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Influence of inverse gas chromatography measurement conditions on surface energy parameters of lactose monohydrate

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Abstract

Surface energy of any powder determined by inverse gas chromatography (IGC) should be independent of the measurement conditions or type of column used. In this study stainless steel and glass columns were filled with lactose powder. Dispersive and polar components of surface free energy were determined at different flow rates of carrier gas using lactose alone or diluted with calcinated diatomite (Chromosorb W). It was found that measurement conditions did not influence the value of the dispersive parameter of surface energy. On the contrary, K_a and K_d values were found to be dependent on dilution of lactose with Chromosorb W. The influence of other parameters on the results was found to be much smaller.

Keywords: Inverse gas chromatography; Lactose monohydrate; Surface free energy; Chromosorb W

1. Introduction

Inverse gas chromatography (IGC) has become widely used technique to characterize the surface properties of solid surfaces including pharmaceutical materials. These properties are of great importance in many processes such as wet granulation, suspension formation, dissolution and film coating. IGC technique consists of measuring the chromatographic retention times of vapour phase probes of known properties in a column packed with the material of interest. The retention times of these probes are measured at infinite dilution to allow determination of the interactions between the organic molecules and the solid, in the absence of interactions between the probe molecules themselves. Peak area of detector signal, one order of magnitude higher than its sensitivity threshold, is used for retention time calculation (Czeremuszkin et al., 1997). Results for the sample properties depend on the preparation of the sample column, on the correct measured values being used for retention volume calculation and the correct parameters for the adsorbate molecules that are used in calculations. The net retention volume is calculated according to Shulz et al. (1987):

$$V_n = jF(t_r - t_0) \quad (1)$$

where t_r is the retention time of the probe; t_0, the zero retention reference time measured with a non adsorbing probe (methane); F, flow rate; and j, a correction

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factor taking into account the compression of the gas given by the following equation:

$$j = \frac{3}{2}\frac{(P_{\mathrm{in}}/P_{\mathrm{out}})^2 - 1}{(P_{\mathrm{in}}/P_{\mathrm{out}})^3 - 1} \quad (2)$$

where P_{in} is the pressure at the inlet and P_{out}, pressure at the outlet of the column (Shulz et al., 1987).

2. Determination of the dispersive component of the surface energy

The free energy of adsorption ΔG° of n-alkanes is given by:

$$\Delta G^\circ = RT \ln V_{\mathrm{n}} + C \quad (3)$$

where R is the ideal gas constant; T, the absolute temperature; and C, a constant depending on the reference state adsorption. In the case of n-alkanes, ΔG° is equal to the free energy of adsorption corresponding to dispersive interactions ΔG^{d} only.

Fowkes relationship is used to calculate the value of the dispersive component $\gamma_{\mathrm{s}}^{\mathrm{d}}$ of the surface energy of solids (Fowkes, 1964):

$$\Delta G^\circ = \Delta G^{\mathrm{d}} = 2Na\sqrt{\gamma_{\mathrm{s}}^{\mathrm{d}}\gamma_{\mathrm{l}}^{\mathrm{d}}} \quad (4)$$

where N is Avogadro's number; $\gamma_{\mathrm{l}}^{\mathrm{d}}$, surface tension of the alkane and a, the area of one adsorbate molecule.

By plotting $RT \ln V_{\mathrm{n}}$ as a function of $2N\sqrt{\gamma_{\mathrm{l}}^{\mathrm{d}}}$ for n-alkanes, a straight line is obtained (Fig. 1) and $\gamma_{\mathrm{s}}^{\mathrm{d}}$ is calculated from the slope of this line.

3. Determination of specific interactions

When polar probes are injected into the column, specific and nonspecific interactions are established between these probes and the free energy of adsorption. ΔG° is now given by:

$$\Delta G^\circ = \Delta G^{\mathrm{d}} + \Delta G^{\mathrm{sp}} \quad (5)$$

where ΔG^{sp} refers to specific interactions as shown in Fig. 1. ΔG^{sp} is further correlated to parameters characterizing surface ability to specific interactions (Riddle and Fowkes, 1990).

$$-\Delta G^{\circ\ \mathrm{sp}} = K_{\mathrm{a}}\mathrm{DN} + K_{\mathrm{d}}\mathrm{AN}^* \quad (6)$$

AN* and DN are the acceptor and donor number of the test solute (Table 1), K_{A} and K_{D} reflect the ability of the examined surface to act as electron acceptor (acid characteristic) and as electron donor (base characteristic) respectively. K_{A} and K_{D} are calculated using a transformed Eq. (6) from the linear relationship for the series of polar probes characterized by different DN and AN* values determined by Gutman (1978) and Riddle and Fowkes (1990).

$$\frac{-\Delta G^{\circ\ \mathrm{sp}}}{\mathrm{AN}^*} = K_{\mathrm{a}}\frac{\mathrm{DN}}{\mathrm{AN}^*} + K_{\mathrm{d}} \quad (7)$$

Stainless steel, copper or glass columns of different lengths and diameters are used for IGC measurements. Samples are introduced into column by use of mechanical vibrator. Vacuum is also sometimes applied. Powders can be used directly or diluted with an

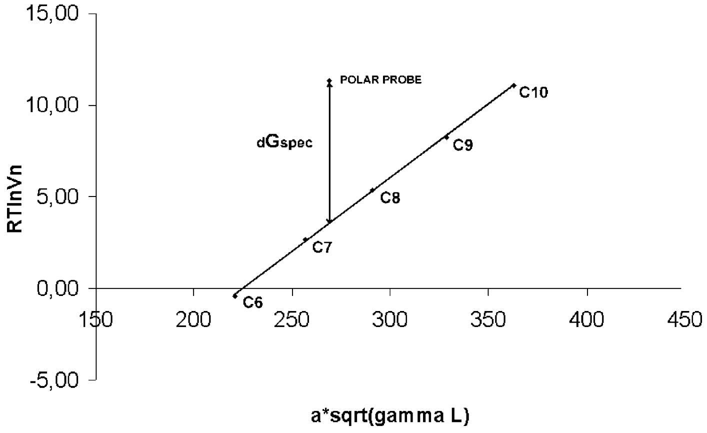

Fig. 1. Schematic representation of a general $RT \ln V_{\mathrm{n}}$ vs. $a(\gamma_{\mathrm{l}}^{\mathrm{d}})^{1/2}$ diagram using alkanes.

Table 1
Surface tension, surface area, donor (DN) and acceptor (AN*) numbers of test probes

Molecule	Surface tension (mN/m)	Surface area (Å^2)	DN	AN*
n-Hexane	19.4	51.5	0	0
n-Heptane	20.3	57	0	0
n-Octane	21.3	63	0	0
n-Decane	22.7	69	0	0
Tetrahydrofuran	23.4	45	20.0	0.5
Acetone	16.5	42.5	17.0	2.5
Ethyl acetate	19.6	50	17.1	1.5
Diethyl ether	15.0	47	19.2	1.4
Chloroform	25.0	45	4.0	5.4
Ethanol	21.1	57	20.0	10.3

appropriate filler. There are no reports in the literature how these parameters influence the results. Samples can also be prepared by coating of carrier from a solution with solvent evaporation.

Correct choice of probe molecules area is another critical parameter in surface energy calculation (Hamieh and Schultz, 2002). Usually probe molecules are not spherical and the correct choice of surface area depends on the orientation of the adsorbed molecule. The extent of the interaction surface area can also be influenced by the interaction forces exerted on the sample. Further experimental uncertainty comes from the assumption that surface area does not change with temperature (Mukhopahayay and Schreiber, 1995).

4. Materials and methods

The investigated material was lactose monohydrate (NF, 200 mesh, DMV International, The Netherlands). Methane (Messer, Slovenia), *n*-hexane, *n*-heptane (Kemika Croatia), *n*-octane, *n*-nonane (Ridel de Haën AG, Germany), diethyl ether, CCl_4, acetone (Merck, Germany), $CHCl_3$, ethyl acetate, tetrahydrofuran (THF) (Kemika Croatia) were used for measurements. All the liquids used were of gas chromatography grade and were employed without further purification.

Inverse gas chromatography was carried out using the Agilent Technologies 6890N chromatograph with flame ionization detector (FID). The carrier gas was nitrogen. The gas flows were 4, 7 and 10 ml/min. The injector and detector were heated at 150 and 250 °C, respectively.

Stainless steel chromatographic columns with an inside dimensions of 2 mm × 50 cm and 2 mm × 100 cm were filled with lactose powder diluted with calcinated diatomite (Chromosorb W, Carlo Erba, Italy) in weight ratio 1:1 (0.5–2 g), with mechanical vibrator. Glass columns with an inside dimensions of 3 mm × 20 cm were filled with pure lactose and diluted with Chromosorb W in weight ratio 1:1 by vertical tapping. Columns were conditioned at 50 °C overnight at 10 ml/min flow of nitrogen. IGC measurements at infinite dilution were undertaken by varying the temperature from 30 to 50 °C.

5. Results and discussion

Carrier gas flows were chosen according to retention time of the probes. With 50 cm stainless steel columns, gas flows were 7 and 4 ml/min and with 100 cm columns, 10 and 7 ml/min (Table 2). Glass columns used were filled with pure lactose and with lactose diluted with Chromosorb W in weight ratio 1:1 at flow rates 4, 7 and 10 ml/min (Table 2). For the determination of the dispersive parameter of surface energy, a series of alkanes from hexane to nonane were used. Correlation of the points on the line was high and the value of the dispersive component (γ_s^d) does not change much with a change of column type and flow rate at all three measured temperatures (Table 3). Results at 30 °C are in agreement with the literature values (Planinšek et al., 2001; Ticehurst et al., 1996) and are similar to values obtained for amorphous and milled lactose (Newell et al., 2000, 2001). The average values of the dispersive component

Table 2
Conditions of IGC experiments of lactose sample

Column label	Column type	Column length (cm)	Flow rate (ml/min)	Dilution with Chromosorb W (w/w, %)
I	Stainless steel	50	4	50
II	Stainless steel	50	7	50
III	Stainless steel	100	7	50
IV	Stainless steel	100	10	50
V	Glass	20	7	0
VI	Glass	20	10	0
VII	Glass	20	7	50
VIII	Glass	20	4	50

of lactose at different temperatures are: 42.70 ± 1.57 mN/m at 30 °C, 39.24 ± 1.76 mN/m at 40 °C and 36.52 ± 2.05 mN/m at 50 °C.

An explanation for the interaction results between lactose and polar probes is much more complex. However, correct determination of polar properties of a solid surface is very important because polar forces are in general stronger than dispersive and most probably dominant for interactions between surfaces. Polar probes that were used for measurements were THF, ethyl acetate, acetone, diethyl ether, ethanol and chloroform. As expected, calculated specific free energy of adsorption shows, that increase in the temperature decreases the strength of interactions (Table 4). Some differences in interactions were also found for different columns and different flow rates used (Table 4). Increase of the carrier gas flow in the same column causes a decrease in the interactions (columns I, II). Increase of the stainless steel column length (and sample mass respectively), at the same carrier gas flow rate, increases the interaction of polar probes with the surface (columns II, III). These results suggest that a higher surface area of the sample can be available for interactions in a longer column using low flow rate and the result seems to provide a better reflection of the surface energy properties. However, according to some authors, only high-energy sites can be assessed by use of IGC (Ticehurst et al., 1994). We believe that an increase in the column length and a decrease in the flow rate can give a more real picture of an average surface energy. Comparison of the columns show that the value of the specific energy of adsorption interactions of most polar probes is more intensive in a stainless steel column than in a glass column filled with the lactose in undiluted form. This can be again explained through exposure of a higher surface area to polar probes with the Chromosorb W diluted sample in stainless steel column (columns I–IV). In the glass columns filled with lactose–Chromosorb W mixture (columns VII, VIII), an increased strength of interaction with most polar probes was observed in com-

Table 3
Dispersive component of surface free energy of lactose determined at different conditions and temperatures

	30 °C	40 °C	50 °C
Column I			
γ_s^d	44.79	41.78	39.07
R^2	0.9995	0.9992	0.9989
Column II			
γ_s^d	41.01	37.67	37.09
R^2	0.9991	0.9995	0.9986
Column III			
γ_s^d	40.75	39.56	36.96
R^2	0.9988	0.9988	0.9987
Column IV			
γ_s^d	41.89	41.43	39.03
R^2	0.9990	0.9984	0.9981
Column V			
γ_s^d	44.19	39.56	37.13
R^2	0.9993	0.9997	0.9999
Column VI			
γ_s^d	43.25	38.29	35.10
R^2	0.9998	0.9997	0.9995
Column VII			
γ_s^d	44.09	38.94	34.03
R^2	0.9988	0.9997	0.9978
Column VIII			
γ_s^d	41.65	36.66	33.77
R^2	0.9993	0.9997	0.9996

Table 4
Specific free energy of adsorption (ΔG^{sp}, kJ/mol) of polar probes with lactose samples at different temperatures

T (°C)	THF	Acetone	Ethyl acetate	Ether	$CHCl_3$	Ethanol
Column I						
30	8.6559	11.0567	8.3878	6.6480	0.8915	6.9866
40	8.7086	10.6241	6.8308	5.9152	0.7276	6.7607
50	7.8013	10.1531	7.1008	5.0283	1.2184	6.0001
Column II						
30	8.4235	10.7454	7.2871	5.6708	1.3019	6.7905
40	7.5362	10.0811	8.2565	4.7849	0.9754	6.3575
50	7.2383	9.6859	6.2532	4.0618	1.2218	5.9604
Column III						
30	9.2268	13.1877	7.8529	6.9715	1.5947	7.0851
40	8.2298	11.0318	7.0134	5.9364	1.3230	6.8629
50	7.2990	10.0001	6.3024	4.9233	1.0324	6.1356
Column IV						
30	9.1691	11.9992	8.0452	6.3334	1.2367	7.2979
40	8.5621	11.2455	7.5327	5.6567	1.1703	7.1083
50	7.7897	9.8532	6.7530	5.0014	1.0807	6.2419
Column V						
30	6.5588	8.3249	6.8019	5.1007	1.8149	5.6970
40	6.0498	7.5244	6.3212	4.7042	1.4491	5.1546
50	5.6584	7.1611	5.9637	4.5337	1.0105	4.7219
Column VI						
30	6.5218	9.6138	7.0783	7.0129	1.6820	5.9346
40	6.0152	8.0141	6.5080	4.8455	1.4234	5.3308
50	5.7303	7.3386	6.2345	4.5294	1.6203	4.9922
Column VII						
30	8.0513	10.9303	7.1023	5.2514	0.8622	7.0171
40	7.0384	9.8152	7.5227	4.2854	0.2570	6.6660
50	5.9542	8.2847	6.5077	3.5747	0.3875	5.3078
Column VIII						
30	8.8802	11.6721	7.8826	6.1172	1.1496	7.0969
40	8.1086	10.6930	7.0974	4.8634	0.7365	6.6734
50	6.6154	9.7062	6.2407	4.0658	1.1270	5.2953

parison with undiluted sample. Generally the values are, higher than in columns with undiluted samples (columns V, VI) and close to the values in stainless steel column with the diluted lactose sample. It was observed additionally that the pressure drop along the columns is much smaller when diluted samples were measured. We suppose that the porous structure of the sample in the column is essential for the uniform carrier gas and probe vapour flow and access to the sample surface. These results are in agreement with statement of Santos et al. (2001) that dilution with the inert material such as Chromosorb W expose more active sites of the material investigated, the values of the specific interactions are higher than measured using the column with the undiluted material.

The acidic probe used in the study was chloroform. Its specific interaction with the lactose surface is relatively weak, especially in comparison to other probes used. For this reason lactose is expected to have a stronger acidic than basic properties. Acid and base properties were calculated according to Eq. (7).

Fig. 2 shows a linear regression line in a graph $\Delta G^{sp}/AN^*$ versus DN/AN^*. Distribution of the points was similar with all columns measured. Appearance of acetone above the line and diethyl ether below the line shows the problem of choice of the surface area

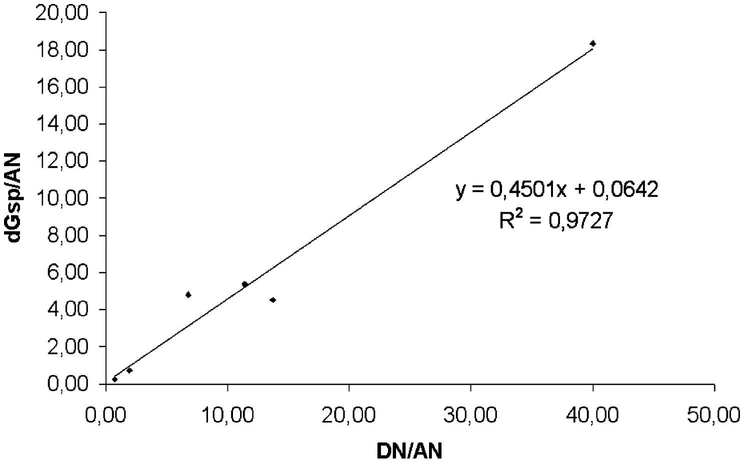

Fig. 2. Evolution of $\Delta G^{sp}/AN^*$ as a function of DN/AN* of polar molecules adsorbed on the lactose (column III).

Table 5
K_a and K_d values of lactose determined in different columns at temperatures 30, 40 and 50 °C

	K_a	K_d	R^2
30 °C			
Column I	0.426	0.189	0.9794
Column II	0.414	0.164	0.9728
Column III	0.451	0.217	0.9712
Column IV	0.450	0.064	0.9727
Column V	0.319	0.275	0.9785
Column VI	0.317	0.646	0.9796
Column VII	0.394	0.069	0.9655
Column VIII	0.436	0.074	0.9721
40 °C			
Column I	0.431	−0.149	0.9764
Column II	0.368	0.232	0.9556
Column III	0.403	0.106	0.9740
Column IV	0.422	0.368	0.9888
Column V	0.296	0.229	0.9791
Column VI	0.293	0.327	0.9755
Column VII	0.343	0.195	0.9504
Column VIII	0.398	−0.031	0.9617
50 °C			
Column I	0.383	0.044	0.9675
Column II	0.353	−0.023	0.9552
Column III	0.357	0.080	0.9674
Column IV	0.383	−0.025	0.9700
Column V	0.278	0.224	0.9793
Column VI	0.279	0.291	0.9764
Column VII	0.290	0.175	0.9479
Column VIII	0.321	0.156	0.9522

of the molecule for calculation of K_a and K_d values. The same deviations from the line were observed with all columns. These results suggest that for better results a higher number of polar probes should be used for calculation of the K_a and K_d parameters of solid surface. Results obtained with stainless steel columns (I–IV) and glass columns with diluted lactose samples (columns VII, VIII) show relatively small differences especially in K_a values (Table 5). Higher deviations of these values were found in the glass columns with undiluted lactose. Comparison of the results shows that dilution of the lactose with Chromosorb W in the glass column causes K_a to become more similar to values obtained with stainless steel columns. When different lengths of the column and flows of the carrier gas in stainless steel are compared relative little differences in K_a were found (columns I–IV).

The results for K_d values show much higher dispersion, some values are even negative. A reasonable explanation for this observation cannot be given.

From both parameters, K_a and K_d, it is possible to conclude that the lactose monohydrate in the interactions with other inactive and active ingredients behaves as an electron acceptor and Lewis acid.

6. Conclusions

The influence of carrier gas flow rate, type of the column, column length and dilution with Chromosorb W on the surface free energy of lactose has been tested using IGC at different temperatures. At different measurement conditions relatively small differences of the dispersion component of the surface energy results were observed. It was found that dilution of the lactose with Chromosorb W affects especially the polar parameters in comparison to undiluted lactose (tested in the glass columns). This is probably due to different packing of the sample in the column. However, it is suggested that dilution of the sample with Chromosorb W increases the access to the surface area that interacts with the polar probes. Consequently, we propose that the analysis of any powder surface with IGC should involve dilution with Chromosorb.

According to the calculated K_a and K_d parameters, it can be concluded that the lactose behaves as an electron acceptor and therefore shows acid characteristics.

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