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Inverse gas chromatographic determination of solubility parameters of excipients

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Abstract

The principle aim of this work was an application of inverse gas chromatography (IGC) for the estimation of solubility parameter for pharmaceutical excipients. The retention data of number of test solutes were used to calculate Flory–Huggins interaction parameter ($\chi^{\infty}_{1,2}$) and than solubility parameter (δ_2), corrected solubility parameter (δ_T) and its components (δ_d, δ_p, δ_h) by using different procedures. The influence of different values of test solutes solubility parameter (δ_1) over calculated values was estimated. The solubility parameter values obtained for all excipients from the slope, from Guillet and co-workers' procedure are higher than that obtained from components according Voelkel and Janas procedure. It was found that solubility parameter's value of the test solutes influences, but not significantly, values of solubility parameter of excipients.

Keywords: Inverse gas chromatography; Solubility parameter; Hansen solubility parameters

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1. Introduction

The solubility parameter concept found an application in pharmacy for explanation different properties of the components forming a formulation. Knowledge of the solubility parameter data for different excipients is important to predict the magnitude of interaction between the components of formulation and further stability of the product. Solubility parameter data are useful in the description and interpretation of different phenomenon occurring between materials like their miscibility, compatibility or adsorption.

There are several different methods used to estimate solubility parameter of materials, such as swelling measurements (Bristow and Watson, 1958; Aharoni, 1992), solubility/miscibility measurements in liquids with known cohesive energy. These methods are often time consuming and laborious. Solubility parameter can also be calculated by using several group additive methods (Van Krevelen, 1990), where knowledge of the molecular structure of a material is required. It is possible to determine solubility parameter for different materials from viscosity measurements (Hansen, 2000), inverse gas chromatography (IGC) (Price, 1989)

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and mechanical measurements (Roberts and Rowe, 1993).

Inverse gas chromatography method is widely used for characterization of polymers and polymer blends (Price, 1989), surfactants (Schaefer et al., 2001; Choi et al., 1996), biopolymers, solid food and petroleum pitches (Voelkel, 1996). In this method an investigated material (stationary phase) is placed in a column and than is characterized using volatile probes of known properties (test solutes), which are carried by a mobile phase. According to DiPaola-Baranyi and Guillet (1978) method, Flory–Huggins interaction parameter ($\chi_{1,2}^{\infty}$) and solubility parameter (δ_2) are calculate from experimentally collected retention data for the series of carefully selected test solutes.

The term solubility parameter is related to cohesive energy density (CED), which indicates the energy of vaporization per unit volume.

$$\delta = (\mathrm{CED})^{1/2} = \left[\frac{\Delta H - RT}{V_\mathrm{m}}\right]^{1/2} = \left[\frac{\Delta E}{V_\mathrm{m}}\right]^{1/2} \quad (1)$$

where δ is the solubility parameter, R the gas constant, T the temperature, ΔH the enthalpy of vaporization, V_m the molar volume and ΔE is the energy of vaporization.

Hence, the cohesive energy of a material is the energy, which holds the molecules of a liquid together and corresponds with the energy of all interactions between molecules: dispersion or London forces, polar interactions (dipol–dipol and dipol–induced dipol) and specific interaction (hydrogen bonding).

The basic thermodynamical relation for solubility/solution process relates the free energy of mixing at constant pressure, ΔG^M to the enthalpy of mixing ΔH^M and to the change of the entropy during the process and ΔS^M as follows (Barton, 1983):

$$\Delta G^\mathrm{M} = \Delta H^\mathrm{M} - T\Delta S^\mathrm{M} \quad (2)$$

Two substances show total miscibility if $\Delta H^\mathrm{M} = 0$ and $\Delta S^\mathrm{M} > 0$, so if ΔG^M is negative. According to theory Hildebrand–Scatchard, energy of mixing for two liquids at constant volume is given by the relation (Hildebrand and Scott, 1950):

$$\frac{\Delta E^\mathrm{M}}{\phi_1\phi_2} = V_\mathrm{m}(\delta_1 - \delta_2)^2 \quad (3)$$

where ΔE^M is mixing energy, $\phi_1\phi_2$ the volume fractions of liquids 1 and 2 and V_m is the volume of the mixture. If values of solubility parameter of two materials are comparable, they will be mutually soluble and they can form a thermodynamically miscible mixture.

Solubility parameter defined by Eq. (1) is called *Hildebrand solubility parameter* or *Hildebrand parameter* (Barton, 1983) and it is applied only for regular solution, i.e. solution where polar and/or specific interactions between molecules are neglected. Due to this limitation approach developed by Hansen (1967, 1972) is the most widely accepted. So-called *Hansen solubility parameter* (HSP) is extension of the Hildebrand solubility parameter to polar and hydrogen bonding systems. Hansen assumed that cohesive energy could be considered as a sum of contributions from dispersive (E_d), polar (E_p) and hydrogen bonding (E_h) interactions:

$$-E_\mathrm{coh} = -E_\mathrm{d} - E_\mathrm{p} - E_\mathrm{h} \quad (4)$$

and the total solubility parameter (δ_T) is expressed as

$$\delta_\mathrm{T}^2 = \delta_\mathrm{d}^2 + \delta_\mathrm{p}^2 + \delta_\mathrm{h}^2 \quad (5)$$

where δ_d, δ_p and δ_h denotes dispersive, polar and hydrogen bonding contribution, respectively.

The HSP concept simplifies the description of research materials. Taking into consideration Hansen's interpretation, it can be assumed that for the spontaneous mixing process between liquids, the values of HSP components for one liquid should be close to another liquid.

The solubility parameter concept was first applied for simple liquid mixtures, later this application expanded to solid/liquid systems and showing usefulness in the cosmetics, pharmacy, coating and painting industry and also useful in determining biological material (Hansen, 2000; Hancock et al., 1997).

The aim of this work was calculation and comparison of solubility parameter data for different excipients, according to different procedures and for different values of solubility parameter of test solute. The main problem, when using IGC method, is the proper choice of test solutes representing the ability to different intermolecular: dispersive, polar and hydrogen bonding interactions.

2. Materials and methods

The examined excipients were Cetiol B (di-*n*-butyladipat) (Cognis), Labrasol (Gattefosse) and Tween 80 (Merck).

Measurements were carried out on *i*GC SMS (Surface Measurements Systems, London, UK) gas chromatograph equipped with a flame ionization detector (FID) and thermal conductivity detector (TCD). Methane was used as a non-interacting marker to correct for dead time retention. Helium was used as a carrier gas with flow rate 20 ml/min. The column fillings packing material were prepared by dissolving the excipient in a suitable solvent, mixing with the support and then coating a solid support by slow evaporation of the solvent. Chromosorb P AW-DMDCS 100/120 mesh (Supelco) was used as a solid support. The loading of the column was 20%. The columns were conditioned at 25 °C before the use. Column parameters and conditions of the measurements are listed in Table 1. Different organic solvents were used as the test solutes (Table 2). Due to limited number (9) of the places in "solvents oven" we had to carry out two series of measurement for each column.

Test solvents were selected to represent the ability to different intermolecular interactions, dispersive – *n*-alkanes; polar – acetonitrile, toluene, 2-butanone, 2-pentanone, 1,2-dichloroethane and 1-nitropropane as well as hydrogen bonding – ethanol, 1-propanol, 1-butanol, 1,4-dioxane and pyridine.

Five injections of the vapor of each solvent were made for each probe and retention time was determined from maximum of the symmetric peak. Further calculations lead to specific retention volume (V_g) which values were used in estimation of physicochemical parameters, as solubility parameter and its components (HSP). Calculations of specific retention volume were performed by using SMS *i*GC Analysis Software v1.2.

Table 2
Solubility parameter values of test solutes δ_1

Test solute	Data 1 $(\mathrm{MPa})^{1/2}$	Data 2 $(\mathrm{MPa})^{1/2}$
Hexane	14.9	14.9
Heptane	15.3	15.3
Octane	15.4	15.5
Nonane	15.6	15.8
1-Nitropropane	21.3	20.6
2-Butanone	19.3	19.0
2-Pentanone	17.6	17.6
Acetonitrile	24.8	24.4
Toluene	18.3	18.2
1,2-Dichloroethane	20.2	20.9
Ethanol	26.1	26.5
Propanol-1	24.9	24.5
Butanol-1	28.7	23.1
Pyridine	21.7	21.8
1,4-Dioxane	20.7	20.5

Flory–Huggins interaction parameter was calculated from the following equation (Voelkel et al., 2001):

$$\chi_{1,2}^{\infty} = \ln\left(\frac{273,15R}{p_1^0 V_g M_{r,1}}\right) - \frac{p_1^0}{RT}(B_{11} - V_1) + \ln\left(\frac{\rho_1}{\rho_2}\right) - \left(1 - \frac{V_1}{V_2}\right) \quad (6)$$

where $M_{r,1}$, p_1^0, B_{11}, V_g, V_1, V_2, ρ_1 and ρ_2 are the molecular mass, saturated vapor pressure of the test solute,

Table 1
Parameters and conditions of the measurements

	Excipient		
	Cetiol B	Labrasol	Tween 80
Loading (%)	20	20	20
Mass coated (g)	0.0864	0.084	0.034
Solid support	Chromosorb P AW-DMDCS 100/120 mesh		
Solvent	Chloroform	Methanol	Methanol
Column length (cm)		30	
Column i.d. (mm)		2	
Column temperature (°C)		25	
Detectors temperature (°C)		150	
Carrier gas		Helium	
Flow (ml/min)		20.1	

second virial coefficient of the test solute, specific retention volume of the test solute, molar volume of the test solute, molar volume of the examined material, density of the test solute and density of the examined material (solvent, drug), respectively.

Second virial coefficient was computed using the equation (Voelkel and Fall, 1995):

$$\frac{B_{11}}{V_C} = 0.500 - 1.144\left(\frac{T_C}{T}\right) - 0.480\left(\frac{T_C}{T}\right)^2 - 0.042\left(\frac{T_C}{T}\right)^3 \qquad (7)$$

where V_C and T_C are the critical molar volume and the critical temperature of the solute and T is the column temperature (K).

Solute vapor pressures (p_1^0) were computed from the *Antoine equation* (Boublik et al., 1973)

$$\log p_1^0 = \frac{A - B}{t + C} \qquad (8)$$

where p_1^0 is the vapor pressure in mmHg, t the temperature (°C) and A, B and C are the constants.

Solubility parameter can be calculated using the following relation (Choi et al., 1996; DiPaola-Baranyi and Guillet, 1978; Price et al., 1986; Voelkel and Grześkowiak, 2001):

$$\frac{\delta_1^2}{RT} - \frac{\chi_{1,2}^{\infty}}{V_i} = \frac{2\delta_2}{RT}\delta_1 - \left(\frac{\delta_2^2}{RT} + \frac{\chi_s^{\infty}}{V_i}\right) \qquad (9)$$

where δ_1 is the solubility parameter of the consecutive test solute. Plotting the left-hand of this equation versus δ_1 it is possible to obtain δ_2 of the examined material from the slope and the intercept of the straight line.

This relation was used by Price (1989) and Price and Shillcock (2002) for the estimation of solubility parameter for compounds with small molecular masses: n-hexadecane, squalane, dinonyl phthalate, di-n-octyl phthalate and compounds with polar groups: N-methyl pyrrolidone and dibutyl-2-ethylhexamide. Price noticed that for the alkanes curvature was downward, indicating to low estimates of δ_2 but for more polar compounds it was upward, denoting to overestimates. According to Hansen's concept of solubility parameter, Price proposed to calculate solubility parameter for systems were dispersive and polar interaction are present:

$$\delta^2 = \delta_d^2 + \delta_p^2 \qquad (10)$$

Voelkel and Janas (1993) proposed to extent the Price's procedure for calculation of Hansen's three component parameters:

$$\delta_T^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \qquad (11)$$

It can be made by plotting linear relationship, according to Eq. (4), for the respective group of solvents representing different intermolecular interactions. Values of each components of the total solubility parameter can be calculated from the slope of straight line by using the following relationships:

$$\begin{aligned} &\text{(a)}\ \delta_d = \frac{m_{n\text{-alkanes}} \times RT}{2} \\ &\text{(b)}\ \delta_p = \frac{(m_1 - m_{n\text{-alkanes}}) \times RT}{2} \\ &\text{(c)}\ \delta_h = \frac{(m_2 - m_{n\text{-alkanes}}) \times RT}{2} \end{aligned} \qquad (12)$$

where $m_{n\text{-alkanes}}$ is the value of the slope for n-alkanes; m_1 the value of the slope for aromatic hydrocarbones, ketones, 1-nitropropane, acetonitrile and 1,2-dichloroethane and m_2 is the value of the slope for alcohols, 1,2-dioxane and pyridine. Then the value of the total solubility parameter is obtained from the relationship (11).

3. Results and discussion

The selection of values of solubility parameter for the test solutes may influence the result of calculation. We have used two series of δ_1 values found in Ref. (Barton, 1983), which are represented in Table 2 as data 1 and data 2. Data 1 were taken from Table 2, p. 94 in Ref. (Barton, 1983), while data 2 from Table 5, p. 153 in Ref. (Barton, 1983).

An example of relation between the left-hand side of Eq. (9) versus solubility parameter of test solute δ_1 is shown in Fig. 1. For all excipients the linear relationship was obtained (correlation coefficient 0.98–0.99).

Values of solubility parameter calculated from the *slope* according to Guillet procedure, with the use of different δ_1 values, are summarized in Table 3.

The selection of δ_1 values to be used in Eq. (9) significantly influences the result, value of δ_2 for the

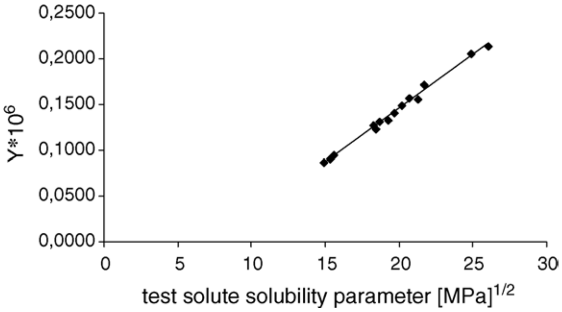

Fig. 1. An example of relationship of left-hand side Eq. (9) (Y) vs. δ_1 of test solute (data 1).

Table 3
Solubility parameter calculated from the slope of Eq. (9) for data 1, (1) and data 2, (2)

Excipient	Solubility parameter data (MPa)$^{1/2}$	
	δ_2 (1)	δ_2 (2)
Cetiol	19.077	17.715
Labrasol	21.059	20.316
Tween	20.935	20.068

examined excipient. For all excipients a little lower δ_2 values were obtained when data 2 series was applied.

Values of the components of solubility parameter determined according to Voelkel and Janas concept (Fig. 2) are summarized in Tables 4 and 5. The result will depend on statistical quality of relationships (12). The correlation coefficient was sufficiently high (0.999) for the correlation from which dispersive component was calculated (for all excipients). Lower value of correlation coefficient (0.96–0.98) was observed when polar and hydrogen bonding components were calculated. It can be noticed that the influence of the selection of solubility parameter for test solutes (δ_1) is the most significant on the hydrogen bonding component's values. Selection of different δ_1 values for alcohols (data 1) results in differences of δ_h component's value. One should notice that for homologous series of alcohols δ_1 values in data 1 series do not relate to the chemical structure. Solubility parameter value for ethanol should be the highest, whereas for butanol the lowest. Such considerable variation may influence the results of further calculation of hydrogen bonding component's value when using data 1 and data 2.

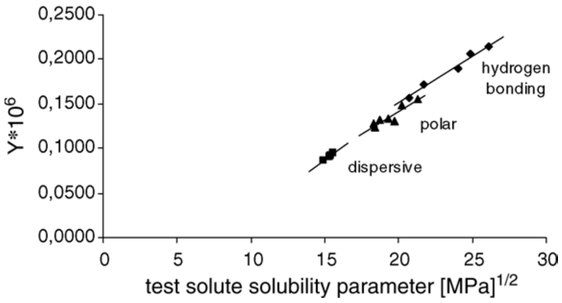

Fig. 2. Calculation of components of solubility parameter.

Table 4
Components calculated according to Voelkel and Janas procedure for data 1

Excipient	Solubility parameter data (MPa)$^{1/2}$ data 1		
	δ_d	δ_p	δ_h
Cetiol	16.517 ± 0.072	1.363 ± 0.214	4.790 ± 0.072
Labrasol	18.045 ± 0.071	0.784 ± 0.072	3.179 ± 0.071
Tween	19.336 ± 0.125	0.863 ± 0.124	2.849 ± 0.248

Table 5
Components calculated according to Voelkel and Janas procedure for data 2

Excipient	Solubility parameter data (MPa)$^{1/2}$ data 2		
	δ_d	δ_p	δ_h
Cetiol	16.352 ± 0.070	1.445 ± 0.189	1.074 ± 0.072
Labrasol	17.550 ± 0.072	1.198 ± 0.072	1.527 ± 0.072
Tween	18.458 ± 0.130	0.967 ± 0.124	0.991 ± 0.240

Once again the influence of different values of solubility parameter for test solutes δ_1 on the obtained values of solubility parameter (δ_2) of all excipients was observed. The use of data 2 series of δ_1 leads, in each case, to slightly higher values of polar component of solubility parameter δ_p and lower values of both other component δ_d and δ_h.

Table 6
Total value (δ_T) of solubility parameter calculated for data 1, (1) and data 2, (2)

Excipient	Solubility parameter data (MPa)$^{1/2}$	
	δ_T (1)	δ_T (2)
Cetiol	17.253 ± 0.043	16.452 ± 0.018
Labrasol	18.340 ± 0.062	17.657 ± 0.061
Tween	19.418 ± 0.128	18.473 ± 0.120

Table 7
Comparison experimental values and data obtained from group contribution methods

Method	Cetiol B			
	δ_d (MPa)$^{1/2}$	δ_p (MPa)$^{1/2}$	δ_h (MPa)$^{1/2}$	δ_T (MPa)$^{1/2}$
Hoy	14.961	7.889	10.117	19.708
Hoftyzer/van Krevelen	16.022	3.635	7.206	17.940
IGC (1)	16.517 ± 0.072	1.363 ± 0.214	4.790 ± 0.072	17.253 ± 0.043
IGC (2)	16.352 ± 0.070	1.445 ± 0.189	1.074 ± 0.072	16.452 ± 0.018

The total value of solubility parameter δ_T for each excipient was calculated from δ_d, δ_p and δ_h Eq. (11) by using Hansen concept (Table 6). The values of total solubility parameter for all excipients calculated from Eq. (11) are smaller than those calculated form Eq. (9) and this difference approximates 2 units.

It is possible to estimate values of solubility parameter for compounds with known chemical structure from group contribution methods. In such case solubility parameter is calculated by summing the contribution made by the various structural groups in the molecule.

In the group of examined excipients only Cetiol B (di-*n*-butyl adipate) has known, simple chemical structure. Comparison of components and total values of solubility parameter, calculated according to Hoy (Van Krevelen, 1990), Hoftyzer/van Krevelen (Van Krevelen, 1990) and IGC method is presented in Table 7. There are significant differences of solubility parameter values for Cetiol B estimated by using different procedures. Values of the dispersive component and total solubility parameters are comparable for IGC and Hoftyzer/van Krevelen procedure. Polar and hydrogen bonding component's values obtained from Hoy's procedure are the highest and also considerably different from values calculated from Hoftyzer's/van Krevelen's procedure. The highest value of total solubility parameter was obtained from calculation according to Hoy's procedure. As mentioned earlier, higher value of δ_h obtained from IGC/data 1 experiments may result from uncertain values of solubility parameter δ_1 for alcohols.

It should be noticed that even for such simple molecule two different additive methods gave different values of solubility parameter. Therefore, the additive methods should be used only for rough estimation of solubility parameter. For larger molecule the presence of several strongly interacting functional groups (e.g. hydroxyl) may result in the intramolecular interaction forces. The lack of information (data) concerning their influence on cohesion energy additionally limits the applicability of additive methods in the estimation of solubility parameter (Konstam and Feairheller, 1970).

To apply the additive methods in determination of solubility parameter one has to know the structure of the examined species. It is very often impossible. Inverse gas chromatography, the method used in this work, has no such limitation.

The main problem when using IGC is the proper choice of test solutes representing the ability to different intermolecular interactions: dispersive, polar and hydrogen bonding. Parameters, influencing also (less significantly) the determined value of solubility parameter (δ_2) are the values of solubility parameter of the test solutes (δ_1) taken from different literature sources.

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