Thermochimica Acta, 222 (1993) 219–229
Elsevier Science Publishers B.V., Amsterdam

Solubility parameters of some high molecular weight alcohols and esters used in pharmaceutical preparations

M.D. Contreras Claramonte [a,*], F. Girela Vilchez [b] and A. Parera Vialard [a]

[a] *Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, University of Granada, E-18071 Granada (Spain)*
[b] *Department of Applied Analytical Chemistry, Experimental Station of Zaidín, C.S.I.C. E-18008 Granada (Spain)*

(Received 12 October 1992; accepted 8 December 1992)

Abstract

Solubility parameters have been determined for oleyl alcohol, 2-octyl dodecanol, isopropyl myristate, isopropyl palmitate, di(2-ethyl hexyl) adipate, dibutyl adipate, decyl oleate, oleyl oleate and propylene glycol dipelargonate, all of which are frequently used in pharmaceutical preparations. These parameters have been determined from measurements of vapour pressure and heat capacity obtained by differential scanning calorimetry.

INTRODUCTION

The solubility parameters of liquids routinely used in pharmaceutical preparations are mainly unknown. This presents difficulties in the selection of solvents. The main purpose of the present study is to determine the solubility parameters of some of these liquids, namely oleyl alcohol, 2-octyl dodecanol, isopropyl myristate, isopropyl palmitate, di(2-ethyl hexyl) adipate, dibutyl adipate, decyl oleate, oleyl oleate and propylene glycol dipelargonate.

THEORY

The basis of the definition proposed by Hildebrand et al. [1] which is now generally referred to as the "solubility parameter" or the "Hildebrand parameter" (δ) is the cohesive molecular energy ($-U$) per unit volume (V)

$$\delta = \left(\frac{-U}{V}\right)^{1/2}$$

In practical terms $-U$ is analogous to the molar vaporization energy $\Delta_l^g U$,

---

* Corresponding author.

i.e. the energy necessary to evaporate a mole of liquid, and is equal to $\Delta_l^g H - RT$. The solubility parameter of a liquid may be defined by the equation

$$\delta = \left(\frac{\Delta_l^g H - RT}{V}\right)^{1/2} \qquad (1)$$

where $\Delta_l^g H$ is the enthalpy of vaporizaton at 25°C, R is the gas constant, T the temperature (K) and V the molar volume of the liquid at 25°C.

To quantify the solubility parameters of liquids, the use of direct methods is recommended; these are based on determining the enthalpy of vaporization at the required temperature, generally 25°C. This constant is obtained by calorimetry [2] or by studying the variation in vapour pressure with respect to the temperature [3], to which the Clausius–Clapeyron equation or different functions closely related to it are applied, among which Antoine's equation is prominent [4].

However, a large number of liquids have low vapour pressures at 25°C, making the calculation of their enthalpy of vaporization ($\Delta_l^g H$) at this temperature difficult. It is therefore necessary in many cases to obtain this value at higher temperatures and then extrapolating to 25°C. To do this, any of the following functions may be used: the critical temperature of the substance [5], the heat capacity [5, 6] or the linear function $\log \Delta_l^g H$ and T [7], which must be applied in the temperature range implicated in the extrapolation.

The enthlapy of vaporization ($\Delta_l^g H$) may also be determined from the boiling point of a liquid, using the function developed by Hildebrand, or using other physical constants such as the coefficient of thermal expansion, the surface tension [8], etc.

PRELIMINARY TESTS

Each of the liquids studied was submitted to a series of preliminary thermal tests in order to choose the most appropriate method of those mentioned above for the determination of the solubility parameters. The thermal behaviour of the liquids at atmospheric pressure (differential scanning calorimetry, DSC) and the variation in weight as a function of temperature (thermogravimetric, TG) [9] were studied.

In DSC studies at atmospheric pressure, it must be borne in mind that all these liquids decompose before reaching their boiling point, which makes the determination of their solubility parameters impossible by direct methods which use the enthalpy of vaporization at boiling point and also those which use temperature, volume and critical pressure. Moreover, applying the TG method at atmospheric pressure in the interval 25–100°C, the rate of evaporation is very low. This is characteristic of liquids with a low vapour pressure and makes the direct determination of the enthalpy of vaporization ($\Delta_{l}^{g}H$) at 25°C problematic.

Because of these two difficulties (decomposition of the substance before reaching boiling point and low vapour pressure), the enthalpy of vaporization is determined from studies of the variation in vapour pressure with temperature.

Of the different techniques which could be used, the thermal method was chosen in this study because it has the following advantages: only a small amount of sample is used, the speed of determination is rapid, and the technique is simple to set up.

MATERIAL AND METHODS

Materials

Glyco Iberica (Madrid, Spain) supplied the isopropyl myristate, isopropyl palmitate (Glyco I-309) and propylene glycol dipelargonate (Glyco PR-827); Henkel (Barcelona, Spain) supplied the oleyl alcohol (Eutanol H-D), 2-octyl dodecanol (Eutanol G), oleyl oleate (Cetiol), decyl oleate (Cetiol V) and dibutyl adipate (Cetiol B); and Aldado-Julia (Barcelona, Spain) supplied the di(2-ethyl hexyl) adipate (Cromadol DOA). All these chemicals are classified by the different companies as technical products for cosmetic use, with an impurity content of less than 4%. All were used as received.

Methods

The differential scanning calorimeter (Mettler T.A. 2000) was calibrated with respect to the melting of indium, and was connected across a safety valve to a mercury manometer (with a mm Hg scale) and a vacuum pump (rotating oil pump). After eliminating air from the entrances to the furnace, the pressure in the apparatus was always maintained above 3 mm Hg.

Aluminium crucibles (6 mm diameter, 40 μl volume) were used as sample containers; a pinhole 0.4 mm in diameter was made in the lids (using a high-velocity drill bit) in order to obtain a high ratio of surface area of effusion/surface area of evaporation [10].

The method used for the vapour pressure determination of a liquid has been previously described [11], and includes the selection of the optimum sample size (5 ± 0.5 mg), heating rate (15°C min^{-1}) and boiling point (maximum on the thermogram).

For each liquid, successive determinations of vapour pressure were carried out in the same crucible, and the liquid sample was introduced via

TABLE 1

Vapor pressure/temperature function: $\log P_V = A - B(1/T_b)$ [a]

Material	P_V [b]/ (mm Hg)	T_b [c]/ K	A	B	N	r^2	$s \times 10^{-2}$	ΔH_V [a]/ $(\mathrm{cal}^{0.5})\ \mathrm{mol}^{-1}$
Oleyl alcohol	3.00	464.95						
	63.50	600.35	10.310	4500.57	13	0.9974	2.191	20594.89
2-Octyl dodecanol	4.00	478.25						
	63.50	552.15	9.751	4338.82	16	0.9972	2.292	19854.68
Isopropyl myristate	4.75	430.15						
	18.50	466.25	7.789	3021.67	6	0.9881	2.812	13872.03
Isopropyl palmitate	4.75	457.95						
	32.59	521.05	8.065	3323.37	7	0.9511	7.308	15207.60
Dibutyl adipate	4.50	430.65						
	23.50	472.35	8.339	3261.53	7	0.9923	2.542	14924.82
Di(2-ethyl hexyl) adipate	5.50	487.05						
	22.50	533.65	7.788	4302.27	6	0.9961	1.647	15568.60
Oleyl oleate	3.00	583.85						
	20.25	633.65	10.738	5935.47	5	0.9986	1.444	27160.75
Decyl oleate	3.00	532.65						
	24.50	584.85	10.179	5095.57	9	0.9861	3.961	23315.03
Polylene glycol dipelargonate	4.00	483.05						
	13.50	514.25	9.279	4163.47	7	0.9894	2.348	19050.14

[a] Equation (2). [b] Range of pressure. [c] Range of boiling point.

the pin-hole in the lid using a micro-syringe, which aids its controlled introduction into the (4 or 5 μl) crucibles. Before and after each test, the empty crucible was weighed on a semi-micro analytical balance, to check for the presence of any liquid remaining after each test.

The sample was placed in the furnace at the initial temperature, generally 25°C, and the pressure was constantly adjusted. To stabilize the system, the apparatus was maintained in this initial condition for 10 min prior to carrying out the test.

RESULTS AND DISCUSSION

The vapour pressure/temperature function: enthalpy of vaporization

In the study of the variation in boiling point as a function of pressure, simple thermograms were observed for each substance, displaying a single, sharp endothermic peak, typical of isothermal boiling in the pressure range described in Table 1.

For the di(2-ethyl hexyl) adipate in the interval from 5.5 to 7.75 mm Hg, a small endothermic peak is seen at 100°C before the boiling point (Fig. 1); this disappears at higher pressures. This peak may be due to the presence of a small quantity of an isomer in addition to the main component, because

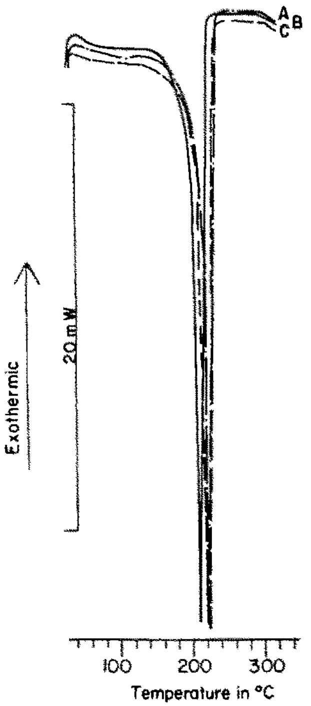

Fig. 1. DSC of di(2-ethyl hexyl adipate) at: A, 7.75; B, 5.5; and C, 10 mm Hg.

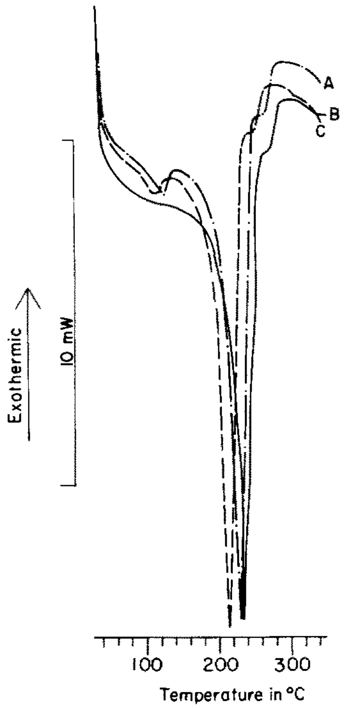

Fig. 2. DSC of 2-octyl dodecanol at: A, 10.75; B, 12; and C, 7.5 mm Hg.

di(2-ethyl hexyl) adipate has two asymmetric carbons. The same effect has also been observed for other similar compounds, i.e. those with two asymmetric carbons. For 2-octyl dodecanol in the pressure interval between 7.5 and 10.75 mm Hg, a small endothermic peak is seen at 105°C and 120°C, respectively (Fig. 2). This effect disappears at higher pressures. This was also observed for propylene glycol dipelargonate at a pressure of 11.5 mm Hg at 110°C, before the main endothermic peak due to boiling was observed (234°C).

To determine the enthalpy of vaporization, the Clausius–Clapeyron equation was applied

$$\log P = A + \frac{B}{T} \qquad (2)$$

where $-B = -\Delta_l^g H/2.303R$, P is the pressure (mm Hg), T the temperature (K), $\Delta_l^g H$ the enthalpy of vaporization, R the gas constant, and A a constant.

The enthalpy of vaporization ($\Delta_l^g H$) of a liquid may be determined from the vapour pressure/temperature range in which there is a high linear correlation (Table 1), assuming that the volume of the liquid is very small compared with the vapour volume, and that the latter behaves as a perfect gas, and that the heat of vaporization is constant in the temperature range studied.

Enthalpy of evaporation at 25°C

The enthalpy of vaporization of each of the substances studied was obtained at elevated temperatures in order to extrapolate to 25°C; any of the methods described in the introduction may be used.

From previous tests carried out by DSC, it was observed that all the liquids decompose before reaching their normal boiling point, which makes the determination of their critical temperature and critical pressure impossible. The enthalpy of vaporization was determined over a narrow temperature range only, because it is practically impossible to reach sufficiently low pressures due to the design of the DSC. Thus, it is not advisable to extrapolate by the logarithmic method [7] which would give unreliable results because of the wide range of temperature (greater than 100°C).

Therefore, the method in which the heat capacity of the compound is determined within the temperature range included in the extrapolation was chosen, as expressed by Klotz and Rosenberg [6]

$$\Delta_l^g H_1 = \Delta_l^g H_2 + \int_{T_1}^{T_2} ((C_V)_p - (C_l)_p)\,\mathrm{d}T \tag{3}$$

whre $\Delta_l^g H$ is the enthalpy of vaporization at the temperature T_2 or T_1 (K) ($T_2 > T_1$), C_V is the heat capacity of the gas and C_l the heat capacity of the liquid, both at constant pressure.

Because the temperature range used is very different from the hypothetical critical temperature of the liquids, the gas behaves as an ideal gas. The heat capacity of a gas in contact with liquid at constant pressure $(C_V)_p$ may be expressed as [6]

$$(C_V)_p = \tfrac{5}{2}R$$

where R is the universal gas constant.

For the heat capacity of the liquid at constant pressure $(C_l)_p$, which is a function of the temperature, it is necessary to determine this value for the liquids studied in the range between 25°C and the temperature at which the energy of vaporization was determined experimentally.

In agreement with the previous experiments, it can be observed for TG that the evaporation is slow but constant for all the liquids studied above 70°C. This means that the heat capacity determination at constant pressure in open crucibles is not possible because the initial quantity of sample does not remain constant. It is therefore necessary to carry out the determination in special high-pressure crucibles where evaporation of the liquids and their subsequent loss in mass is prevented. In this case the function is determined at constant volume and not at constant pressure. These functions have been previously determined by DSC [9] within the range between 25°C and the maximum temperature, above which the liquid begins its decomposition, and which varies according to the substance tested but is always greater than 100°C.

Solubility parameter

The solubility parameters were determined by applying the Hildebrand equation (eqn. (1)). The molar volume of each of liquid was determined experimentally from density values obtained by the pycnometric method (Table 2).

DISCUSSION

The solubility parameter values may be divided into two groups: those for which the heat capacity function obtained covers the whole temperature range for the extrapolation of the vaporization energy of the liquid from its boiling point up to 25°C (isopropyl myristate, isopropyl palmitate, and dibutyl adipate); and the second group which contains the rest of the liquids, for which for reasons previously discussed (the impossibility of obtaining low pressures in the furnace and the decomposition of the substance), the function was determined for a temperature range lower than that necessary. This difference is never greater than fifty degrees; therefore the energy of vaporization determined at a higher temperature may be considered similar to that obtained at this temperature. For oleyl oleate and decyl oleate, where the difference in the temperature range is near to 100°C, these parameter values may only be considered as guidelines.

Barton [8] reports solubility parameter values of 9.10 $\mathrm{cal}^{0.5}\,\mathrm{cm}^{-1.5}$ for oleyl alcohol, and 7.76 $\mathrm{cal}^{0.5}\,\mathrm{cm}^{-1.5}$ for isopropyl myristate, although the latter value is inaccurate. The experimental value obtained here for oleyl alcohol differs from this value by only 0.6 units ($\mathrm{cal}^{0.5}\,\mathrm{cm}^{-1.5}$). According to James et al. [12] differences of up to one unit are acceptable owing to the influence of the method on the results. It can therefore be said that the method used is acceptable for determining the solubility parameter of a liquid. The experimental value obtained for isopropyl myristate is acceptable because of the known low polarity of this compound.

The group contribution method enable values of the molar volume and the solubility parameter to be calculated, although these may only be considered as approximations. The values obtained for both constants using Fedors' group contribution method [13] are used as references against which the experimental results may be compared (Table 2). From the analysis of the molar volume, it can be seen that the values obtained by Fedors' group contribution method, although they can only be considered as rough approximations, are very similar to those obtained experimentally, although the latter are slightly higher.

TABLE 2

Material	$\Delta_l^g H_2$/ (cal$^{0.5}$ mol^{-1}) [a]	$\int_{T_1}^{T_2}((C_V)_p - (C_l)_p)\,dT$/ (cal$^{0.5}$ mol^{-1}) [b]	$\Delta_l^g H_1$/ (cal$^{0.5}$ mol^{-1}) [c]	V_{Exp}/ (cm^3 mol^{-1}) [d]	V_{Theor}/ (cm^3 mol^{-1}) [e]	δ_{Exp}/ (cal$^{0.5}$ cm$^{-1.5}$) [f]	δ_{Theor}/ (cal$^{0.5}$ cm$^{-1.5}$) [g]
Oleyl alcohol	20594.89	9902.35 (370.15)	30497.24	315.4	315.0	9.73	9.10
2-Octyl dodecanol	19854.68	24015.26 (440.15)	43869.95	355.4	352.7	11.04	9.01
Isopropyl myristate	13872.03	16355.93 (426.15)	30227.95	317.4	307.3	9.66	8.70
Isopropyl palmitate	15207.60	13571.38 (450.15)	28778.98	350.3	342.9	8.96	8.64
Di(2-ethyl hexyl) adipate	15568.60	22475.89 (426.15)	38044.49	400.3	393.4	9.67	8.98
Dibutyl adipate	14924.82	15617.93 (433.15)	30542.75	262.2	257.2	10.68	9.60
Decyl oleate	23315.03	26141.71 (426.45)	49456.74	490.3	478.9	9.98	8.85
Oleyl oleate	27160.75	33512.18 (438.15)	60672.18	614.3	602.5	9.88	8.69
Propylene glycol dipelargonate	19050.14	20308.30 (428.15)	44883.23	387.6	370.3	10.00	9.26

[a] Enthalpy of evaporation at high temperature (Table 1). [b] $(C_V)_p = (5/2)R$; $(C_l)_p$ from ref. 9; the energy calculated by Simpson's method of integration is between 298.15 K and the maximum which is the number in parentheses. [c] Enthalpy of evaporation at 25°C (eqn. (3)). [d] Molar volumes, obtained by the pycnometric method; mean of five determinations. [e] Molar volumes. [f] Solubility parameter, eqn. (1). [g] Solubility parameter. (Molar volumes and solubility parameters were both obtained using Fedors' group contribution method [13].)

With respect to the experimental solubility parameters, the value for isopropyl myristate differs only slightly (by a few tenths) from the theoretical value, which confirms the observations previously described. For the rest of the liquids, with the exception of 2-octyl dodecanol, the differences from the theoretical values are never greater than one unit. As previously discussed, the values for 2-octyl dodecanol may be considered as guidelines only.

For the solubility parameters obtained experimentally, the products used, even though classified as technical and labelled as specific chemical compounds, mostly contain mixtures of a variety of different compounds such as those described by USP XXII [14]. Given the component character of the excipient of this type of product, its quantitative composition may vary according to the manufactured lot to which it belongs; thus it is difficult to know its exact composition. The presence of additional compounds may increase the boiling point and the molar heat of vaporization with respect to values obtained for the pure substance, thus altering the parameter value.

In any case, it must not be forgotten that the heat capacity/temperature function has been determined at constant volume $(C_l)_V$, and the function which is implicated in the extrapolation of the heat of vaporization at different temperatures (eqn. (2)) is at constant pressure $(C_l)_p$. Also, the relationship between both these constants is affected by the coefficient of heat expansion (α) and the liquid compression coefficient (β) (15), which are also functions of temperature; therefore

$$(C_l)_p - (C_l)_V = TV\left(\frac{\alpha^2}{\beta}\right)$$

For some liquids, the influence of both these coefficients (α, β) on this constant is negligible, and $(C_l)_p = (C_l)_V$. For the liquids studied, α and β are unknown. Both values probably influence the parameter values obtained to a small extent (a few tenths of their value).

REFERENCES

1 J.E. Hildebrand, J.M. Prausnitz and R.L. Scott, Regular and Related Solutions, Van Nostrand Reinhold Company, New York, 1970, Appendix 5.
2 G. Cave, R. Ceolin and F. Puisieux, Pharm. Acta Helv., 58 (1983) 172.
3 Ch. Sunwoo and H. Eisen, J. Pharm. Sci., 60 (1971) 238.
4 J.E. Lundeen and J.E. House, Thermochim. Acta, 75 (1984) 183.
5 S. Glasstone, Tratado de Química Física, 7rd. edc. Aguilar, Madrid, 1979, Chap. 6.
6 I.M. Klotz and R.M. Rosenberg, Termodinamica Química, A.C., Madrid, 1977, Chap. 9.
7 K.L. Hoy, J. Paint Technol., 12 (1970) 76.
8 A.F.M. Barton, CRC Handbook of Solubility and Other Cohesion Parameters, CRC Press Inc., Boca Raton, 1983, Chap. 8.
9 M.D. Contreras Claramonte, F. Girela Vilchez and A. Parera Vialard, Thermochim. Acta, 222 (1993) 209.
10 R.J. Seyler, Thermochim. Acta, 17 (1976) 129.

11 M.D. Contreras Claramonte, F. Girela Vilchez and A. Parera Vialard, Thermochim. Acta, 222 (1993) 203.
12 K.C. James, C. Tek-Ng and P.R. Noyce, J. Pharm. Sci., 65 (1976) 656.
13 R.F. Fedors, Polym. Eng. Sci., 14 (1974) 147.
14 The United States Pharmacopeia, The National Formulary, (USP XXII), United States Pharmacopeial Convention, Inc., Rockville, 1989.
15 S. Glasstone, Tratado de Química Física, 7rd. edc., Aguilar, Madrid, 1979, Chap. 3.