (S, entropy).

the isobars of the solid modifications of the corresponding substance. With increasing temperature the heat capacity of a liquid increases more than those of the solid modifications (Fig. 2). In principle the energy difference between the curves could be determined experimentally. It is the difference between the enthalpy of fusion of the two polymorphs.

Another important thermodynamic parameter is the Gibbs free energy or free enthalpy G. This is related to the enthalpy H as follows:

$$G = H - T \cdot S \tag{5}$$

This equation is known as the Gibbs function. It relates G and H to the absolute temperature T and entropy S. At absolute zero it follows:

$$G = H \tag{6}$$

With the first and second laws of thermodynamics, the Gibbs function yields a relationship that describes entropy as the partial derivative of the free energy with respect to temperature at constant pressure:

$$\left(\frac{\delta G}{\delta T}\right)_p = -S \tag{7}$$

S is always positive. Therefore, G decreases with increasing temperature (Fig. 3). Using statistical-mechanical arguments (Burger and Rambergen, 1979a) it can be shown that the G isobars of two modifications converge and intersect only once (Fig. 4). The exact course of G isobars cannot be followed experimentally, since the entropy cannot be determined. However, the relative position of the G isobars of solids is experimentally accessible using solubility data. Eq. (11) shows that at a given temperature the ratio of the ideal solubilities of two modifications of a substance is always the same. The ratio of ideal solubilities is independent of the solvent. Let us consider the following equations:

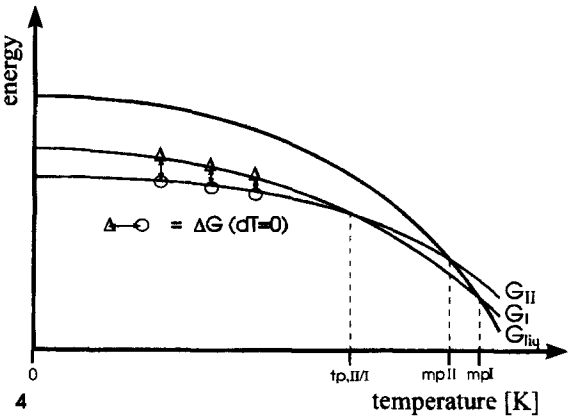

Fig. 4. Construction of the G-isobars of Mod. I and II with aid of solubility determinations (cf. Eq. (11)) (Gibbs free energy of Mod. I (Δ) and Mod. II (○) at a given temperature, t_p: transition point); relative course of the G-Isobars of Mod. I, Mod. II and the liquid phase (mp, melting point).

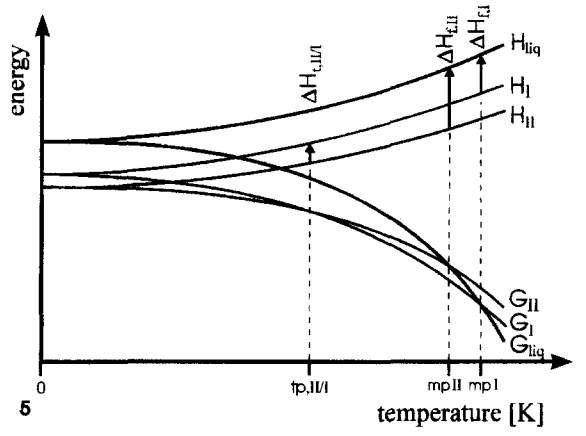

Fig. 5. Fundamental E/T diagram of a dimorphic enantiotropic system.

$$G_{I_{(s)}} = G_{(l)} + R \cdot T \cdot \ln X_I \quad (8)$$

$$G_{II_{(s)}} = G_{(l)} + R \cdot T \cdot \ln X_{II} \quad (9)$$

$$\Delta G_{I_{(s)}-II_{(s)}} = G_{I_{(s)}} - G_{II_{(s)}} = R \cdot T \cdot \ln \frac{X_I}{X_{II}} \quad (10)$$

$$\Delta G_{I_{(s)}-II_{(s)}} = R \cdot T \cdot \ln \frac{L_I}{L_{II}} \quad (11)$$

with $G_{(l)}$ = Gibbs free energy of the substance in solution; $G_{I_{(s)}}$, $G_{II_{(s)}}$ = Gibbs free energy of modifications I and II; X_I, X_{II} = mole fraction of modifications I and II; L_I, L_{II} = solubility of modifications I and II.

At the thermodynamic transition point of an enantiotropic system the solubilities L_I and L_{II} are the same. At other temperatures the G isobar of the modification with the higher solubility lies above the less soluble crystal form (Fig. 4), e.g., nimodipine (Fig. 7). The G isobar of the liquid is located above the G isobars of the solid modifications at absolute zero (Fig. 4). The relative positions of the G isobars can be deduced from their intersections and their theoretically expected courses.

The G isobars of an enantiotropic system intersect before reaching the melting point of the lower-melting modification (Fig. 5). Two monotropically related forms have no intersection of the G isobars below the melting point (Fig. 6). The transition point is virtual. Graphically presented, the point of intersection lies above the melting point of the lower-melting modification. Experimental data can be used to differentiate between enantiotropic and monotropic transitions using the following rules (Burger and Ramberger, 1979a; Burger and Ramberger, 1979b): (a) heat-of-transition rule; (b) heat-of-fusion rule; (c) density rule. These rules enable the deduction of the relative positions of the H and G isobars.

2.1. Heat-of-transition rule

If an endothermic phase change is observed at a particular temperature, the transition point lies below this temperature. This occurs if two polymorphs are enantiotropically related. If the phase transition is exothermic then there is no thermodynamic transition point below that transition temperature. This is either observed if two modifications are monotropic or for an enantiotropic system, when the thermodynamic transition point is higher than the measured transition temperature. Exceptions to this rule were discussed by Burger and Ramberger (1979a).

2.2. Heat-of-fusion rule

In an enantiotropic system the higher melting polymorph has the lower heat of fusion. Otherwise the modifications are monotropic. However, the heat-of-fusion rule is suspended if the enthalpy curves for the liquid and the solid modifi-

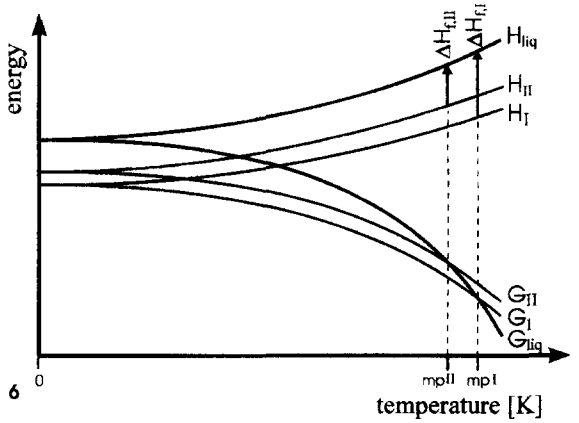

Fig. 6. Fundamental E/T diagram of a dimorphic monotropic system.

cations diverge widely and the melting points of the solid forms are not close together. Even if the form with the higher melting point has the higher heat of fusion, the system may still be enantiotropic. In practice this can occur when the melting points of the two forms differ by more than about 30°C. To avoid such problems, this can be corrected by substitution of the enthalpy of fusion through the entropy of fusion. Thus, two other rules are preferred. The *entropy-of-fusion rule* and the *heat-capacity rule.*

2.2.1. Entropy-of-fusion rule

At the melting point the difference between the Gibbs free energy of a polymorph and the melt is zero. The entropy-of-fusion (ΔS_f) follows Eq. (12):

$$\Delta S_f = \frac{\Delta H_f}{T} \tag{12}$$

If a polymorph with the higher melting point has the lower entropy of fusion, the two modifications are enantiotropic. If the lower melting form has the lower entropy of fusion they are monotropic (Burger, 1982b).

2.2.2. Heat-capacity rule

If the higher melting polymorph has, at a given temperature, a higher heat capacity than another modification, the system is enantiotropic. Otherwise the system is monotropic.

2.3. Density rule

If a polymorph has a lower density than another polymorph at room temperature, then it may be assumed that at absolute zero this form is metastable. The energetically most favourable packing of molecules in a crystal has the strongest interactions between the molecules and hence the greatest density. The best possible packing also means thermodynamic stability. This modification requires more energy than any other modification to break up its crystalline lattice (melting). At absolute zero the form with the greatest density is thermodynamically stable. This approximation assumes that there is no great variation in the density of the solid forms over a wide range of temperature. Deviations from the density rule may be expected for some compounds (e.g., resorcinol; Burger and Ramberger, 1979b).

3. Construction of the E/T diagram

All experimentally measured data obtained for a polymorphic system contribute to the understanding of the transitions and stabilities of the individual modifications. To ensure that inconsistencies are cleared up and to avoid misinterpretations, it is useful to relate the thermodynamic values obtained to each another. One possibility is the graphical solution of the Gibbs equation for a polymorphic system by constructing the E/T diagram. One of the advantages of the E/T diagram is that less data are required for its construction than the theoretical derivation of the thermodynamic expressions suggests (Burger, 1982a). It should be borne in mind that it is not possible to detect the exact courses of the H and G isobars but only their relative positions and their points of intersection (Fig. 5 and 6). To construct an E/T diagram showing the theoretical courses of the G and H isobars for a compound which crystallizes in n modifications, $2n$ parameters are needed.

(1) To determine the relative thermodynamic stability at high temperature, at least the order of the *melting points* or the *solubilities* (T » room temperature) of the modifications are required. The determination and the use of melting points has certain advantages when compared to solubilities. (a) The knowledge of the relative stability at absolute zero (Figs. 5 and 6) gives precise evidence to monotropy or enantiotropy of the modifications. At the melting point the G isobars of the polymorph and the liquid intersect. Crystal and melt are in equilibrium: $\Delta G = 0$. The melting point is the maximum temperature at which a meaningful statement about stability can be made. In contrast: solubility determinations of crystalline compounds must be carried out at temperatures below the melting point. The order of the temperature-dependent solubility can qualitatively be determined by thermomicroscopy (Kuhnert-Brandstätter, 1982a). (b) Usually melting points

Table 1
Relative size of parameters, that could be taken from an energy/temperature diagram

	Monotropism	Enantiotropism		
		$<t_p$		$>t_p$
Heat of transition	exothermic	exothermic		endothermic
Heat of fusion	I > II		II > I	
Heat capacity	II > I		I > II	
Entropy	II > I		I > II	
Entropy of fusion	I > II		II > I	
Solubility[a]	II > I	I > II		II > I
Density	I > II		II > I	
Physical stability	I > II	II > I		I > II

I = Mod. I higher melting form; II = Mod. II lower melting form; $<t_p$, below the thermodynamic transition point; $>t_p$, above the thermodynamic transition point.
[a]In given solvents.

(at least the order of the melting points) can be easily determined thermomicroscopically (Kuhnert-Brandstätter, 1982b).

(2) The *density*, *heat of fusion* or *entropy of fusion* of the modifications indicate the relative stability of the polymorphs at absolute zero (density rule, heat-of-fusion rule, entropy-of-fusion rule). The heat of fusion and the melting point are usually easily measured calorimetrically. Densities of solids can be determined pycnometrically or theoretically from X-ray diffraction data.

Data which cannot be determined experimentally can be calculated. If a compound crystallizes in more than two modifications the procedure described must be carried out for each possible pair of modifications.

4. Interpretation

Some technically important parameters and their relative sizes can be found from the E/T diagram. Table 1 shows some of the possibilities. The classifications are partly based on empirical observations. The ratio of the saturation solubility of two modifications is at a given temperature a constant and independent of the solvent (association in solution excluded; Burger and Ramberger, 1981). In an enantiotropic system below the thermodynamic transition point the higher melting modification is more soluble than the lower melting crystal form. In a monotropic system this ratio is greater than 1 over the whole temperature range. A further important point is the physical stability of the modifications. In an enantiotropic system below the thermodynamic transition temperature the low-melting modification is the thermodynamically stable form. This modification does not convert. In a monotropic system the higher-melting modification is the thermodynamically stable one over the entire temperature range.

5. Construction of E/T diagrams, exemplified by nimodipine and acemetacin

An E/T diagram is a semiquantitative representation of the thermodynamic properties of the modifications of a compound. The ordinate represents the relative energies and the abscissa the temperature. The abscissa is subdivided arbitrarily, but compressed at low temperatures so that the points of intersection of the G isobars are better illustrated. Most intersections are in the high temperature range of the diagram: between room temperature and the melting points.

5.1. Polymorphism of nimodipine

Polymorphism of nimodipine INN: ((2-methoxyethyl-1,4-dihydro-5-isopropoxycarbonyl)

Table 2
Physical properties of nimodipine polymorphs (Grunenberg et al., 1995)

	Mod. I	Mod. II
Melting point (DSC-onset temperature) (°C)[a]	124 ± 1	116 ± 1
Heat of fusion (kJ mol^{-1})[a]	39 ± 1	46 ± 1
True density (g cm^{-3})[a]	1.27 ± 0.01	1.30 ± 0.01
Calculated density (data from X-ray diffraction analysis) (g cm^{-3})	1.271	1.303
Solubility in water at 25.0 ± 0.1°C (mg pro 100 ml)[a]	0.036 ± 0.007	0.018 ± 0.004

[a]95% CI.

-2,6-dimethyl-4-(3-nitro-phenyl)-3-pyridine carboxylate) was investigated by Grunenberg et al. (1995). The drug substance crystallizes in two enantiotropic modifications. Table 2 summarizes the physicochemical data of the two polymorphs. Construction of an E/T diagram starts with the principle course of the G and H isobars of the liquid (Fig. 7). The melting points of the modifications are indicated by the points of intersection of the G isobars of each modification with that of the liquid. The form with the higher melting point is the thermodynamically stable modification at that temperature. The experimentally determined heat of fusion gives evidence for the relative positions of the H and G isobars at absolute zero. According to the heat of fusion rule, mod. II of nimodipine is the thermodynamically stable form at absolute zero. At 0 K the free energy and, since $G = H$ (at $T = 0$ K), the enthalpy of mod. II are both lower than those of mod. I. Since the order of stability differs between absolute zero and the melting point, the G isobars of the two modifications must intersect: the modifications are enantiotropic. Application of the density rule leads to the same result. The transition temperature may be found by determination of the solubilities of the pure forms or of mixtures of modifications at various temperatures. The latter method involves stirring a suspension which is then filtered off and dried. The modification will be identified by suitable methods like hot stage microscopy, DSC or X-ray diffraction. With a few exceptions, after a sufficiently long period of stirring the mixture of modifications will convert to the thermodynamically stable form. Heating and cooling of samples in the DSC calorimeter or hot stage microscope can also define the thermodynamic transition temperature. In the case of nimodipine, it was found by stirring tests carried out at various temperatures (Table 3), that the thermodynamic transition temperature for the enantiotropic transition mod. I ↔ mod. II is between +80 and +95°C (mean +88°C). According to the heat of fusion rule, the heat of transition corresponds approximately to the difference in the enthalpies of fusion of the two modifications: 7 kJ mol^{-1}. Mod. II is thermodynamically stable from −273 to about +88°C and mod. I is stable from about +88 to +124°C. This value is predicted by interpretation of the E/T diagram. The heat of transition could not be determined experimentally.

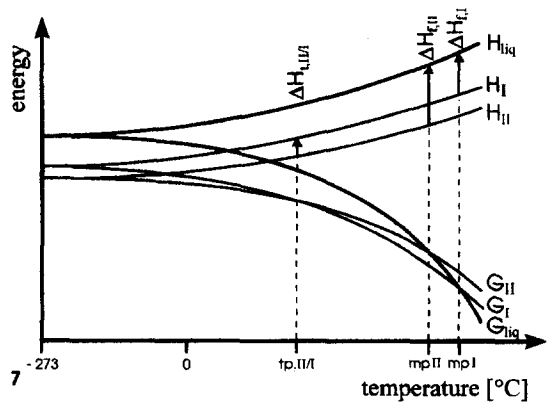

Fig. 7. E/T diagram of nimodipine (Grunenberg et al., 1995).

5.2. Polymorphism of acemetacin

The polymorphism of acemetacin was examined by Burger and Lettenbichler (1993). Acemetacin INN: (*O*-[1-4(chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetyl]-glycolic acid) crystallizes in five

Table 3
Determination of the thermodynamic transition point of nimodipine

Solvent	Stirring time (h)	Temp. (°C)	Modification	
			Used	Residue
2-propanol	22	25	I	II
	8	25	II	II
ethanol/water	96	40	I	II
1:3	96	40	II	II
ethanol/water	32	80	I	I/II
1:5	32	80	II	II
	8	95	I	I
	8	95	II	I / II

modifications and one hydrate. Table 4 summarizes the physicochemical properties of the modifications. The transition enthalpy for the monotropic transition of Mod. IV to Mod. II is -1.39 ± 0.26 kJ mol^{-1} at 130–134°C and of Mod. V to Mod. II is -2.45 ± 0.95 kJ mol^{-1} at 55–67°C. The relative stability of the modifications and the theoretical transition behaviour are found using the density, heat-of-fusion and heat-of-transition rules. The expected courses of the G and H isobars of the liquid are shown in Fig. 8. Mod. I and II are monotropically related to the other modifications. Mod. I possesses the lower Gibbs free energy over the entire temperature range. Mod. II is monotropically related to Mod. I and IV, being less stable than Mod. I and more stable than Mod. IV. Mod. IV is thermodynamically more stable than Mod. V over the entire temperature range. Mod. III is monotropic to Mod. I and II but enantiotropic to Mod. IV and V. The E/T diagram for acemetacin therefore appears as outlined in Fig. 8.

5.3. Application of E/T diagrams

Polymorphic drug substances often show several modifications (Table 5). With the aid of E/T diagrams it is possible to show the order of thermodynamic stability of the crystalline forms at a given temperature. For example, the order of entropy could be read off the E/T diagram. The knowledge of the order of entropy of the modifications is a fundamental parameter in 'Molecular Pharmaceutics' (Hüttenrauch, 1988). In the production of solid or semi-solid dosage forms, in most cases the modification with the greatest thermodynamic stability under ambient conditions should be used (cf. Sections 5.1 and 5.2).

A well-known exception of using the room temperature stable crystal form of a drug substance is chloramphenicol palmitate (Burger, 1977). This modification shows no pharmaceutical activity. A thermodynamically metastable modification has to be used for solid dosage form production. Another exception is acemetacin. Burger and Lettenbichler (1993) showed that Mod. II is the crystal form with the best properties for usage in solid pharmaceutical formulations.

6. Discussion

The knowledge of the E/T diagram of a drug substance allows the prediction of numerous physicochemical parameters. This will be illustrated using nimodipine and acemetacin as examples.

6.1. Thermodynamic stability

The free enthalpy G is a measure of the stability of a modification. At a given temperature the polymorph with the lowest free enthalpy is the thermodynamically stable one. The G isobar of Mod. II of nimodipine lies below the G isobar of Mod. I between absolute zero and about 88°C.

Table 4
Physical properties of the acemetacin polymorphs (Burger and Lettenbichler, 1993)

	Mod. I	Mod. II	Mod. III	Mod. IV	Mod. V
Melting point (DSC-onset temperature) (°C)	150.5	150			75
Heat of fusion (kJ mol^{-1})[b]	50.7 ± 0.7	48.4 ± 0.9	36.6 ± 0.7	47.0[a]	
True density (g cm^{-3})[b]	1.446 ± 0.001	1.428 ± 0.004	1.432 ± 0.020	1.405 ± 0.023	1.334 ± 0.005
Solubility in 1-butanol at 20°C (μmol l^{-1})	9340	15 580	43 330	19 060	25 350

[a]Calculated by using the heat-of-transition rule.
[b]Mean ± 95% CI.

Mod. II is the thermodynamically stable modification in this temperature range and Mod. I is metastable. At temperatures above about 88°C the relationship between the energies is reversed. Between the point of intersection of the G isobars and 124°C (melting point) Mod. I is stable and Mod. II metastable. In the case of acemetacin, Mod. I is thermodynamically stable from −273°C to its melting point.

6.2. Monotropism and enantiotropism

If the free energy curves of two polymorphs intersect between absolute zero and the melting point of the lower melting form, the modifications are enantiotropic. If not, they are monotropically related. An intersection can be seen in the E/T diagram of nimodipine. Mod. I and II are enantiotropic. Concerning the five modifications of acemetacin, Mod. I, II, IV and V are all monotropically related. Their free energy curves do not intersect. Mod. III is enantiotropic to Mod. IV and V.

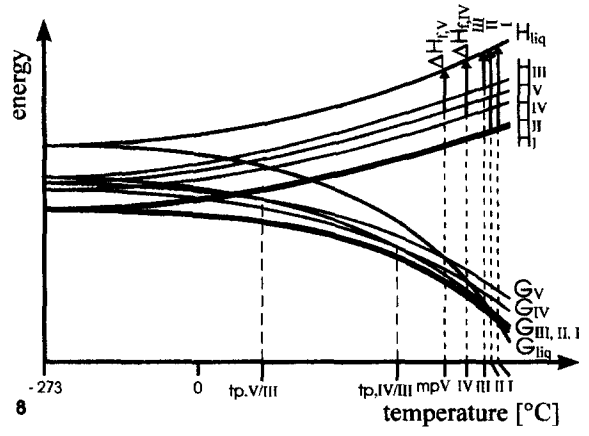

Fig. 8. E/T diagram of acemetacin (Burger and Lettenbichler, 1993).

6.3. Thermodynamic transition temperature

The temperature at which the free energy curves of enantiotropes intersect is their thermodynamic transition temperature. For the pair of modifications of nimodipine the temperature was experimentally found to be 88 ± 8°C. The enantiotropic forms of acemetacin, modifications III/IV and III/V have transition points at temperatures below room temperature.

6.4. Entropy

Relative entropy can easily be read off the E/T diagram (Eq. (8)). The larger the gradient of the G isobars the higher the entropy of the modification. It can be seen from the E/T diagram for nimodipine that the entropy of Mod. I is greater than that of Mod. II. For acemetacin the order derived from the E/T diagram is $S_I < S_{II} < S_{IV} < S_V < S_{III}$.

Table 5
List of published energy/temperature diagrams of drug substances (n = number of polymorphic modifications)

Drug substance	n	Reference
Acemetacin	5	Burger and Lettenbichler, 1993
Acetohexamide	3	Burger, 1978
Carbamazepine	3	Krahn and Mielck, 1987
Chloramphenicol palmitate	4	Burger, 1977
Chlorpropamide	5	Burger, 1982a
p-Dichlorbenzene	3	Burger and Ramberger, 1979b
Flufenamic acid	8	Burger and Ramberger, 1980
Glymidine-Na	2	Burger, 1976
Mannitol	3	Burger et al., 1994
Mefenamic acid	2	Burger and Ramberger, 1980
Metahexamide	4	Burger, 1979
Metolazone	3	Burger, 1975a
Mofebutazone	2	Müller and Beer, 1984
Nimodipine	2	Grunenberg et al., 1995
Paracetamol	3	Burger, 1982a
Pimelic acid	3	Burger et al., 1995
Piracetam	6	Kuhnert-Brandstätter et al., 1994
Pyrithyldione	4	Burger and Ramberger, 1981
Sulfamethoxydiazine	8	Burger et al., 1980a
Sulfanilamide	3	Burger, 1973
Sulfapyridine	6	Burger et al., 1980b
Sulfathiazole	4	Burger and Dialer, 1983
Tolbutamide	4	Burger, 1975b

6.5. Relative solubility

The saturation solubility of a compound decreases with increasing stability. The ratio of solubilities depends on the temperature but not on the solvent. It should be pointed out that there can be exceptions. An example is the composition of aggregates in solution. Such cases are rare.

Because of the lower energy content of Mod. II of nimodipine compared to Mod. I, it would be expected that between -273 and $+88$°C the solubility of Mod. II would be lower than that of Mod. I, and that above the latter temperature the solubility of Mod. I would be lower. These predictions were experimentally varified at 25 and 37°C.

The solubility of acemetacin was determined in 1-butanol (Table 4). The solubilities increase in the order Mod. I < II < IV < V < III. This can be derived from the E/T diagram. It can further be predicted that this solubility series will not change below room temperature because G isobars do not intersect. On the other hand, above the points of intersection of the G isobars of Mod. III with IV and V, the solubility of Mod. III will be less than that of Mod. IV and V.

6.6. Density

According to the density rule, the thermodynamically stable form at 0 Kelvin has the highest density. The rule depends on the assumption that the order of density found experimentally for polymorphs at room temperature remains the same at 0 Kelvin. The E/T diagram for nimodipine shows that Mod. II has a lower energy content than Mod. I at absolute zero and should therefore have a higher density at ambient conditions. Experimental results agree with this statement. The density of Mod. I is 1.27 g cm^{-3}, less than that of mod. II (1.30 g cm^{-3}). The rule can also be applied to acemetacin. The order of stability at absolute zero, $G_{\mathrm{I}} < G_{\mathrm{II}} < G_{\mathrm{IV}} < G_{\mathrm{V}} < G_{\mathrm{III}}$, agrees with the decreasing order of densities at room temperature, Mod. I (1.446 g cm^{-3}) > II (1.428 g cm^{-3}) > IV (1.405 g c^{-3}) > V (1.334 g cm^{-3}). An exception (Burger, 1982a) is Mod. III with a density of 1.432 g cm^{-3}.

6.7. Heat capacity

Due to the heat-capacity rule, divergence of the enthalpy isobars and Eq. (1), the most stable form at absolute zero has the lowest enthalpy between absolute zero and the melting point. The heat capacities of the modifications of nimodipine and acemetacin were not determined experimentally. The expected order is given by the relative enthalpies at absolute zero.

6.8. Heat of fusion/heat of transition

If the melting point of polymorphs are not too far apart (< 30°C), heat of fusion and heat of

transition which have not been or cannot be determined experimentally may be calculated approximately from available data.

In the case of nimodipine, the transition enthalpy for Mod. II → I could not be determined. It can be calculated from the difference in heat of fusion:

$\Delta H_{\text{Mod. I} \rightarrow \text{liquid}} = 39 \text{ kJ mol}^{-1}$;

$\Delta H_{\text{Mod. II} \rightarrow \text{liquid}} = 46 \text{ kJ mol}^{-1}$;

$\Delta H_{\text{Mod. II} \rightarrow \text{I}} = \Delta H_{\text{Mod. II} \rightarrow \text{liquid}} - \Delta H_{\text{Mod. I} \rightarrow \text{liquid}}$;

$\Delta H_{\text{Mod. II} \rightarrow \text{I}} = 46 \text{ kJ mol}^{-1} - 39 \text{ kJ mol}^{-1}$;

$\Delta H_{\text{Mod. II} \rightarrow \text{I}} = +7 \text{ kJ mol}^{-1}$.

Since the enthalpy curves diverge this is only an approximate value.

The calculation of the heat of fusion may be illustrated using Mod. IV of acemetacin to show the principle of the procedure. The calculation uses the mean value for heat of fusion and heat of transition. No statistical error analysis was carried out here. Mod. IV was heated until it turned into Mod. II and the transition enthalpy was measured as -1.4 kJ mol^{-1}. The fusion enthalpy of Mod. II is 48.4 kJ mol^{-1}.

(a) $\Delta H_{\text{Mod. II} \rightarrow \text{liquid}} = 48.4 \text{ kJ mol}^{-1}$;

(b) $\Delta H_{\text{Mod. IV} \rightarrow \text{II}} = -1.4 \text{ kJ mol}^{-1}$

yielding:

$\Delta H_{\text{Mod. II} \rightarrow \text{IV}} = +1.4 \text{ kJ mol}^{-1}$;

$\Delta H_{\text{Mod. IV} \rightarrow \text{liquid}} = \Delta H_{\text{Mod. II} \rightarrow \text{liquid}} - \Delta H_{\text{Mod. II} \rightarrow \text{IV}}$;

$\Delta H_{\text{Mod. IV} \rightarrow \text{liquid}} = 48.4 \text{ kJ mol}^{-1} - 1.4 \text{ kJ mol}^{-1}$;

$\Delta H_{\text{Mod. IV} \rightarrow \text{liquid}} = 47.0 \text{ kJ mol}^{-1}$.

The calculated heat of fusion of Mod. IV is 47.0 kJ mol^{-1}.

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