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Significance of Partial and Total Cohesion Parameters of Pharmaceutical Solids Determined from Dissolution Calorimetric Measurements

Catherine Rey-Mermet,[1] Paul Ruelle,[1] Hô Nam-Trân,[1] Michel Buchmann,[1] and Ulrich W. Kesselring[1,2]

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The total and partial adhesion-derived cohesion parameters of three solid pharmaceutical substances (caffeine, theophylline, and phenylbutazone) were determined from dissolution calorimetric measurements, a new technique devised for this purpose. Calorimetry has the advantage of leading directly to enthalpies, from which the solute cohesion parameter(s) is(are) deduced. An equation was developed that relates partial molar enthalpies of mixing (obtained by subtracting enthalpies of fusion from enthalpies of dissolution) to the cohesion parameters of the solute and of the solvents. Solvents were selected on the basis of their known cohesion parameters by applying the experimental research methodology.

KEY WORDS: cohesion parameter; dissolution; calorimetry; enthalpy of mixing.

INTRODUCTION

Cohesion parameters describing molecular interaction capacities are commonly used in paint technology (1–4) and cosmetics (5,6) to establish liquid formulations. Appropriate solvents or excipients can thus be chosen on the basis of the respective cohesion parameters of the partners to be mixed.

In the pharmaceutical field, cohesion parameters may be useful in preformulation studies (7–11) and may help predict the pharmacological activity of a drug. Drugs and their formulations must undergo two main steps or phase changes, i.e., the dissolution in the gastrointestinal tract and the passage through the gastrointestinal barrier, governed by the lipid–water partition coefficient. The thermodynamic quantity linked to all phase changes is free enthalpy or Gibbs free energy. Therefore, cohesion parameters, being related solely to the enthalpy of mixing, can account for only part of the dissolution or partition phenomena. Other factors controlling solubility are the free enthalpy of fusion and the entropy of mixing. For regular solutions, the cohesion parameters of a molten solute are directly related to its partial internal energy, hence its enthalpy of mixing. For real solutions, in which strong specific orientated interactions such as hydrogen bonding can occur, the enthalpy of mixing is not, as for regular solutions, always positive. Consequently, a new equation had to be developed.

THEORY

For a liquid, the cohesion parameter, δ (MPa$^{1/2}$), is defined as the square root of the cohesion energy, E_{coh} (kJ/mol), divided by its molar volume, V (mL):

$$\delta = (E_{\mathrm{coh}}/V)^{1/2} \approx [(\Delta_{\mathrm{vap}}H - \mathrm{RT})/V]^{1/2} \qquad (1)$$

Cohesion energy can be decomposed into a vaporization and an expansion term and is approximately equal to the molar enthalpy of vaporization, $\Delta_{\mathrm{vap}}H$ (kJ/mol) minus RT. The cohesion parameter is therefore an intrinsic parameter stemming only from pure-component properties of a substance in the liquid state. It is often split into partial components accounting for the various types of interaction capacities of a substance. For this work, Hansen's three-component splitting (12) has been adopted: the total cohesion parameter, δ, is divided into its dispersive, δ_d, polar, δ_p, and hydrogen-bonding, δ_h, partial components. As the hydrogen-bonding partial cohesion parameter represents an unsymmetrical interaction involving a proton donor and a proton acceptor, it should be further decomposed into two separate components: a Lewis acid cohesion parameter, δ_a, and a Lewis base cohesion parameter, δ_b. However, the Lewis acid–base cohesion parameter values are known for very few compounds. Therefore, a single parameter expressing hydrogen-bonding has been maintained:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (2)$$

For solid substances, the reference state being the supercooled liquid, cohesion parameters cannot simply be established from their volumes and enthalpies of vaporisation. They are generally deduced from thermodynamic quantities characterizing binary systems, i.e., involving the solid of interest and a solvent, the cohesion parameter value of which has previously been established. In the case of regular solutions, the relation between adhesion (interaction between unlike *i* and *j* molecules) and cohesion (interaction between like *i* and *j* molecules) is expressed by the geometric mean assumption, which states that the adhesive interaction energy of an *i–j* pair of unlike molecules is equal to the geometric mean of the cohesive interaction energy of the *i–i* and *j–j* pairs of like molecules. The Scatchard–Hildebrand treatment of regular solutions relates the heat of mixing to the squared difference between the cohesion parameters of the solute and the solvent by the following equation:

$$\Delta_{\mathrm{mix}}H = \Delta_{\mathrm{mix}}E = V\,\Phi_i\Phi_j(\delta_i - \delta_j)^2 \qquad (3)$$

where $\Delta_{\mathrm{mix}}H$ (kJ/mol) and $\Delta_{\mathrm{mix}}E$ (kJ/mol) are the molar enthalpy and internal energy of mixing, V is the volume of the solution, and Φ and δ are the volume fraction and the total cohesion parameter of the *i* or *j* components of the mixture.

Because of the underlying geometric mean assumption, $E_{ij} = (E_{ii}E_{jj})^{1/2}$, and the presence of the $\Phi_i\Phi_j$ product, the application of this equation is restricted to the description of endothermic mixing processes, whereby the contacts between molecules are randomly distributed. Such a model is valid only in the case of regular solutions and should be dealt with cautiously when extended beyond the limits of regular solutions. It is completely erroneous when specific interactions are involved, such as hydrogen bonds, which are

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[1] Institut d'Analyse Pharmaceutique, Ecole de Pharmacie, Université de Lausanne, 3, Place du Château, CH-1005 Lausanne, Switzerland.

[2] To whom correspondence should be addressed.

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orientated unsymmetrical interactions which generally lead to exothermic heats of mixing.

To deal with real solutions, corrections must be brought to the above model. The entropy is no longer ideal and excess-entropic corrections must enter real-solution equations. This, fortunately, need not be considered when direct enthalpy measurements are made. However, as the volume of the solution components may either expand or contract upon mixing, the internal energy of mixing is no longer equal to the enthalpy of mixing, and the following expression must be used:

$$\Delta_{\mathrm{mix}}H = \Delta_{\mathrm{mix}}E + P_{\mathrm{int}}\,\Sigma_k N_k(\overline{V}_k - V_k) \qquad (4)$$

where P_{int} (J/ml) is the internal pressure of the solution, and N_k, $\overline{V}_k$, and V_k, respectively, stand for the numbers of moles, the partial molar volumes, and the molar volumes of i, respectively j.

Provided that the solution considered is sufficiently dilute for the internal pressure of the mixture, P_{int}, to be considered equal to that of the pure solvent j, $P_{\mathrm{int},j}$, the internal pressure may be calculated according to Allen *et al.* (13):

$$P_{\mathrm{int},j} = n_j\,\delta_j^2 \qquad (5)$$

δ_j is the total cohesion parameter of the solvent, and n_j is a dimensionless constant characteristic of the solvent which Bagley *et al.* (14) suggests calculating by the following relationship:

$$n_j = \frac{\delta_{jd}^2 + 3\mathrm{RT}/2V_j}{\delta_j^2} \qquad (6)$$

where δ_{jd} and V_j are, respectively, the partial dispersive cohesion parameter and the molar volume of the pure solvent j.

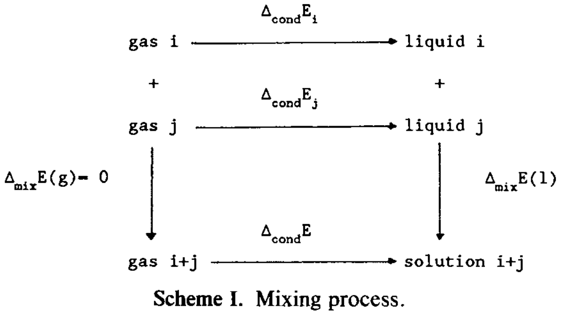
According to Scheme I, the internal energy of mixing, $\Delta_{\mathrm{mix}}E(1)$, associated with the mixing of liquids i and j is

$$\Delta_{\mathrm{mix}}E(1) = \Delta_{\mathrm{cond}}E - \Sigma_k N_k \Delta_{\mathrm{cond}}E_k \qquad (7)$$

where $\Delta_{\mathrm{cond}}E$(kJ/mol) is the internal condensation energy of the mixture of gases i and j, and $\Delta_{\mathrm{cond}}E_k$ is the molar internal energy change due to the condensation of 1 mol of pure i and 1 mol of pure j.

For a two-component solution, $\Delta_{\mathrm{cond}}E$ is given by (15)

$$\begin{aligned}\Delta_{\mathrm{cond}}E &= (\mathrm{RT}/V)\Sigma_i\Sigma_j N_iN_j\beta_{ij} = (\mathrm{RT}/V)(N_i^2\,\beta_{ii} \\ &\quad + N_j^2\beta_{jj} + 2\,N_iN_j\,\beta_{ij})\end{aligned} \qquad (8)$$



Scheme I. Mixing process.

where

$$\begin{aligned}\beta_{ii} &= -\delta_i^2V_i^2/\mathrm{RT} \\ \beta_{jj} &= -\delta_j^2V_j^2/\mathrm{RT} \\ \beta_{ij} &= -\delta_i\delta_jV_iV_j/RT \\ V &= N_i\overline{V}_i + N_j\overline{V}_j \simeq N_i\overline{V}_i + N_jV_j\end{aligned}$$

Taking Eqs. (7) and (8) into account, the enthalpy of mixing, $\Delta_{\mathrm{mix}}H$, can be written thus:

$$\begin{aligned}\Delta_{\mathrm{mix}}H &= (\mathrm{RT}/V)\Sigma_i\Sigma_jN_iN_j\beta_{ij} - \Sigma_kN_k\Delta_{\mathrm{cond}}E_k \\ &\quad + P_{\mathrm{int},j}\Sigma_kN_k(\overline{V}_k - V_k)\end{aligned} \qquad (9)$$

and the partial enthalpy of mixing of solute i in solvent j, $\Delta_{\mathrm{mix}}\overline{H}_i$ (kJ/mol), is obtained by differentiating Eq. (9) with respect to the number of moles N_i of the substance i (for a dilute solution $N_i \ll N_j$):

$$\begin{aligned}\Delta_{\mathrm{mix}}\overline{H}_i &= 2\mathrm{RT}N_j\beta_{ij}/V - \mathrm{RT}\overline{V}_iN_j^2\beta_{jj}/V^2 \\ &\quad - \Delta_{\mathrm{cond}}E_i + P_{\mathrm{int},j}(\overline{V}_i - V_i)\end{aligned} \qquad (10)$$

Finally, according to the definitions of β_{ij} and of β_{jj} and with the condensation energy ($-\Delta_{\mathrm{cond}}E_i = \Delta_{\mathrm{vap}}E_i$) expressed in terms of cohesion parameters, the following equation is obtained:

$$\begin{aligned}\Delta_{\mathrm{mix}}\overline{H}_i &- \overline{V}_iV_j^2\delta_j^2N_j^2/V^2 - P_{\mathrm{int},j}(\overline{V}_i - V_i) \\ &= V_i\delta_i^2 - 2N_jV_jV_i\delta_i\delta_j/V\end{aligned} \qquad (11)$$

or when the total cohesion parameter δ_i is split into three components δ_{ki} (k: d,p,h):

$$\begin{aligned}\Delta_{\mathrm{mix}}\overline{H}_i &- \overline{V}_iV_j^2\delta_j^2N_j^2/V^2 - P_{\mathrm{int},j}(\overline{V}_{\mathrm{i}} - V_i) \\ &= V_i\delta_i^2 - 2(N_jV_jV_i/V)\Sigma_k\delta_{kj}\delta_{ki}\end{aligned} \qquad (12)$$

Equations (11) and (12) are adapted to solutions for which volume expansion or contraction exist, provided that they are not too concentrated. In the case of concentrated solutions, Eq. (9) cannot be simplified to give Eq. (10), and therefore, the following more complete equations have been derived:

$$\begin{aligned}\Delta_{\mathrm{mix}}\overline{H}_i &- \overline{V}_iV_j^2\delta_j^2N_j^2/V^2 - P_{\mathrm{int},j}(\overline{V}_i - V_i) \\ &= (V_i + \overline{V}_iV_i^2N_i^2/V^2 - 2N_iV_i^2/V)\delta_i^2 \\ &\quad + 2(\overline{V}_iN_iN_jV_jV_i/V^2 - N_jV_iV_j/V)\delta_i\delta_j\end{aligned} \qquad (13)$$

or when the total cohesion parameter δ_i is split into three components δ_{ki} (k: d,p,h):

$$\begin{aligned}\Delta_{\mathrm{mix}}\overline{H}_i &- \overline{V}_iV_j^2\delta_j^2N_j^2/V^2 - P_{\mathrm{int},j}(\overline{V}_i - V_i) \\ &= (V_i + \overline{V}_iN_i^2V_i^2/V^2 - 2N_iV_i^2/V)\delta_i^2 \\ &\quad - 2(N_jV_iV_j/V - \overline{V}_iN_iN_jV_iV_j/V^2)\Sigma_k\delta_{kj}\delta_{ki}\end{aligned} \qquad (14)$$

To calculate the total and partial cohesion parameters of solid pharmaceutical substances, the binary thermodynamic quantities, i.e., the partial molar enthalpies of dissolution, $\Delta_{\mathrm{dis}}\overline{H}_i$ (kJ/mol), of the solid i in different solvents j are determined experimentally by calorimetry. The partial molar enthalpies of mixing, $\Delta_{\mathrm{mix}}\overline{H}_i$, needed to solve Eqs. (11) to (14) are then obtained [Eq. (15)], provided the enthalpy of

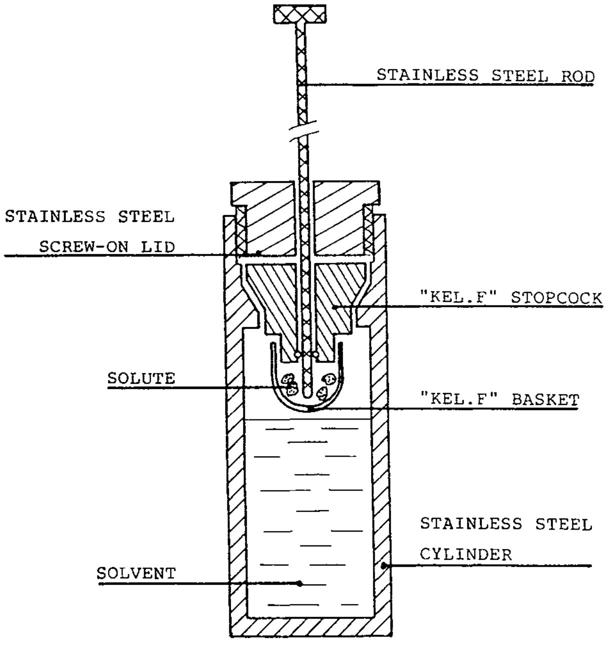


Fig. 1. Calorimetric dissolution cell.

fusion, $\Delta_{\mathrm{fus}}H_i$ (kJ/mol), and the melting point, T_{fus} (K), of the solid i are known.

$$\Delta_{\mathrm{mix}}\overline{H}_i = \Delta_{\mathrm{dis}}\overline{H}_i - \Delta_{\mathrm{fus}}H_i + (\Delta_{\mathrm{fus}}H_i/T_{\mathrm{fus}})(T_{\mathrm{fus}} - 298.15) \quad (15)$$

The third term in this equation estimates the variation of the melting enthalpy of the solute i between 25°C and the melting point.

EXPERIMENTAL

Three solid pharmaceutical substances, caffeine, theophylline, and phenylbutazone (Siegfried AG, CH-4800 Zofingen), were selected on the basis of the following criteria: they are currently used therapeutically, behave largely as neutral nonelectrolytes, and are solid at room temperature. Further, these drugs have been the subject of previous work for the sake of comparison.

Four solvents, i.e., dioxane, methanol, formamide, and nitroethane, all of analytical grade, were chosen among a set of solvents by means of an experimental design optimization technique (16–18) described previously (19–21). The solvents had to meet the following criteria: to have known partial cohesion parameters, to dissolve solutes sufficiently to obtain measurable calorimetric signals, and not to be too viscous since measurements are rendered impossible with high-viscosity solvents. All measurements were made on a Calvet-type microcalorimeter, Setaram C80 (69451 Lyon, France). The device is such that the solid solute and the solvent remain separated as long as the operator does not initiate the reaction. Once the baseline is stable, the rod is firmly pressed down, which causes the small basket to drop to the bottom of the cell, and the solid solute is thus liberated into the solvent. The whole calorimeter rocks back and forth, thus permitting easy dissolution, once the initially isolated solute and solvent are put in contact with each other. The enthalpies of dissolution were measured in a stainless-steel cell (Fig. 1) especially designed for this work (sample volume, 6.7 cm^3; height, 7 cm; diameter, 1.5 cm).

All measurements were carried out at 25.0 ± 0.01°C. Both reference and sample cells A and B were introduced simultaneously into the calorimeter and left overnight to reach thermic equilibrium. For the first measurement, cells A and B were the experimental and reference cells, respectively, with the reverse order for the second measurement. All experiments, i.e., potential change with time, were recorded on a Zenith personal computer. Blank measurements showed that the dropping of the basket into the cell did not give rise to any significant signal.

Partial molar volumes, $\overline{V}_k$, were determined by means of a DMA 60 + DMA 601 densitometer (Anton Paar K.G., A-8054 Graz, Austria) coupled to an automatic sample changer SP2 (Anton Paar K.G., A-8054 Graz, Austria).

RESULTS

The calorimetric measurements of partial molar enthalpies of dissolution were carried out over a wide concentration range, limited by the detection threshold of the signal and by the solubility of the solutes. Enthalpies of dissolution did not appear to be concentration dependent.

With the exception of phenylbutazone in formamide, all partial molar enthalpies of dissolution were positive (endothermic dissolution) (Table I). Despite the positive enthalpies of dissolution in 11 of 12 cases, the dissolution process took place in all cases, because of the gain in entropy.

Partial molar enthalpies of dissolution of a given drug vary greatly depending on the solvents used. Such variations must be attributed to the mixing process, since for a given drug the enthalpy of melting remains constant, whatever the solvent. Partial molar enthalpies of mixing (Table II) were obtained according to Eq. (15) by subtracting enthalpies of fusion at 25°C from partial enthalpies of dissolution.

Athermic mixing, $\Delta_{\mathrm{mix}}\overline{H}_i \approx 0$, was observed for caffeine and theophylline in formamide and phenylbutazone in

Table I. Partial Molar Enthalpies of Dissolution, $\Delta_{\mathrm{dis}}\overline{H}_i$ (kJ/mol)[a]

	Solvent			
Solute	Dioxane	Methanol	Formamide	Nitroethane
Caffeine	21.0 ± 2.8	31.1 ± 0.9	13.0 ± 0.4	18.7 ± 0.4
Theophylline	19.5 ± 0.6	23.7 ± 1.6	15.6 ± 1.6	23.7 ± 1.7
Phenylbutazone	19.6 ± 1.6	28.6 ± 2.5	−23.5 ± 1.8	20.2 ± 0.9

[a] Each measurement has been repeated six times.

Table II. Enthalpies of Fusion, $\Delta_{\text{fus}}H$, Melting Points, T_{fus}, and Partial Molar Enthalpies of Mixing, $\Delta_{\text{mix}}\bar{H}_i$, of the Solutes

Solute	$\Delta_{\text{fus}}H$ (kJ/mol)	T_{fus} (K)[a]	$\Delta_{\text{mix}}\bar{H}_i$ (kJ/mol) Dioxane	Methanol	Formamide	Nitroethane
Caffeine	21.1[b]	509.9	8.7 ± 2.8	18.8 ± 0.9	0.7 ± 0.4	6.3 ± 0.4
Theophylline	29.7[b]	545.9	3.3 ± 0.6	7.5 ± 1.5	−0.6 ± 1.6	7.4 ± 1.6
Phenylbutazone	25.5[c]	378.8	−0.3 ± 1.6	8.5 ± 2.5	−42.7 ± 1.8	0.2 ± 0.9

[a] Determined experimentally by a Mettler PF 51 instrument.
[b] From Ref. 22.
[c] From Ref. 23.

dioxane and nitroethane, which would indicate uniformity of adhesive and cohesive interaction energies, hence approximate equality of the cohesion parameters of the partners.

To determine cohesion parameters of the solutes, the partial molar volumes of the solutes as well as the internal pressure of the solvents are needed. The partial molar volumes, $\bar{V}_i$, of the solutes dissolved in the different solvents are obtained from densitometric measurements. The density of a binary mixture, d_{ij} (g/ml), is linked to the partial molar volumes of its components by the following relationship:

$$(x_iM_i + x_jM_j)/d_{ij} = x_i\bar{V}_i + x_j\bar{V}_j = V \qquad (16)$$

where M_k (g) and x_k are the molecular weight and the mole fraction of substances i and j, and V (ml) is the volume of the solution. Provided the solute is sufficiently dilute, the partial molar volume of the solvent may be assumed to be identical to that of the pure solvent. Consequently, the following simplified relationship can be used:

$$[(x_iM_i + x_jM_j)/d_{ij}] - x_jV_j = x_i\bar{V}_i \qquad (17)$$

The differences observed between the molar volumes of the solutes in the pure state, V_i, and dissolved in the different solvents, $\bar{V}_i$, were less than 10% (Table III).

The internal pressures of the solvents, P_{int_j}, were calculated by means of Eqs. (5) and (6). The values of their total, δ_j, and partial dispersive, δ_{jd}, cohesion parameters as well as of their molar volumes, V_j, are taken from the literature (Table IV).

Finally, the total and partial cohesion parameters of the pharmaceutical solids considered as supercooled liquids are obtained by solving Eqs. (11) to (14) (Table V). There is no significant difference in the results obtained from the simplified Eq. (12) [Eq. (11)] or from the more elaborate Eq. (14) [Eq. (13)]. This observation is valid for all three solutes and indicates that the simplified equations are even applicable to fairly concentrated solutions. However, differences can be observed in the results obtained from Eqs. (11) and (12) [or from Eqs. (13) and (14)]. The values of total cohesion parameters calculated directly by nonlinear regression of Eq. (11) or (13) do not always agree with those obtained from the partial cohesion parameter models [Eq. (12) or (14)], which, via Eq. (2), produce total cohesion parameters of approximately 25 $\text{MPa}^{1/2}$.

The partial dispersive cohesion parameters, δ_d, all have about the same value, amounting to approximately 17 $\text{MPa}^{1/2}$, whereas the values of polar and hydrogen bonding components fluctuate somewhat from one compound to another.

DISCUSSION AND CONCLUSION

Two types of cohesion parameters of three pharmaceutical solid substances have been derived from dissolution calorimetric measurements, i.e., the total and the partial cohesion parameters.

The values of the total cohesion parameters determined are compared with those previously obtained by various methods and authors in Table VI. True cohesion parameters, by definition, reflect self-interaction capacities and can be considered as such only when obtained from measurements made on pure substances: heat of vaporization for liquids, heat of sublimation for solids. They are useful tools for evaluating whether two substances in contact with each other can easily break their inner cohesive bonds and thus engage in solute/solvent interaction. True cohesion parameters should therefore be related to "cavity formation" in the case of solvents and to a parameter reflecting the capacity of the molten molecule for leaving the "solute bulk." The extent of breaking of cohesion bonds depends on the nature of the partners put together: if there is no mutual attraction, cohesive bonds will remain whole. The mixing itself is related to the binary interaction capacities of the solute and of the

Table III. Molar Volumes, V_i (mL), and Partial Molar Volumes, $\bar{V}_i$ (mL), of the Solutes

Solute	V_i	$\bar{V}_i$ Dioxane	Methanol	Formamide	Nitroethane
Caffeine	144.0[a]	144.49 ± 0.286	144.0 ± 3.44	143.09 ± 0.692	141.5 ± 2.07
Theophylline	124.0[a]	124.36 ± 0.455	132.0 ± 3.32	110.02 ± 1.79	120.04 ± 2.59
Phenylbutazone	274.0[b]	261.5 ± 1.48	243.9 ± 2.22	241.9 ± 5.59	274.7 ± 3.65

[a] From Ref. 22.
[b] From Ref. 23.

Table IV. Physicochemical Properties[a] of the Solvents

Solvent	$P_{\text{int},j}$ (J/mL)	V_j (mL)	δ_j (MPa$^{1/2}$)	δ_{jd} (MPa$^{1/2}$)	δ_{jp} (MPa$^{1/2}$)	δ_{jh} (MPa$^{1/2}$)
Dioxane	441.64	85.7	20.5	19.0	1.8	7.4
Methanol	72.96	40.7	29.6	15.1	12.3	22.3
Formamide	85.79	39.8	36.6	17.2	26.2	19.0
Nitroethane	153.60	71.5	22.7	16.0	15.5	4.5

[a] The molar volumes and the cohesion parameters are taken from Ref. 24.

solvent. As binary interactions are at least partly determined by differences in cohesive interaction capacities, they can be predicted to some extent from self-interaction capacities of solutes and solvents. Thus, water and isooctane do not mix because their self-interaction capacities are too different: isooctane self-interacts only by nonspecific dispersion forces, whereas water essentially does so by specific hydrogen-bonding forces. Their very low mutual solubility reflects what could easily have been predicted from the big difference in their cohesion parameter values. Therefore, total cohesion parameters issued from pure-component data (energies of sublimation or of vaporization), as well as from energy and volume increment addition, are useful references, because they represent the actual self-interaction capacities of the substances and they do not involve any bias because of adhesive interactions.

Among the different indirect techniques mentioned in Table VI, calorimetry provides the most direct way of obtaining cohesion parameters from binary thermodynamic quantities involving a solute and a solvent. It permits directly enthalpy measurements, whereas methods based on solubility or partition yield free enthalpy-related values requiring entropic corrections.

It is difficult to determine total cohesion parameters because their numerical values do not indicate the forces involved and lie within fairly small range. This is especially true for pharmaceutically active drugs. Barbiturates (31), for instance, despite their different functional groups, all have total cohesion parameters ranging from approximately 24 to 26 MPa$^{1/2}$.

Partial cohesion parameters should therefore lead to a better differentiation of substances. They must, however, be considered with caution when obtained from binary thermodynamic quantities in which unsymmetrical interactions are involved.

As previously observed with the total cohesion parameters, the values of the partial cohesion parameters of the three pharmaceutical substances obtained by various methods fluctuate depending on the experimental method: solubility, partition, chromatography, or calorimetry (Table VII). The variations can also partly be accounted for by differences in that the solvents or the probes used to assess the self-interaction capacity of a drug. Depending on the choice of a set of solvents with or without hydrogen-bonding or other strong specific interaction with the solute, total and partial cohesion parameters of the solute will fluctuate. Further, the values of the cohesion parameters of solvents taken from the literature correspond to pure-substance properties. Nitroethane, which does not self-interact by hydrogen bonding because it is mainly a hydrogen-bond acceptor, has a low δ_h value. As the cohesion parameters of solutes are established from binary interactions involving both the solute and the solvent, any incorrect value attributed to the solvent will have a direct effect on that of the solute. Finally, it must be pointed out that experimentally obtained partial cohesion parameters cannot be automatically considered an intrinsic property of the pure drug.

In conclusion, total and partial cohesion parameters obtained from calorimetry or from any indirect method are in fact adhesion-derived cohesion parameters. They express average heterointeraction capacities. In fact, as shown in Table VIII for the three pharmaceutical substances, the adhesion-derived cohesion parameter values significantly differ from one solvent to another when calculated by solving Eq. (11) for each solute in one single solvent.

The average heterointeraction capacities can be assimilated to cohesion parameters only provided that the values of cohesion parameters of the solvents used cover a wide range including those of the solute. Under these conditions, values derived from binary thermodynamic quantities in-

Table V. Partial, δ_k (k: d,p,h), and Total, δ, Cohesion Parameters (MPa$^{1/2}$) of the Pharmaceutical Solids

Solute	δ_d	δ_p	δ_h	δ^a		δ
Caffeine						
Eq. (12)	18.14	14.83	12.53	26.57	Eq. (11)	29.83
Eq. (14)	17.58	14.59	12.76	26.17	Eq. (13)	29.92
Theophylline						
Eq. (12)	17.01	11.47	13.63	24.63	Eq. (11)	23.97
Eq. (14)	17.00	12.17	13.61	24.95	Eq. (13)	23.99
Phenylbutazone						
Eq. (12)	17.98	14.59	11.15	25.70	Eq. (11)	26.56
Eq. (14)	17.76	14.54	11.44	25.64	Eq. (13)	26.64

[a] Obtained from δ_k values by Eq. (2).

Table VI. Total Cohesion Parameters, δ ($MPa^{1/2}$), Obtained from Various Methods

Method	Caffeine	Theophylline	Phenylbutazone
Sublimation[a]			
β-Caffeine	28.1[b]	34.4[c]	
α-Caffeine	27.1[b]		
Vaporization[d]	22.4[e]	31.9[f]	
Surface tension[g]	26.0	29.1	
Gas chromatography	26.6[g]	28.7[g]	28.1[h]
Solubility			
Martin	28.2[i]	28.7[i]	
Reuteler			25.2[j]
Rey-Mermet[k]	27.2	28.2	25.8
Partition[k]	24.3		
Increment addition[l]	25.6	28.8	23.9
This work [Eq. (13)]	29.9	24.0	26.6

[a] Calculated as $[(\Delta_{sub}H - 2RT)/V_{cryst}]^{1/2}$.
[b] From Refs. 25 and 26.
[c] From Refs. 27 and 28.
[d] Calculated as $[(\Delta_{vap}H - RT)/V_{liq}]^{1/2}$.
[e] From Refs. 22 and 25.
[f] From Refs. 22 and 27.
[g] From Ref. 20.
[h] From Ref. 23.
[i] From Ref. 22.
[j] From Ref. 15.
[k] From Ref. 29.
[l] From Ref. 30.

volving a solvent and a solute represent the nearest approximations of true cohesion parameters. Therefore, adhesion-derived cohesion parameters, calculated from measurements in a set of solvents in which very different adhesive interactions are generated, do not lead to precise solubility predictions.

Cohesion parameters account only to a small extent for the solubility of solid solutes. The enthalpy of fusion largely determines solubility. When the latter is high, the energy which has to be supplied from the solvent to ensure complete disruption of the crystal is so high that, even when entropy is gained and the mixing process is exothermic, solubility remains low.

Table VII. Partial Cohesion Parameters, δ ($MPa^{1/2}$), Obtained by Various Methods

Solute	Method	δ_d	δ_p	δ_h
Caffeine	Partition[a]	21.4	3.8	8.3
	Solubility[a]	20.1	13.9	10.5
	Solubility[b]	20.6	7.2	18.6
	Gas chromatography[c]	17.0	11.7	17.0
	This work [Eq. (14)]	17.3	13.7	13.4
Theophylline	Solubility[a]	23.8	13.4	11.9
	This work [Eq. (14)]	16.8	11.3	13.7
Phenylbutazone	Solubility[a]	16.9	13.0	10.7
	Solubility[d]	24.5	9.2	7.6
	This work [Eq. (14)]	17.5	12.5	10.7

[a] From Ref. 29.
[b] From Ref. 33.
[c] From Ref. 32.
[d] From Ref. 15.

Table VIII. Total Cohesion Parameter Values ($MPa^{1/2}$) of the Pharmaceutical Solids Obtained by Solving Eq. (11) in One Single Solvent

Solvent	Caffeine	Theophylline	Phenylbutazone
Dioxane	28.03	25.41	26.51
Methanol	18.17	—	16.80
Formamide	32.64	22.84	29.67
Nitroethane	30.30	30.01	—

The model developed by Hildebrand in 1920 with a view to predicting solubilities was intended for nonpolar liquids. His regular-solution theory leads to reasonable solubility predictions in the case of mixtures of nonpolar substances, because the geometric mean rule is applicable; thus, adhesion can be predicted from the cohesion of both solute and solvent molecules. It is, however, not appropriate to extend Hildebrand's model beyond the limits of regular solutions, i.e., to real solutions. To describe mixing in real solutions, a satisfactory way of obviating binary interaction parameters has yet to be found.

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