Partial Solubility Parameters of Lactose, Mannitol and Saccharose Using the Modified Extended Hansen Method and Evaporation Light Scattering Detection

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The modified extended Hansen method was tested for the first time to determine partial solubility parameters of non-polymeric pharmaceutical excipients. The method was formerly tested with drug molecules, and is based upon a regression analysis of the logarithm of the mole fraction solubility of the solute against the partial solubility parameters of a series of solvents of different chemical classes. Two monosaccharides and one disaccharide (lactose monohydrate, saccharose and mannitol) were chosen. The solubility of these compounds was determined in a series of solvents ranging from nonpolar to polar and covering a wide range of the solubility parameter scale. Sugars do not absorb at the UV-vis region, and the saturated solutions were assayed with a recent chromatographic technique coupled to an evaporative light scattering detector. This technique was suitable to determine the concentration dissolved in most solvents. The modified extended Hansen method provided better results than the original approach. The best model was the four parameter equation, which includes the dispersion δ_d, dipolar δ_p, acidic δ_a and basic δ_b partial solubility parameters. The partial solubility parameters obtained, expressed as MPa$^{1/2}$, were δ_d=17.6, δ_p=28.7, δ_h=19, δ_a=14.5, δ_b=12.4, δ_T=32.8 for lactose, δ_d=16.2, δ_p=24.5, δ_h=14.6, δ_a=8.7, δ_b=12.2, δ_T=32.8 for mannitol and δ_d=17.1, δ_p=18.5, δ_h=13, δ_a=11.3, δ_b=7.6, δ_T=28.4 for saccharose. The high total solubility parameters δ_T obtained agree with the polar nature of the sugars. The dispersion parameters δ_d are quite similar for the three sugars indicating that the polar δ_p and hydrogen bonding parameters (δ_h, δ_a, δ_b) are responsible for the variation in the total solubility parameters δ_T obtained, as also found for drugs. The results suggest that the method could be extended to determine the partial solubility parameters of other non-polymeric pharmaceutical excipients.

Key words lactose monohydrate; saccharose; mannitol; light scattering; partial solubility parameter

Solubility parameters and other cohesion parameters provide a means to correlate and predict cohesive and adhesive properties of materials from a knowledge of the properties of their components.[1)] Hansen determined the partial solubility parameters of polymers, resins and plasticizers to predict paint component affinities[2)] but these parameters are unknown for most pharmaceutical excipients. The knowledge of cohesion parameters would help to predict drug-excipient interactions and to allow selection of the most suitable excipients for a drug. Hansen divided the Hildebrand solubility parameter[3)] δ_T into partial solubility parameters δ_d, δ_p, and δ_h, related to van der Waals dispersion forces, Keesom dipole interactions and hydrogen bonding, respectively.[2,4)] The partial solubility parameters of solvents are found in the literature[1)] and the extended Hansen method was proposed for solid drug molecules.[5)] Hansen determined the cohesion parameters of polymers and resins from semiquantitative solubility measurements.[2)] The usual procedure is to contact the polymer or resin with a given amount of solvent and to examine the solubility behavior using a qualitative scale (clear solution, almost soluble, strongly swollen, slight solubility, swollen, little swelling and no visible effect). These data are then plotted in a suitable manner and a region of solubility is defined including the solvents dissolving the polymer. The use of techniques based on quantitative solubility measurements would provide more accurate values for the cohesion parameters. The partial solubility parameters of sugars have not been determined; only the values for lactose are reported.[6)] In earlier work, we modified the extended Hansen method of Beerbower[5)] to determine the partial solubility parameters of drugs.[7—9)] The modified method relates the logarithm of the experimental mole fraction solubility of the drug to the solubility parameters of the solvents, using the three- and four-partial solubility parameter models. The modified method improved the significance of the partial parameters obtained in relation to those determined with the original extended Hansen method.

With the three parameter model, the logarithm of the experimental mole fraction solubility X_2 is regressed against the partial solubility parameters of the solvents:

$$\ln X_2 = C_o + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1h}^2 + C_6\delta_{1h} \quad (1)$$

In a similar fashion, the four parameter model is written:

$$\ln X_2 = C_o + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a} + C_6\delta_{1b} + C_7\delta_{1a}\delta_{1b} \quad (2)$$

In Eqs. 1 and 2, $\ln X_2$ replaces the original variable of the extended Hansen method, $\ln \alpha_2/U$, where α_2 is the activity coefficient defined as the ratio of the ideal to the experimental mole fraction solubility, and U is related to the molar volume of the drug and the volume fraction of the solute. In Eq. 2, the hydrogen bonding parameter is divided into the acidic and basic partial solubility parameters related to the proton donor and proton acceptor capability.

The partial solubility parameters of solid drugs were calculated from the regression coefficients of Eqs. 1 and 2. From Eq. 1:

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$$\delta_{2d}=-(C_2/2C_1);\ \delta_{2p}=-(C_4/2C_3)\text{ and }\delta_{2h}=-(C_6/2C_5) \quad (3)$$

and from Eq. 2:

$$\delta_{2d}=-(C_2/2C_1);\ \delta_{2p}=-(C_4/2C_3);\ \delta_{2a}=-(C_6/C_7)\text{ and }\delta_{2b}=-(C_5/C_7) \quad (4)$$

The modified extended Hansen method (Eqs. 1—4) is applied here for the first time to three pharmaceutical excipients, lactose, saccharose and mannitol. These saccharides are widely used in pharmaceutical industry and drug formulation. The partial solubility parameters of mannitol and saccharose are reported in this work for the first time. Since the dispersion, dipolar and hydrogen bonding parameters of lactose were obtained from a different experimental method[6] these values serve to test the validity of the method used here. In addition, the acidic and basic partial solubility parameters of lactose are obtained in this work for the first time. The UV-vis spectrophotometric technique cannot be applied to accurately determine the solubility of sugars because these compounds do not present absorption peaks. An evaporative light scattering detector (ELSD) was proposed for the analysis of compounds that do not absorb UV radiation or do so at inconvenient wavelengths where sensitivity is low.[10—12] This is a quite recent technique and was used in this work.

Experimental

Materials Lactose monohydrate, mannitol and saccharose were kindly provided by UPSA (France). D-Fructose (Fluka Biochemika) was used as internal standard for the assay. The solvents employed (spectrophotometric or analytical grade, Table 1) include several chemical classes from nonpolar to highly polar to cover a wide range of the solubility parameter scale.

Methods The water content of lactose, mannitol and saccharose was determined in triplicate using the Karl Fischer rapid test as previously reported.[8] The molar heats and temperatures of fusion were determined by differential scanning calorimetry (Mettler TA 4000). The solubility experiments were performed as follows. An excess of the sugar powders was placed in contact with the solvents. The suspensions were shaken at 25± 0.2 °C in a temperature-controlled bath (Heto SH 02/100, Germany) during 5—6 days. After equilibrium solubility was achieved, the nondissolved solid phase was removed by filtration (0.2 μm pore size membranes Nylaflo, Durapore or Fluoropore). The saturation concentrations were determined by a liquid chromatographic procedure associated with an evaporative light scattering detector (see below). The densities of the solutions were measured in 10 ml-pycnometers. All the results are the average of at least three replicated experiments. Weighted multiple regression analysis was performed with a number cruncher statistical system (NCSS Software, Kayesville, UT, U.S.A.). Residual analysis and the Cook distance were used to detect deviations of individual cases from the overall regression. A smaller weight (0.001) was assigned to the solvents that least fitted the models.

Liquid Chromatographic Procedure The liquid chromatograph (LC) consisted of Waters 600E multisolvent delivery system and a Waters 717 plus autosampler (both from Milford, MA, U.S.A.). The measurements were carried out on a gel column packed with a micro-particulate resin in the calcium form (300×6.5 mm) from Waters and thermostated at 80 °C. The flow rate of the mobile phase (distilled water) was 0.5 ml/min and the injection volume 20 μl. The LC column was coupled to a Sedex 55 evaporative light scattering detector (Sedere, Alfortville, France). Nebulization of the eluent in the ELSD was provided by a stream of pressurized air at 2.5 bar with a flow rate of approximately 4 l/min. The nebulization was performed at room temperature, and the nebulized solvent was evaporated at 40 °C. The detection output was interfaced to a computer using a Chrom–Card software (Fisons Instruments, Milan, Italy) for data handling and chromatogram generation. Samples of water-miscible saturated solutions of lactose monohydrate, mannitol and saccharose were either diluted with distilled water or evaporated to concentrate the solute. Samples of non-water-miscible saturated solutions were directly evaporated and the residues were then diluted in water. To avoid variations in the ELSD response over time, fructose was used as an internal standard for all the sugars studied. The experimental error of the solubility measurements of lactose, mannitol and saccharose ranges between 0.2—7%, except for the solutions of lactose in propionic acid (23%) and in acetone (21.7%).

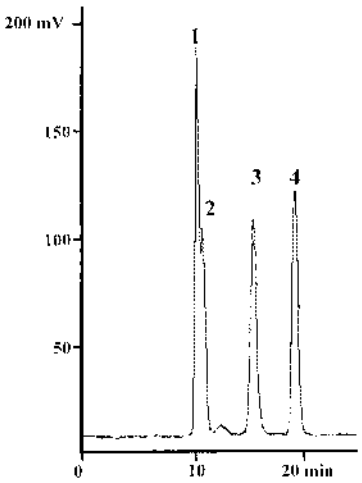

Fig. 1. Separation by Liquid Chromatography of Different Sugars Detected by Evaporative Light Scattering

1: saccharose, 2: lactose monohydrate, 3: fructose, 4: mannitol.

Results and Discussion

Evaporative Light Scattering Technique The detection principle of ELSD is based on column effluent nebulization into droplets which are carried by a nebulizing gas in an evaporator tube and then directed towards a light beam.[13,14] Light is scattered by residual particles of non-volatile material and measured by a photomultiplier. Then, the signal intensity is related to the mass of the analyte in the eluent.

Detector response linearity was determined by preparing five calibration samples covering a 0.05—0.50 mg/ml concentration range. Each sample was injected in triplicate. Because ELSD gives a nonlinear response, a plot of the ratio between the peak areas of the solute and the internal standard *versus* the sample concentration in double logarithmic coordinates was used,[14]

$$\log A=\log a+b\log C \quad (5)$$

where A is the peak area ratio, C the concentration, and a and b constants determined principally by the nature of the mobile phase. Separation of the different sugars with the internal standard (fructose) was quite efficient as illustrated in Fig. 1.

Solubility of Lactose, Mannitol and Saccharose as Related to the Total Solubility Parameter of the Solvents The water content was 6.12%, 0.41% and 2.6% for lactose monohydrate, mannitol and saccharose, respectively. The ideal solubility was obtained from the molar heat and temperature of fusion.[7] At a heating rate of 5 °C/min, lactose shows a dehydration peak at 141 °C and then melts at 214.2 °C. The heat of fusion is 98.48 kJ/mol. Chidavaenzi *et al.*[15] reported endothermic peaks for dehydration (152 °C) and fusion (204 °C) at a heating rate of 20 °C/min. The temperatures and heats of fusion are 166.6 °C and 50.5 kJ/mol for mannitol and 189.8 °C and 44.53 kJ/mol for saccharose. The ideal solubilities X_2^i of mannitol ($X_2^i=1.6\times10^{-3}$) and saccharose ($X_2^i=1.7\times10^{-3}$) are very similar. The lowest value corresponds to lactose ($X_2^i=2\times10^{-4}$). This means that the energy needed to liquefy the crystal to enter into the solution is larger for lactose than for the other two saccharides.

Figures 2—4 show the logarithm of the solubility mole fraction against the total solubility parameter δ_T which serves as a measure of the overall polarity of the solvents. The plots illustrate in a qualitative way the polarity region and the kind of solvents providing maximum solubility. Lactose is much more soluble in strongly dipolar solvents of high dielectric constant values (formamide and water) than in alcohols and nonpolar solvents. The region of maximum solubility corresponds to large solubility parameter values (from 36 to 50 $MPa^{1/2}$), the highest solubility being observed in formamide. Alcohols of low solubility parameter values are poor solvents whereas lactose is quite soluble in glycols. The solubility in basic solvents such as dioxane is similar to that observed in acidic solvents and increases as the solubility parameter of the solvent becomes larger.

As for lactose, the maximum solubility of mannitol occurs in the region corresponding to the highest solubility parameter values (from 36 to 50 $MPa^{1/2}$). The solubilities are larger than for lactose in most of the solvents owing to the higher ideal solubility of mannitol. Strongly dipolar solvents (formamide, *N*,*N*-dimethylformamide and water) with large solubility parameter values are the best solvents for mannitol, and the experimental solubilities are similar to those found for lactose in these solvents.

The solubility of saccharose in propionic acid, diethyl ether and in most of the nonpolar solvents was too low to be detected by the method of assay. The structure of saccharose which contains two closed rings is similar to that of lactose and both sugars differ from the open structure of mannitol. However, the solubility in formamide and in strongly dipolar solvents is less than for the other two sugars. Among the solvents tested, formamide, *N*,*N*-dimethylformamide and water provide the maximum solubility. Glycols are better solvents than alcohols, and the region of maximum solubility is located at large polarity values (δ_T above 35 $MPa^{1/2}$). The solubility plots against the total solubility parameter are scattered (Figs. 2—4) because this single parameter does not differentiate the several kinds of interactions (dispersion, polar, hydrogen bonding). Using a polynomial in the second degree (theoretical curves of Figs. 2—4) the correlation of $\ln X_2$ against the total solubility parameter (δ_T) is poor ($r^2=0.73$ for lactose and mannitol and $r^2=0.68$ for saccharose). This justifies the use of partial solubility parameters in the models used in this work (Eqs. 1 and 2).

Partial Solubility Parameters of Lactose, Mannitol and Saccharose The experimental logarithm of the mole fraction solubility (Table 1) was fitted to Eqs. 1 and 2. The values of the partial solubility parameters used in the regression analysis were previously published.[8] The original variable of the extended Hansen approach was also tested using $\ln \alpha_2/U$ instead of $\ln X_2$ in Eqs. 1 and 2. The activity coefficient α_2 was obtained from the ratio of the ideal to the experimental solubility mole fraction $\alpha_2=X_2^i/X_2$. The term U was calculated from the volume fraction of the solvent ϕ_1 and the molar volume of the solute V_2, $U=V_2\phi_1^2/\boldsymbol{R}T$ where $\boldsymbol{R}$ is the gas constant and T the absolute temperature. For lactose, $\ln \alpha_2/U$ did not give good results; the signs of some of the regression coefficients were not correct with either the three- or the four parameter model; therefore, this variable is not included in Table 1. The best results were obtained with the dependent variable of the modified method, $\ln X_2$, and the four parameter model (Eq. 2). The solvents that least fitted the model were ethanol, methanol, 1,2 propanediol and ethyl acetate. Water was included in the regression analysis because

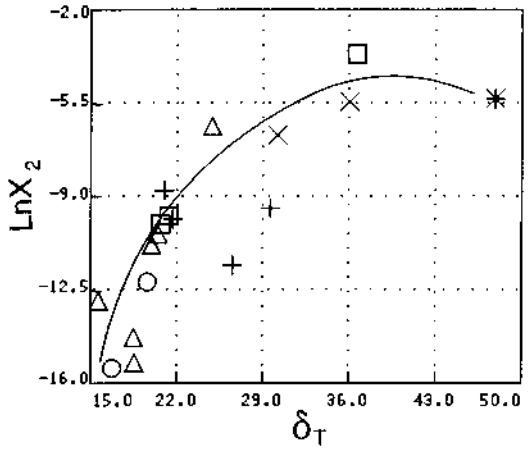

Fig. 2. Experimental Log Mol Fraction Solubility of Lactose against the Solubility Parameter of the Solvents

○, nonpolar; △, bases; □, acids; +, alcohols; ×, glycols; ∗, water.

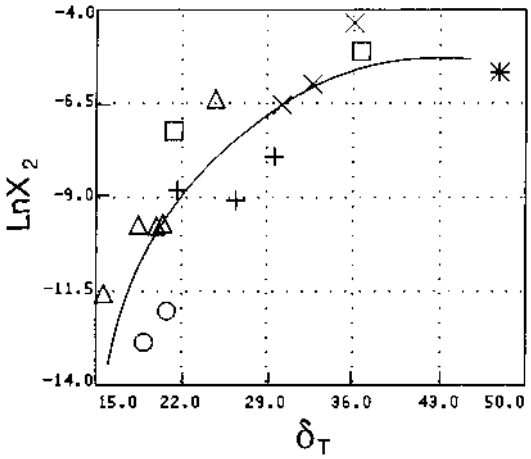

Fig. 3. Experimental Log Mol Fraction Solubility of Mannitol against the Solubility Parameter of the Solvents

○, nonpolar; △, bases; □, acids; +, alcohols; ×, glycols; ∗, water.

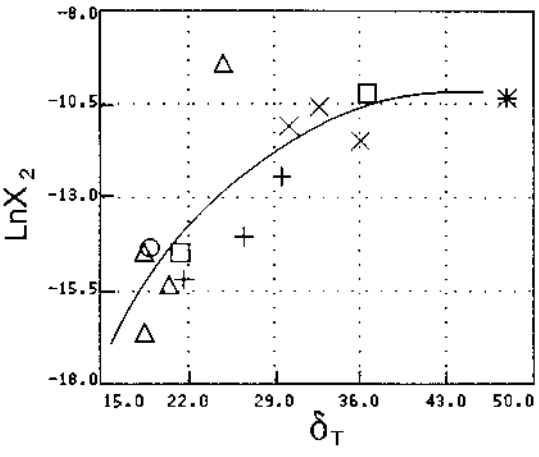

Fig. 4. Experimental Log Mol Fraction Solubility of Saccharose against the Solubility Parameter of the Solvents

○, nonpolar; △, bases; □, acids; +, alcohols; ×, glycols; ∗, water.

Table 1. Dependent Variables for Lactose, Mannitol and Saccharose

Solvents	Lactose $\ln X_2$	Mannitol $\ln X_2$	Saccharose $\ln X_2$
Ethanol	−11.6131	−9.0891	−16.4608
Chloroform	*b)*	*b)*	−168667
Methanol	−9.4781	−7.9205	−14.2283
Benzene	−15.2384	*b)*	−20.0631
Dioxane	−10.4385	−9.6962	−18.2647
Acetic acid	−9.7587	−7.2356	−17.0504
Pentanol	−9.8703	−8.80489	−18.0534
Cyclohexane	−15.4443	*b)*	*b)*
Ethylene dichloride	*b)*	*b)*	*b)*
1,2-Propanediol	−6.7154	−6.5430	−12.3425
Formamide	−3.6711	−5.1104	−11.1010
Ethylene glycol	*c)*	−5.9881	−11.6191
Glycerol	−5.4614	*c)*	−12.8991
Octanol	−8.8128	*c)*	*b)*
Ethyl acetate	−14.2996	−9.73011	−17.0410
Heptane	*b)*	*b)*	*b)*
Chlorobenzene	−12.2240	*b)*	*b)*
Propionic acid	−10.0713	*b)*	*b)*
Diethyl ether	−12.9426	−11.5626	*b)*
Water	−5.3507	−5.6732	−11.2876
Acetone	−10.8519	*b)*	*b)*
Acetophenone	*c)*	*c)*	*b)*
N,*N*-Dimethyl formamide	−6.3961	−6.3834	−9.9817

a) $\ln \alpha_2 = \ln X_2^i / \ln X_2$ and $U = V_2 \Phi_1^2 / \boldsymbol{R}T$. See Barra *et al*.[7] *b*) The concentration dissolved was not detectable by evaporative light scattering detection. *c*) A problem appeared during the measurement, probably because of degradation of the sugar during the drying of the saturated phase.

this solvent is located at the region of maximum solubility of lactose and was compatible with the model. Water is usually very influent for less polar solutes showing a high Cook distance and should not be included in these cases.[8] The three parameter model also provided significant partial parameters for lactose, but the number of incompatible solvents with the model was larger, and the polar partial solubility parameter obtained was too high ($\delta_p = 37.25\ \mathrm{MPa}^{1/2}$) to be realistic.

The parameters listed in Table 2 for lactose were obtained with the four parameter model and are quite close to those reported by Huu-Phuoc *et al*.[6] ($\delta_{2d} = 19.6$, $\delta_{2p} = 26.2$, $\delta_{2h} = 23.1$, $\delta_{2T} = 39.9\ \mathrm{MPa}^{1/2}$) using a completely different method. Instead of solubility measurements, these authors employed chromatographic parameters obtained from gas-solid chromatography. The set of solvents was different from the one used here. Highly polar solvents (glycols and water) were not employed, and the acidic and basic partial solubility parameters of lactose were not determined. Examination of the parameters obtained in the present study shows that lactose is very polar (high δ_{2p} value) which agrees with the large number of polar groups of the molecule. The Lewis acid ability is somewhat larger than the Lewis base properties (δ_{2a} is about two units higher than δ_{2b}). The dispersion partial solubility parameter is like the values determined for drug molecules. Therefore, the large values of the dipolar and hydrogen bonding parameters are responsible for the high total solubility parameter obtained.

As for lactose, the four parameter model associated with the dependent variable $\ln X_2$ (Eq. 2) provided the best results for mannitol. The solvents that least fitted the model were pentanol, ethylene glycol and ethylene dichloride. The partial solubility parameters obtained are listed in Table 2. Water

Table 2. Partial Solubility Parameters ($\mathrm{MPa}^{1/2}$) of Lactose, Mannitol and Saccharose with $\ln X_2$ as the Dependent Variable.[a)]

Dependent variable, $\ln X_2$	δ_d	δ_p	δ_h[b)]	δ_a	δ_b	δ_T	r^2
Lactose	17.57	28.67	18.99	14.50	12.43	38.61	0.96
Mannitol	16.15	24.53	14.56	8.71	12.18	32.78	0.99
Saccharose	17.09	18.52	13.05	11.26	7.57	28.38	0.99

a) The total and partial solubility parameters of the solvents used in the regression analysis are found in Bustamante *et al*. (1998a).[8] The parameters were obtained with Eqs. 2 and 4. The standard errors of the regression are: lactose, S.D.=0.77, mannitol, S.D.=0.25 and saccharose, S.D.=0.21. *b*) Calculated from $\delta_h^2 = 2\delta_a\delta_b$.

was compatible with the overall regression. Mannitol has high δ_{2p}, δ_{2h} and δ_{2T} values although they are lower than for lactose. The dispersion partial parameters of lactose and mannitol are very similar, as expected.

The variable $\ln \alpha_2/U$ was not calculated for saccharose. This compound decomposed near fusion and accurate heats of fusion could not be determined. As for lactose and mannitol, the four parameter model associated with the dependent variable $\ln X_2$ provided the best results, with significant regression coefficients. Ethanol and 1-pentanol were the solvents that least fitted the model.

As observed in Table 2, the dispersion partial solubility parameter is similar for the three compounds studied. Lactose, mannitol and saccharose are quite polar showing high dipolar and total solubility parameters. The two cyclic sugars, lactose and saccharose are better Lewis acids ($\delta_{2a} > \delta_{2b}$) whereas mannitol, with an open structure, is a better Lewis base ($\delta_{2a} < \delta_{2b}$) against the solvents used. The ratio δ_a/δ_b of the three sugars increases from mannitol (0.72) to lactose (1.17) and saccharose (1.49). The three compounds have a high overall hydrogen bonding capability, showing δ_h values above $13\ \mathrm{MPa}^{1/2}$.

The results show that the modified extended Hansen method can be applied to obtain partial solubility parameters of sugars. The parameters determined for lactose are close to those obtained by Huu-Phuoc[6] using another technique and a different set of solvents. The modified extended Hansen method has been applied for the first time to pharmaceutical excipients and the most suitable model was the four parameter equation, as earlier found for drug molecules.[7—9] The partial solubility parameters obtained for lactose, mannitol and saccharose provide a quantitative measure of their ability to interact through dispersion, dipolar and hydrogen bonding with other excipients and drugs. The large values of the dipolar and hydrogen bonding parameters agree with the highly polar nature of these excipients, being larger than those previously found for semipolar drugs. The values of δ_a and δ_b are also large, indicating the ability of the sugars to interact through both Lewis acid and Lewis base interactions. Therefore, the interaction of the excipients studied will be larger either with acidic or basic drugs showing high δ_p values. The partial solubility parameters very much improve the fit of solubility when compared with the results obtained with a single parameter (δ_T). According to the r^2 values shown in Table 2, more than 96% of the solubility change is accounted for by the model (Eq. 4). With a single parameter, only 68—70% of the variance is explained, resulting in scattered plots (Figs. 2—4). The evaporative light scattering technique of assay provided good results with most solvents and was suit-

able to accurately measure the solubility of sugars in individual solvents. The results suggest that the modified extended Hansen method could be applied to determine partial solubility parameters of other non-polymeric pharmaceutical excipients, provided that an accurate method to measure the experimental solubility is available.

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