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Experimentally optimized determination of the partial and total cohesion parameters of an insoluble polymer (microcrystalline cellulose) by gas–solid chromatography

Nguyen Huu-Phuoc, Hô Nam-Tran, Michel Buchmann and Ulrich W. Kesselring

Institut d'Analyse Pharmaceutique, Ecole de Pharmacie, Université de Lausanne, Lausanne (Switzerland)

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Summary

The partial solubility parameters of microcrystalline cellulose ($\delta_d = 9.5 \pm 0.5$, $\delta_p = 6.2 \pm 1.0$, $\delta_h = 15.3 \pm 0.7$, $\delta_t = 19.2 \pm 0.4$) were obtained, on the basis of the Snyder/Karger-Hansen interaction model, where $\Delta E^A = V_i(\delta_d^i d_d^i + \delta_p^i \delta_p^j + \delta_h^i d_h^j)$. They were deduced from the internal adsorption energy of *n*-decane, carbon tetrachloride, benzene, acetonitrile, methanol and ethanol, determined by gas–solid chromatography. In order to get the highest accuracy and precision possible with minimal experimental work and the most appropriate solutes, the planification of the experiments was achieved by optimization of the experimental matrix. This revealed that the best results are obtained when 6 out of the 14 solutes were chosen.

Introduction

Tablets and pharmaceutical powders are widely used medicinal forms, in which the drug is mixed with one or several excipients chosen to optimize the fabrication, the stability and the rapid absorption of the drug by the gastrointestinal tube.

The excipients should be inert, which implies that they should in no way interact with the drugs. In the absence of all physical and chemical interactions, it is conceivable that neither the liberation nor the stability of the drug is perturbed. The excipients used in industry are far from qualifying for all these criteria and may strongly modify the bioavailability (Lerk et al., 1982) as well as the rates and mechanisms of decomposition of a drug (Taillens and Kesselring, 1983). Up to now, excipients have always been chosen in an empirical way by means of accelerated stability studies at temperatures higher than room temperature, the results of which are extrapolated to room temperature. Since these experiments are tedious, a theoretical evaluation of the behaviour of a drug in a mixture is highly justified. Therefore it is necessary to find and determine a quantitative intrinsic parameter characterizing the aptitude of the excipients, as well as that of the drugs, to interact. A first attempt led to a classification of a few excipients according to their adsorption energy of nitrogen (Perrier and Kesselring, 1983), which could be linearly related to the decomposition rate constant of nitrazepam, normalized with respect to the surface of the excipients and of the drug.

Correspondence: U.W. Kesselring, Institut d'Analyse Pharmaceutique, Ecole de Pharmacie, Université de Lausanne, 3 Place du Château, CH-1005 Lausanne, Switzerland.

However, this energy term is insufficient, because it only involves induction and dispersion interactions; in other words, only the forces able to account for nitrogen adsorption on excipients. The parameter required must include all the forces leading to a reversible physical adsorption. This is the case for the cohesion parameter δ ($cal^{1/2} \cdot cm^{-3/2}$), the initial definition of which was given by Hildebrand and Scott under the name of solubility parameter (Hildebrand et al., 1970). The subdivision proposed by Hansen (1969) into dispersion (d), polar (p) and hydrogen bonding (h) could be the solution aimed at, provided the determination of these values is possible for solids:

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (1)$$

These terms indeed express cohesion energy densities ($\Delta E^v/V$) (cal/mol) or else the aptitude to interact by dispersion, polar or hydrogen bonding forces. V ($cm^3 \cdot mol^{-1}$) is the molar volume. The application of these parameters, primarily defined for liquids, may be extended to solids, which will henceforth be considered as supercold liquids (Barton, 1985).

While numerous tables of partial solubility parameters exist for liquids (Barton, 1983), the situation is quite different in the case of solids, the experimental determination of their cohesion parameters being difficult. A new experimental method (Phuoc et al., 1986), different from Martin's solubility method (Martin et al., 1983) and from the calculation technique consisting of adding energy increments related to molecular functional groups (Beerbower and Hansen, 1971), is suggested: it is based on the equation proposed by Keller et al. (1971), and implies the determination by gas–solid chromatography of the internal adsorption energy which is linked to Hansen's parameters δ_d, δ_p, δ_h characterizing the solute i and the unknown cohesion parameters of the solid j, used as the stationary phase:

$$-\Delta E^A = V_i\left(\delta_d^i\delta_d^j + \delta_p^i\delta_p^j + \delta_h^i\delta_h^j\right) \qquad (2)$$

Up to now, this seems to be the only method which enables the experimental evaluation of partial cohesion parameters of excipients which are insoluble polymers such as, for instance, microcrystalline cellulose.

It consists of introducing the excipient into a chromatographic column and determining the adsorption energies of a series of molecular probes, of which the partial cohesion parameters are known, on the stationary phase, according to the procedure described earlier (Phuoc et al., 1986). One of the difficulties linked to this technique is the determination of the number and the nature of the molecular probes to be injected. Another one is to define the experimental domain ensuring the highest possible precision and exactitude of the smallest number of experiments.

The problem can be solved by using the experimental matrix optimization technique (Mathieu, 1981; Mathieu et al., 1980; Cativiela et al., 1983), applied in this work to find the best and the smallest set of volatile molecular probes at low temperatures, representing the whole of the interaction forces which can arise between the solutes and the stationary phase. The adsorption energies of the corresponding N molecules, expressed by their δ_k (k = d, p, h) values according to Hansen (1969) can thus be expressed in a matrix form:

$$\begin{bmatrix} -\Delta E_1^A \\ -\Delta E_n^A \\ -\Delta E_N^A \end{bmatrix} = \begin{bmatrix} V_1\delta_{1d} & V_1\delta_{1p} & V_1\delta_{1h} \\ V_n\delta_{nd} & V_n\delta_{np} & V_n\delta_{nh} \\ V_N\delta_{Nd} & V_N\delta_{Np} & V_N\delta_{Nh} \end{bmatrix} \times \begin{bmatrix} \beta_d \\ \beta_p \\ \beta_h \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_n \\ \epsilon_N \end{bmatrix} \qquad (3)$$

or more generally,

$$Y = X\beta + \epsilon \qquad (4)$$

$$\hat{Y} = XB \qquad (5)$$

where Y is the column vector containing the N values of the experimental determinations of the adsorption energy ($-\Delta E_n^A$) of the N solutes, $\hat{Y}$ is the column vector containing the values of the adsorption energy estimated by the theoretical model (Eqn. 2) and X is the experimental matrix,

formed of elements (X_{nk}), where (X_{nk}) = ($V_n \cdot \delta_{nk}$), V_n is the molar volume of the n^{th} solute and δ_{nk} is the partial solubility parameter k of this solute.

The experimental matrix has (N, k) dimensions with N lines representing the total number of N solutes, and k columns (in this case 3), representing the 3 types of interaction d, p and h. The B vector contains the estimated values of β, which are the parameters of the model. The ϵ vector corresponds to the experimental errors, ϵ_n, composed of N elements (the number of equations).

Before starting the experiment, it is necessary to know whether the experimental domain defined by the N chosen probe molecules will give sufficient information to provide a good estimation of the coefficients of the model (β_d, β_p, β_h, i.e. δ_d^j, δ_p^j and δ_h^j) forming the column vector β. This supposes that:

(1) $\mathrm{cov}(b_k^j, b_{k'}^j) \rightarrow 0$

(2) $|b_k^j - \beta_k^j| \rightarrow$ minimum

b_k^j is the component of the vector B and k and k′ are two different types of interaction.

The first criterion expressed is that of independency between b_k^j and $b_{k'}^j$. The degree of independence is estimated by the inflation factors, which are the diagonal elements of the inversed matrix of the correlation matrix R ($r_{kk'}$), of which the elements are given by (Mathieu, 1981):

$$r_{kk'} = \sum (V_n\delta_{nk} - V\,d_k)(V_n\delta_{nk'} - V\,d_{k'})/ \left[\sum (V_n\delta_{nk} - V\,d_k)^2 \cdot \sum (V_n\delta_{nk'} - V\,d_{k'})^2\right]^{1/2} \quad (6)$$

where

$$V\,d_k = 1/N \sum V_n\delta_{nk} \text{ and } V\,d_{k'} = 1/N \sum X_n\delta_{nk'}$$

A good experimental domain is one for which the values of the different inflation factors are in the [1,10] interval (Marquardt, 1970; Snee, 1973; Hahn et al., 1976). To fulfill the second criterion, defining the overall precision, a statistical evaluation of the plan of experiments defined by the N solutes must be undertaken by the optimization of the matrix X. The overall precision, indeed, depends on the choice of a sub-matrix Z of the matrix X, formed of the optimal number of solutes. It is the D-criterion which enables the choice of the matrix Z, which is called D-optimal when the determinant of the matrix (Z^tZ) is maximum. Z^t is the transpose of the sub-matrix Z. If the matrix Z has been well chosen, the variance of the coefficients β_k^j and the volume v of the confidence ellipsoid are minimal.

$$v = C/|Z^tZ| \quad (7)$$

where C is a constant.

The determinant $|Z^tZ|$ depends both on the $V_n\delta_{nk}$ values and on the number n of the solutes. It is possible to compare the values of $|Z^tZ|$ determinants containing a different number of n molecular probes only by means of the normalized determinants M(n):

$$M(n) = |Z^tZ|/n^k = |Z^tZ|/n^3 \quad (8)$$

According to the values of M(n), the number and the nature of the molecular probes to be injected on the stationary phase will be determined.

Materials and Methods

Microcrystalline cellulose (Avicel PH101, Interchemie AG, CH-Zürich) was used as such, without any further purification. It was packed into stainless steel chromatographic columns by Tranchant's technique (Tranchant, 1982) and conditioned at 80°C for 48 h with nitrogen as a carrier gas and passed through a Carrier Gas Purifier (Supelco SA, CH-1299 Crans). The 14 molecular probes retained (from Fluka AG, CH-9470 Buchs and E. Merck, Darmstadt, F.R.G.), of analytical grade, are listed in Table 1. They were used without any further purification.

Measurements were carried out on a Varian gas chromatograph (CH-1213 Genève) equipped with an FID detector.

TABLE 1

MOLAR VOLUME, V ($cm^3 \cdot mol^{-1}$) AND PARTIAL (δ_d, δ_p, δ_h) AND TOTAL (δ_t) SOLUBILITY PARAMETERS ($cal^{1/2} \cdot cm^{-3/2}$) OF SOME ORGANIC COMPOUNDS ACCORDING TO HANSEN (1969)

Compound	V	δ_d	δ_p	δ_h	δ_t
(1) *n*-Hexane	131.6	7.24	0.0	0.0	7.24
(2) *n*-Heptane	147.4	7.42	0.0	0.0	7.42
(3) *n*-Octane	164.0	7.55	0.0	0.0	7.55
(4) *n*-Nonane	180.0	7.65	0.0	0.0	7.65
(5) *n*-Decane	196.9	7.72	0.0	0.0	7.72
(6) Carbon tetrachloride	96.0	8.65	0.0	0.0	8.65
(7) Benzene	89.4	8.95	0.5	1.0	9.15
(8) Ethyl Ether	105.0	7.05	1.4	2.5	7.62
(9) Chloroform	81.0	8.65	1.5	2.8	9.21
(10) Acetone	74.0	7.58	5.1	3.4	9.77
(11) Acetonitrile	52.6	7.50	8.8	3.0	11.90
(12) Tetrahydrofuran	81.7	8.22	2.3	3.9	9.52
(13) Methanol	41.0	7.42	6.0	10.9	14.28
(14) Ethanol	59.0	7.73	4.3	9.5	12.92

The experimental conditions are indicated in Table 2. The molecular probes were injected in extremely small quantities, at the limit of detectability. In order to achieve this, the needle of the Hamilton syringe (CH-7402 Bonaduz, Liechtenstein) was put into contact with the vapour of the molecular probe. Any excess was removed by aspiration with a water pump before introduction of the remaining traces into the injection chamber.

The determination of the dead time was accomplished by injection of *n*-pentane, *n*-hexane, *n*-heptane, *n*-nonane and *n*-decane, according to the method proposed by Smith et al. (1978).

The cohesion parameters are calculated by multilinear regression from the adsorption energies determined for the molecular probes chosen according to the D-criterion.

TABLE 2

CHROMATOGRAPHIC CONDITIONS FOR THE DETERMINATION OF ADSORPTION ENERGIES ON MICROCRISTALLINE CELLULOSE

Column	Stainless steel
Length	150 cm
Internal diameter	2.36 mm
Detector	FID
Carrier gas	N_2
Flow rate	20 ml/min
Column temperature	30–90 °C
Injection temperature	30–90 °C
Detection temperature	90–100 °C
Weight of the filling	1.38 g

Results

The partial cohesion parameters of microcrystalline cellulose obtained in this work are: $\delta_d = 9.8 \pm 0.5$; $\delta_p = 6.2 \pm 1.0$; $\delta_h = 15.3 \pm 0.7$; $\delta_t = 19.2 \pm 0.4$ ($cal^{1/2} \cdot cm^{-3/2}$).

The choice of the experimental domain formed of 14 molecular probes was good considering the values of the inflation factors [$f(\delta_d) = 1.056$; $f(\delta_p) = 1.927$; $f(\delta_h) = 1.859$], i.e. with respect to accuracy. However, the experimental matrix which yields better precision and yet acceptable accuracy is that which contains *n*-decane, carbon tetrachloride, benzene, acetonitrile, methanol and ethanol (Table 3). The adsorption energies of only these six solutes (Table 4) were required to calculate the partial cohesion parameters. The applicability of the Keller, Karger, Snyder-Hansen model (Eqn. 2) was confirmed by recalculation of the adsorption energies of the 14 solutes on microcrystalline cellulose using the partial cohesion parameters obtained (Table 5).

TABLE 3

VALUES OF THE NORMALIZED DETERMINANT, M(n), AS A FUNCTION OF THE NUMBER OF MOLECULAR PROBES, n, FORMING THE EXPERIMENTAL MATRIX Z, SUB-MATRIX OF X

n	M(n)	Number of molecular probes [a]
3	0.168×10^5	6, 11, 13
4	0.137×10^5	6, 7, 11, 13
5	0.129×10^5	6, 7, 11, 13, 14
6	0.105×10^5	5, 6, 7, 11, 13, 14
7	0.858×10^4	4, 5, 6, 7, 11, 13, 14
8	0.723×10^4	4, 5, 6, 7, 10, 11, 13, 14
9	0.616×10^4	3, 4, 5, 6, 7, 10, 11, 13, 14
10	0.525×10^4	2, 3, 4, 5, 6, 7, 10, 11, 12, 13, 14

[a] cf. Table 1.

TABLE 4

INTERNAL ADSORPTION ENERGIES OF 6 MOLECULAR PROBES ON MICROCRYSTALLINE CELLULOSE, OBTAINED BY GSC

Molecular probes	$-\Delta E^A$ (kcal·mol^{-1})		
	Column 1	Column 2	Mean value
n-Decane	13.57	14.82	14.19
Carbon tetrachloride	8.97	8.45	8.71
Benzene	9.25	8.96	9.11
Acetonitrile	9.99	8.53	9.26
Methanol	12.26	10.06	11.16
Ethanol	15.03	14.95	14.99

TABLE 5

EXPERIMENTAL AND ESTIMATED INTERNAL ADSORPTION ENERGIES, $-\Delta E^A$ (kcal·mol^{-1}) OF MOLECULAR PROBES ON MICROCRYSTALLINE CELLULOSE

Molecular probes	$-\Delta E^A$		$\Delta(\Delta E^A)$ (%)
	Experimental	Estimated	
n-Hexane	9.26	9.34	+11.6
n-Heptane	9.50	10.72	+11.4
n-Octane	11.12	12.13	+8.3
n-Nonane	12.79	13.50	+5.3
n-Decane	14.19	14.82	+4.3
Carbon tetrachloride	8.71	8.14	−7.0
Benzene	9.10	9.49	+4.1
Ethyl ether	12.55	12.18	−3.0
Chloroform	9.83	11.09	+11.3
Acetone	12.59	11.69	−7.6
Acetonitrile	9.26	9.15	−1.2
Tetrahydrofurane	13.70	12.62	−6.3
Methanol	11.16	11.34	+1.5
Ethanol	14.99	14.62	−2.5

Discussion

The two fundamental criteria which enable one to judge the quality of a result are precision and accuracy. The values of these parameters, depend, on the one hand, on the perfect execution of the experimental manipulations and, on the other, on the choice of the most appropriate molecular probes. To obtain the best precision on the cohesion parameters of microcrystalline cellulose, it would have been sufficient, according to the D-optimal criterion, to work with 3 molecular probes: carbon tetrachloride, acetonitrile and methanol which yield the maximum normalized determinant M (Table 3). However, if the inter-independence of the δ_d^j, δ_p^j, δ_h^j terms of the solid is considered by means of the inflation factors calculated for these 3 solutes, a loss in accuracy is indicated by the fact that their values largely exceed 10. High precision has therefore been achieved at the cost of exactitude. Moreover, adsorption energies of acetonitrile and methanol are poorly reproducible (Table 4) and their negative influence on the final overall precision of the cohesion parameters of the solid is amplified by the small number (injection of three solutes on only two columns each) of the measurements retained for their calculation (Table 6).

Since any result should possess the best possible precision and accuracy, a compromise has to be chosen, characterized, in the statistical evaluation of the experimental plan, by the choice of the solutes yielding inflation factors lower than 10 and an experimental matrix with the biggest possible normalized determinant. In our experiment, this compromise was obtained with the six following solutes: *n*-decane, carbon tetrachloride, benzene, acetonitrile, methanol and ethanol. They belong to an experimental plan having both good inflation factors [$f(\delta_d) = 2.245$; $f(\delta_p) = 2.241$; $f(\delta_h) = 1.691$] and an experimental matrix with a normalized determinant amounting to 0.105×10^5 (Table 3).

Table 6 enables comparison of the partial and the total cohesion parameters of microcrystalline cellulose obtained with, respectively, 3, 6 and 14 molecular probes. The values collated clearly show what a time-saver this optimization of the experimental matrix is, since the values of the cohesion parameters calculated from the adsorption energies of six or fourteen molecular probes are similar in value. Furthermore, the evolution of the *F*-test values indicates that the strength of the relation between the random variables (adsorption energies) and the non-random ones (cohesion parameters) is improved if the results obtained with 6 solutes are retained instead of those obtained with 3 or 14 solutes (Table 6).

Once the partial cohesion parameters are known, the prediction and description qualities of

TABLE 6

PARTIAL AND TOTAL COHESION PARAMETERS ($cal^{1/2} \cdot cm^{-3/2}$) OF MICROCRYSTALLINE CELLULOSE CALCULATED BY MEANS OF THE ADSORPTION ENERGIES OF, RESPECTIVELY, 3, 6 AND 14 SOLUTES

Number of solutes	δ_d	δ_p	δ_h	δ_t	r^2	F-test
3	10.5 ± 2.0	6.1 ± 3.0	15.5 ± 2.5	18.9 ± 2.4	0.9919	123
6	9.8 ± 0.5	6.2 ± 1.0	15.3 ± 0.7	19.2 ± 0.4	0.9994	1549
14	9.6 ± 0.4	7.1 ± 1.2	15.2 ± 0.9	19.3 ± 0.9	0.9936	1295

the Karger, Keller, Snyder/Hansen model can be verified by recalculation of the adsorption energies of the 14 molecular probes on microcristalline cellulose by means of Eqn. 2. Comparison of the recalculated values with the experimental ones shows that they are in excellent agreement (Table 5). The deviations observed, at the most of 11.6%, speak in favour of this adsorption model.

Conclusion

On the basis of the results obtained in this work, a general method may be proposed for the determination of the partial cohesion parameters of insoluble solid polymers. It consists in the gas-chromatographic determination of the adsorption energies on the polymers of interest of solutes with sufficiently high vapour pressure and known cohesion parameters. To ensure the best accuracy and precision of the results, the nature and the number of solutes to be used are chosen by optimization of the experimental matrix with respect to its inflation factors and to the value of the normalized submatrix Z.

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