Development of a Small-Scale Automated Solubility Measurement Apparatus

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A semiautomated device for solubility measurements in solution volumes as low as 1 mL was developed for pharmaceutical applications. The device operates nonisothermally, and can measure multiple samples simultaneously. Solubilities of model compounds such as paracetamol, mannitol, adipic acid, and glycine were measured and showed a maximum deviation of 5 wt % compared to literature data. Extrapolation of solubility data in the form of activity coefficients was found in good agreement with the literature value over a wide range of temperatures for paracetamol in 2-propanol and adipic acid in ethanol, while some deviation was observed for mannitol in water. The use of the solubility-measuring device to perform solvent screening on multiple solvents for early-stage pharmaceutical compounds was also examined. Results indicate that the slope of the solubility curve with temperature can be estimated with limited data for multiple solvents.

1. Introduction

Crystallization processes in aqueous and organic solvents and solvent mixtures are employed in the manufacture of pharmaceuticals, organic fine chemicals, and specialty chemicals.[1,2] The solubility of solid compounds in pure solvents and solvent mixtures plays a crucial role in the development and operation of crystallization processes.[3] The determination of solubility data of developed pharmaceutical compounds in pure solvents, including water and mixed solvents, is important for both process development and determining the drug delivery methods to be used. Solubility determines supersaturation generation methods and the yield in the crystallization process. In addition, identification of crystallization solvents based on relative solubility order is necessary, because appropriate selection of solvent may enhance the reaction yield and determine the quality of the product and the manufacturing processes.[4−6] The solubility measurement appears to be simple, but it is easy to implement it incorrectly and produce erroneous measurements. Numerous methods to measure the solubility of organic compounds, such as high-performance liquid chromatography (HPLC),[7] attenuated total reflection (ATR)-FTIR spectroscopy,[8−10] Raman spectroscopy,[11] and focused beam reflectance mode (FBRM) measurement,[12] have been reported. The isothermal solubility measurement method, which allows for an extended time to reach equilibrium, to sample and weigh the residue, and to measure the concentration of a dissolved compound by a suitable analytical method, is reliable.[1] But these methods require a substantial amount of material, and a careful calibration or data extrapolation is needed to calculate solubility. Thus, determination of solubility using the existing methods is time-consuming with significant demands on manpower. In the pharmaceutical industry, to improve predicting bioavailability and solvent screening, rapid experimental methods of accurately measuring solubility have been investigated.[13−15] In addition, new developed pharmaceuticals, which are available for analysis only in small amounts, intensified the need for methods that use progressively smaller samples.

Direct solubility data in different solvents are not always available in the pharmaceutical industries. Solubility prediction methods are valuable in reducing the time and resources required to measure solubility. In estimating solubility, it is important to determine the deviation of the solution from ideality in terms of activity coefficients. The activity coefficient approach to estimate the aqueous solubility of amino acids was first proposed by Nass.[16] Universal functional group activity theory (UNIFAC) [4,17−19], modified UNIFAC,[20,21] the nonrandom two-liquid (NRTL) model,[22] and perturbation theory[23] have been applied to predict the solubility of amino acids and their mixtures in water, organic solvents, and solvent mixtures. Direct application of these methods to other compounds of interest in the pharmaceutical industry is often not possible, because group interaction or solubility parameters, depending on the particular method, are usually not available. It is often useful to extrapolate limited solubility points and fit the solubility curve over a wide range of temperatures.[24,25] The general form of the solubility

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equation is[26]

$$\ln(\gamma x) = \frac{\Delta H_f}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \frac{\Delta C_p}{R}\left(\ln\frac{T_m}{T} - \frac{T_m}{T} + 1\right) \quad (1)$$

It is normally assumed that the heat capacity term is negligible, and eq 1 is written as

$$\ln(\gamma x) = \frac{\Delta H_f}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (2)$$

In ideal solutions, e.g., when the solvent is of polarity similar to that of the solute, eq 2 is reduced to the van't Hoff equation.[24]

In this paper, a semiautomated apparatus that measures turbidity and can measure multiple samples of 1 mL each simultaneously is introduced and its reliability is demonstrated by measurements of several organic compounds. Solubilities of glycine and mannitol in water, paracetamol in 2-propanol, and adipic acid in ethanol as model systems were measured. These compounds have been investigated by a number of researchers for the solubilities and polymorphism.[10,24,27−31,34−44] The apparatus presented here offers substantial savings in material, time, and labor. Finally, activity coefficients of solutes were estimated, and their dependence on temperature was extrapolated over a wide temperature range. These extrapolated activity coefficients were then used to calculate the solubility of solutes of interest at temperatures outside the range of the measurements. Comparison of solubility values obtained with the apparatus presented here with data from the literature showed good agreement and demonstrated the reliability of our method.

2. Experimental Section

2.1 Materials. Glycine ($CH_2(NH_2)COOH$; 99+% pure), D-mannitol ($CH_2OH(CHOH)_4CH_2OH$; 99+% pure), paracetamol ($CH_3CONHC_6H_4OH$, acetaminophen; 98% pure), and adipic acid ($HOOC(CH_2)_4COOH$; 99% pure) were supplied from Aldrich Co., Ltd. These materials were used as received, without further purification. Two drugs, compounds A and B, were provided by Pfizer without any solubility data for solubility measurements and solvent screening. The chemical formula and physical properties of compounds A and B cannot be released for the sake of confidentiality. In all the experiments, distilled deionized water and HPLC purity grade solvents were used. Values of the heat of fusion and melting temperature used in the solubility equation are shown in Table 1. Since most amino acids decompose before reaching melting temperature, data for the heat of fusion, melting temperature, and heat capacity of glycine are not available for the application of the solubility equation. The heat of fusion and melting temperature of paracetamol were calculated by Grant et al.[24] and measured by Neau et al.,[27] Nichols et al.,[28] and Granberg et al.[29] The most recently measured values by Granberg et al.[29] are employed in this work for paracetamol. For D-mannitol, the values measured by Barone et al.,[30] Neau et al.,[27] and Burger et al.[31] are reported. The values reported by Burger et al.[31] are employed for D-mannitol in this work, because Burger et al. reported the value with an identified polymorph. Grant et al.[24] reported the heat of fusion and the melting temperature of adipic acid. The differential heat capacities for paracetamol and mannitol were reported by Neau et al.[27] to be 99.8 and 163.7 J/(mol K), respectively.

Table 1. Physical Properties of Compounds in the Present Study

compound		ΔH_f (kJ/mol)	T_m (K)
paracetamol	Grant et al.	30.2	170[a]
	Neau et al.	27	441.7
	Nichols et al.	28.1	171[a]
	Granberg et al.	27.1	443.6
D-mannitol	Barone et al.	56.1	439.1
	Neau et al.	50.6	438.7
	Burger et al.	53.5	166[a]
adipic acid	Grant et al.	47.5	153[a]

[a] T_m is reported in °C.

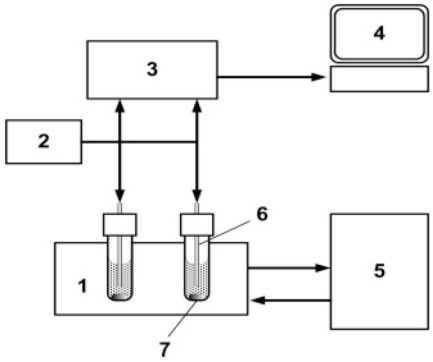

Figure 1. Schematic of the experimental setup: (1) reaction station, (2) light source, (3) multiplexor, (4) PC, (5) chiller, (6) turbidity probe, (7) micro magnetic stirring bar.

2.2. Experimental Apparatus and Procedure. Measurements of solubility were performed using dipping-type fiber optic turbidity probes. The apparatus used in the present work was constructed from laboratory components and is shown in Figure 1. It consists of a reaction station, turbidity probes, light sources, a multiplexor, a chiller, and a custom-designed Labview program. The Stem RS10 reaction station (from Barnstead International) has multiple glass tubes. For small-scale experiments (1 mL solvent volume), 8 mm i.d. glass tubes were customized with adaptor sleeves for thermal contact inside the reaction station. Solvents were dispensed using micropipets. Each glass tube could be controlled individually for temperature and stirring. Each glass tube was sealed with a customized cap, and the temperature was monitored with a 10/100 Mbps Ethernet network interface (from National Instrument) and T-type thermocouples (from Omega Engineering, Inc.) attached to adaptor sleeves. Micro magnetic stirring bars were used for stirring. The six-channel transmission spectrometer (from World Precision Instruments, $\lambda = 300-1020$ μm) consists of 1.8 mm o.d. fiber optic probes, FO-6000 tungsten light sources, and a multiplexor that interfaces between the computer and the six-channel probes. The total beam path length is 5 mm. All parts of the apparatus, which are connected to an IBM computer, are monitored and controlled by the custom-designed Labview program. The data from the experiments are also analyzed by a custom-designed program.

2.3. Procedure. The protocol for solubility measurements calls for six samples of slurry solution with different solute weight percents placed in test tubes in the reaction chamber of the apparatus. The temperature of each sample is increased 1 °C at a time, and held at

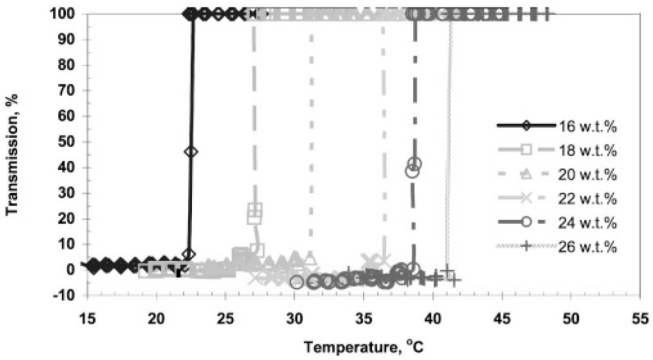

Figure 2. Typical transmission versus temperature profiles for samples of different solute concentrations for the mannitol−water system.

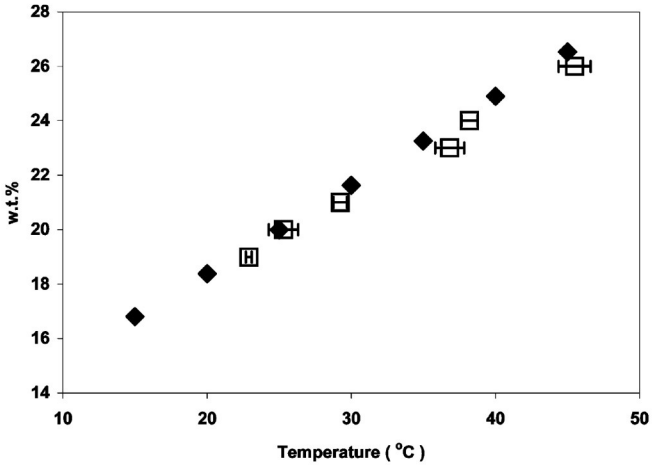

Figure 3. Solubility of glycine in water at various temperatures: ◆, Dalton and Schmidt;[34] □, present work.

Table 2. Solubility Measurements of Glycine in Water

wt %	measd temp (°C)			T_{av} (°C)	error (wt %)[a]
19	22.7	23.1	22.9	22.9	2.1
20	26.4	25.1	24.4	25.3	0.9
21	29.6	29.4	28.7	29.2	2.7
23	35.7	37.6	37.2	36.8	5.8
24	38.1	37.7	38.8	38.2	2.7
26	44.3	46.5	45.7	45.5	5.4

[a] Error (wt %) = $|(M_{meas} - M_{lit})/M_{meas}| \times 100$.

that level for about 40−60 min. This process is repeated until all crystals in all samples disappear. The slurry inside each sample is stirred vigorously by a magnetic stirrer to keep the particles in suspension. The disappearance of crystals can be detected by fiber optic turbidity probes in all samples. The mass of solute added was predetermined to make six samples of different concentrations in 1 mL of solution volume.

To determine the heating range for the measurements, all samples were heated from 10 to 20 °C below the boiling point of the solvent within 30 min. From this step, the critical dissolution temperature of each sample could be estimated, and the appropriate heating temperature range for each sample was identified. For fast heating rates, the temperature measured at the point of disappearance of the crystals may be significantly higher than the actual saturation temperature because, during the heating process, as the point of saturation is approached, the driving force of dissolution decreases and, as a result, the rate of dissolution decreases. This is the reason that the start temperature for each sample

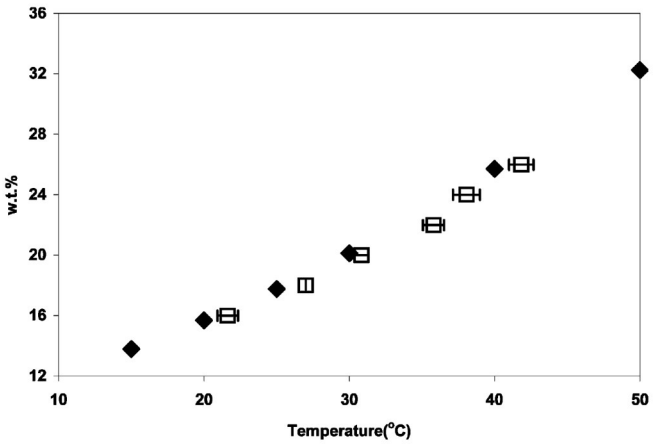

Figure 4. Solubility of D-mannitol in water at various temperatures: ◆, Seidell;[40] □, present work.

Table 3. Solubility Measurements of Mannitol in Water

wt %	measd temp (°C)			T_{av} (°C)	error (wt %)
16	22.4	21.5	21	21.6	2.6
18	26.7	27.1	26.5	26.8	3.7
20	30.3	30.8	31.2	30.8	3.4
22	35.6	34.7	36.4	35.6	6.5
24	38.5	37	38.7	38.1	2.9
26	41.4	42.8	41.3	41.8	4.4

Table 4. Solubility Measurements of Paracetamol in 2-Propanol

wt %	measd temp (°C)			T_{av} (°C)	error (wt %)
9	16.6	16.4	17.7	16.9	2.5
10	21.3	21.9	21.2	21.5	1.5
11	26.3	25.3	27.3	26.3	1.3
12	30.5	32.5	31.6	31.5	3.0
13	34.7	35.7	35.5	35.3	2.4
14	36.5	37.2	37.4	37	2.8

was selected to be 10 °C lower than the critical dissolution temperature of the same sample and the end temperature for each sample 5 °C higher than the critical dissolution temperature of the same sample.

After heating range estimation, each sample was discarded and new samples were prepared again. According to the preprogrammed heating and stirring profile in reaction station software, the temperature of the samples, being raised 1 °C at a time, was held constant at each level for 40 min in the beginning of the heating cycle and 60 min in the later stages, with the dissolution rate decreasing as temperature increased. The procedure was repeated with new samples for reproducibility. At each temperature level, light transmission of each sample was recorded at 5 min intervals. The temperature at which all crystals in a sample were dissolved was determined from the transmission versus temperature profile, which follows a step change from 0% to 100% at the dissolution temperature of interest of the sample with the predetermined solute concentration. The initial temperature at which the value of transmission was close to 100% and that kept this value constant at higher temperature until the end of heating was determined as the solubility temperature for the sample. The use of a stepwise heating profile and turbidity has been previously employed in measurements of inorganic compounds and proteins.[32,33] The transmission versus temperature profiles for samples of different solute concentrations are shown in Figure 2. Because of the unstable background in the reference

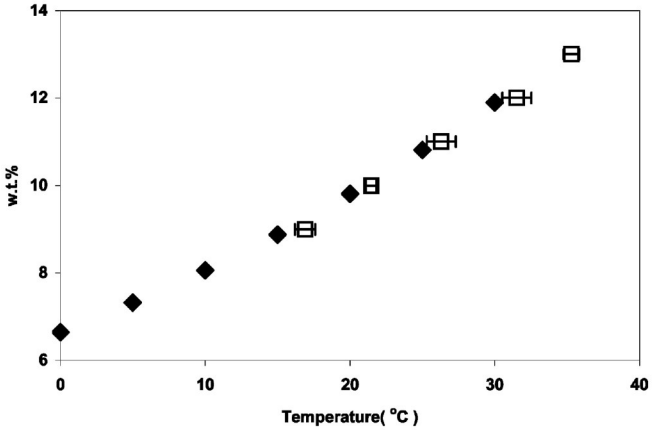

Figure 5. Solubility of paracetamol in 2-propanol at various temperatures: ◆, Granberg and Rasmuson;[29] □, present work.

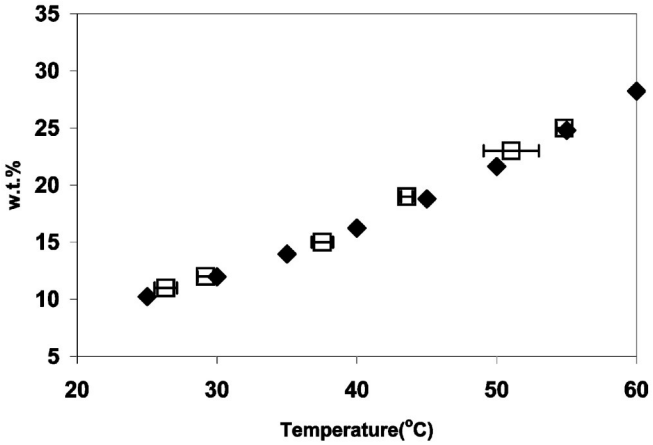

Figure 6. Solubility of adipic acid in ethanol at various temperatures: ◆, Mohan et al.;[44] □, present work.

Table 5. Solubility Measurements of Adipic Acid in Ethanol

wt %	measd temp (°C)			T_{av} (°C)	error (wt %)
11	25.5	26.4	27.1	26.3	3.6
12	28.7	29	29.8	29.2	3.1
15	37.7	36.7	38.2	37.5	0.4
19	43.1	43.7	43.9	43.6	6.1
23	51.4	52.8	48.9	51.0	4.2
25	55.4	54.8	54.3	54.8	1.8

and dark spectra of some samples, transmission of some samples is below zero, as can be seen in Figure 2. The procedure for solubility measurements in one solvent was applied for solvent screening of other one-solute systems.

Regarding solvent screening for the pharmaceutical substances provided by Pfizer, the procedure is as follows. Samples of 1% per weight of substances A and B in preselected solvents are prepared at the chiller temperature (5 °C). Some of the samples are totally dissolved at that temperature before heating commences because the particular compound is very soluble in the selected solvent. A higher weight percent sample is prepared again for the sample which is totally dissolved at the chiller temperature. After solubility points of the low weight percent sample in each solvent are measured, higher weight percent samples are prepared in each solvent. The slope of the solubility point versus solute concentration curves for the same solvent is used to rank the different solvents in terms of their ability to dissolve the substance in question.

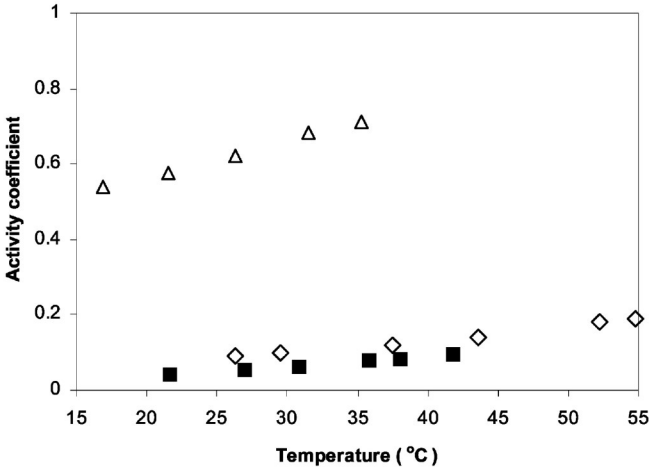

Figure 7. Activity coefficients at measured solubility points: △, paracetamol−2-propanol; ■, mannitol−water; ◇, adipic acid−ethanol.

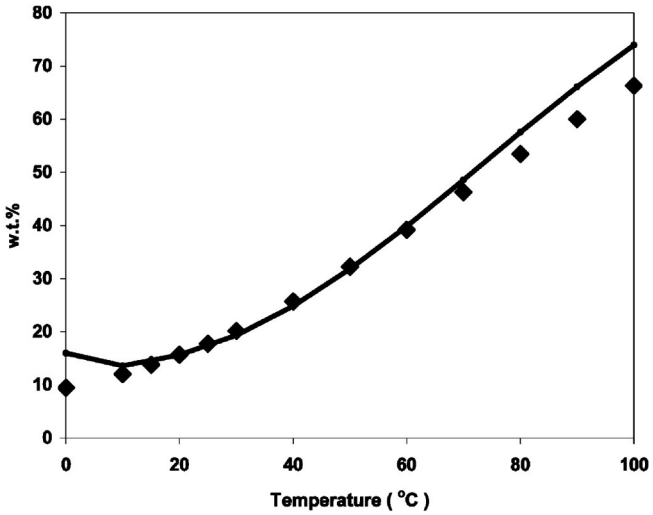

Figure 8. Predicted solubility of mannitol in water at various temperatures: ◆, Seidell;[40] —, result of prediction.

3. Results and Discussion

Solubility measurements of glycine, mannitol, paracetamol, and adipic acid as model compounds were performed to demonstrate the reliability of the apparatus. Reliability here is presented as reproducibility of measurements and error between solubilities measured by the technique presented here and those reported in the literature at the same temperatures. Each experimental data point in the figures shown below is the average of three measurements, each made with a fresh sample. Typically, the solubility measurements for each model compound take up to 10 h.

3.1. Glycine−Water. Solubilities of glycine in water at various temperatures were reported by Dalton and Schmidt and by Dunn et al.[34,35] Glycine has three polymorphic forms: α-, β-, and γ-forms.[36−38] In the aqueous solution, kinetically stable α-glycine does not transform to the β- or γ-form by the solution-mediated polymorphic transition. It is unlikely that glycine undergoes a polymorphic change during the solubility measurement. The earlier solubility studies of glycine in water by Dalton and Schmidt and Dunn et al. seem to suggest that the glycine they used and the one available commercially are of the α-form.[34,35] Figure 3 shows a comparison between our measurements and

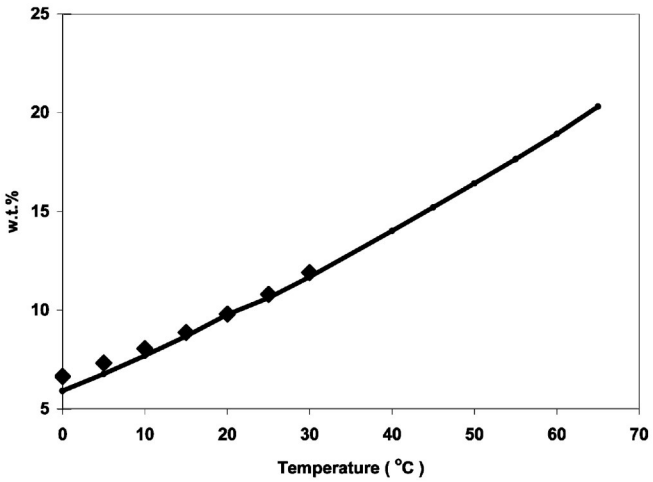

Figure 9. Predicted solubility of paracetamol in 2-propanol at various temperatures: ◆, Granberg and Rasmuson;[29] —, result of prediction.

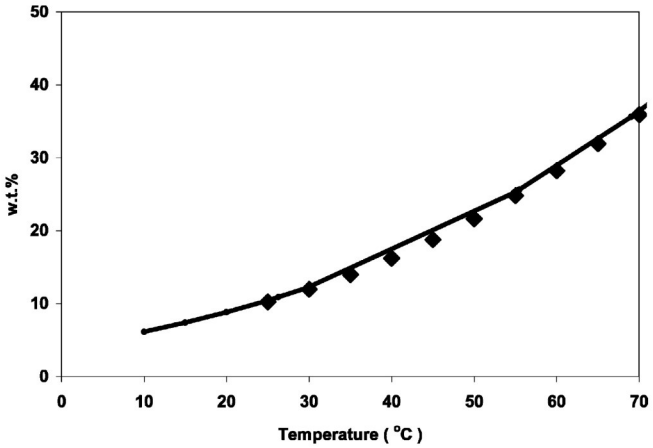

Figure 10. Predicted solubility of adipic acid in ethanol at various temperatures: ◆, Mohan et al.;[44] —, result of prediction.

those by Dalton and Schmidt.[34] The reproducibility and accuracy of our measurements are shown in Table 2. On the basis of the calculated errors, the error in the solubility measurements of glycine in water is within 5% of the solute amount used in the experiments.

3.2. Mannitol−Water. Concerning the polymorph of D-mannitol, Burger et al. pointed out the discrepancies in the literature.[31] In aqueous solution, the β-form polymorph (phase I) of D-mannitol is the stable form and it does not transform to the α-form (phase II) or δ-form (phase III) polymorph.[39] The commercially obtained D-mannitol which is used in our measurements is the thermodynamically stable β-form (phase I). Figure 4 shows a comparison of our measurements and those by Seidell et al.[40] The reproducibility and accuracy of the measurements are shown in Table 3. On the basis of Table 3, the error in the solubility measurements of D-mannitol in water is approximately 6.5% of the mannitol concentration.

3.3. Paracetamol−2-Propanol. The three polymorphs are reported in the literature for paracetamol.[28,41−43] The monoclinic form, I, of paracetamol does not transform to the orthorhombic form, II, or form III in 2-propanol. Comparisons of solubility measurements in this work with those by Granberg and Rasmuson[29] are shown in Figure 5. Measured temperatures and errors are reported in Table 4. On the basis of Table 4, the error in the solubility measurements of paracetamol

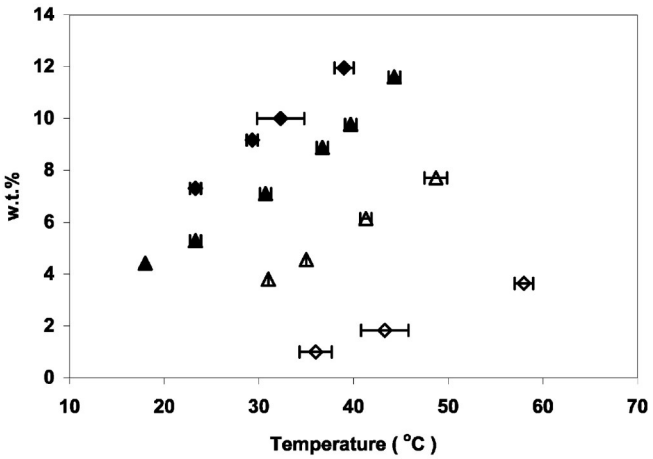

Figure 11. Solubility of compounds A and B in various solvents: ◆, A−acetone; ◇, A−2-propanol; ▲, B−ethyl acetate; △, B−benzyl alcohol.

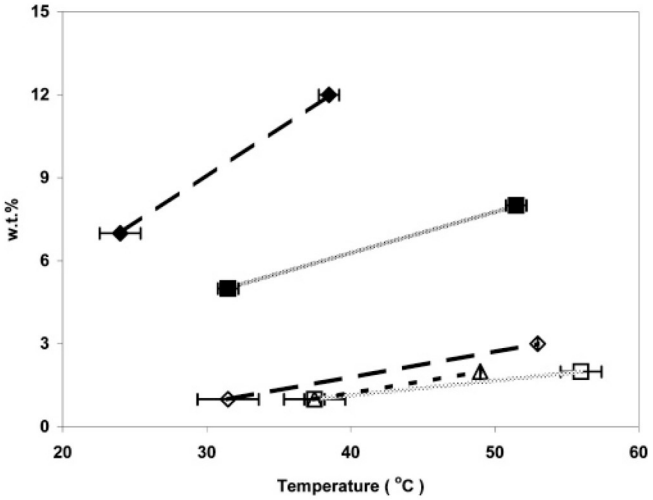

Figure 12. Solvent screening of compound A: ◆, acetone; ■, ethyl acetate; ◇, 2-propanol; △, ethanol; □, methanol.

in 2-propanol is approximately 3.0% of the paracetamol concentration.

3.4. Adipic Acid−Ethanol. There is no reported polymorphic transition of adipic acid in any solvent, and the solubility data of adipic acid in ethanol are very scarce in the literature. One exception is the solubility equation given by Mohan et al.[44] From the equation, solubility values at the selected temperatures are referenced. Comparisons of our measurements with solubility estimates from the equation by Mohan et al. are shown in Figure 6. Measured temperatures are shown in Table 5. The error in the solubility measurements of adipic acid in ethanol is around 6% of the solute amount used in the experiments.

3.5. Activity Coefficients. In the previous sections, solubility measurements for mannitol, paracetamol, and adipic acid were reported. Activity coefficients estimated by eq 2 at the measured points are shown in Figure 7 for mannitol, paracetamol, and adipic acid. No activity coefficients are estimated for glycine, because of a lack of physical properties to be used in eq 2 (most amino acids decompose at temperatures below melting). Equation 2, which is used for these estimates, ignores the effect on solubility of the difference in the heat capacities of the solute in the solid and liquid phases. As a result, activity coefficients for the mannitol in water and adipic acid in ethanol systems are slightly underestimated.

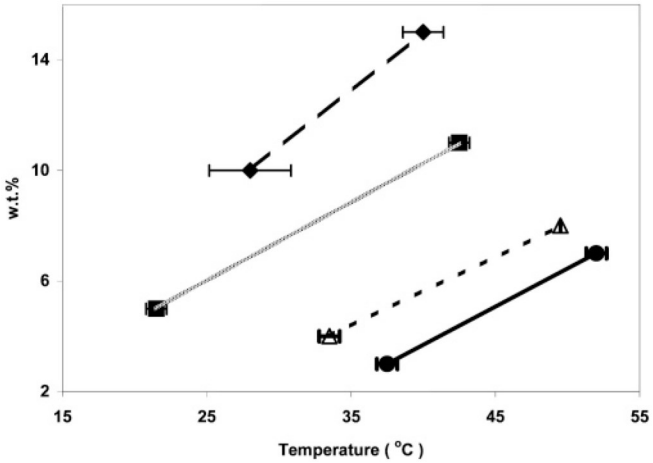

Figure 13. Solvent screening of compound B: ◆, acetone; ■, ethyl acetate; △, benzyl alcohol; ●, toluene.

Activity coefficients of the test compounds from Figure 7 were extrapolated beyond the temperature range of the solubility measurements. Solubilities of the test compounds, estimated by extrapolation of activity coefficients, are shown in Figures 8−10. For mannitol in water, the difference between solubilities from this work and those in the literature is larger than for the other two systems of interest. Figure 8 shows that differences are larger at low and high temperatures. For paracetamol in 2-propanol and adipic acid in ethanol, solubilities from this work compare well with those in the literature (solubility data for paracetamol in 2-propanol are available in the literature only for temperatures lower than 30 °C). Inclusion of the differential heat capacity contribution in extrapolating for solulibities beyond the temperature range of measurements in this work did not improve the estimates noticeably.

3.6. Compounds A and B. After confirmation of the reproducibility and accuracy of the technique presented in this paper for the test compounds, solubilities of compounds A and B, provided from Pfizer, in several solvents were measured and screening to rank the solvents of interest was performed. Solubilities of compounds A and B in different solvents are shown in Figure 11. Figures 12 and 13 show solvent screening for these compounds. For compound A, acetone, ethyl acetate, methanol, ethanol, 2-propanol, and water were the solvents screened. Acetone and ethyl acetate are identified as the process solvents for compound A. For compound B, acetone, ethyl acetate, methanol, toluene, and benzyl alcohol were the solvents screened. Acetone and ethyl acetate are identified as the process solvents for compound B. Water and methyl alcohol are identified as poor solvents for compounds A and B, respectively. In 1 wt % solute loading, percent transmissions in these solvents never reached more than 10%, even at 50 °C.

Conclusions

A semiautomated technique that can measure solubility in small solution volumes (1 mL), in a short time, and for multiple samples, was developed. The technique can be useful in the pharmaceutical industry for several reasons. During drug development, fast solvent screening and solubility measurements are critical early in the development. The amount of pharmaceutical substances for analysis purposes is often limited, a restriction that makes the technique presented here more useful. For moderately soluble systems (compounds A and B), less than 0.5 g of solute was required to measure multiple solubility points in each solvent. The minimum amount of solute employed in these experiments was 8 mg in 1 mL of solvent. Comparisons of solubilities of test compounds in this work and the literature showed that the error is within 5 wt %, thus advocating for the accuracy of the technique. The results of the measurements by this technique were also shown to be reproducible. Extrapolation of solubility versus temperature data beyond the range of measurement temperatures leads to accurate estimates of solubility. Finally, results from simultaneous measurements of the solubility of different substances in various solvents suggest that this technique could be used for rapid but reliable screening of solvents for compounds of interest.

Acknowledgment

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Nomenclature

x = mole fraction of the solute in solution
γ = activity coefficient
ΔH_f = heat of fusion of the solute, kJ/mol
T_m = melting temperature of the pure solute, K
ΔC_p = difference between the heat capacities of the solute in the liquid and solid phases
R = universal gas constant, 8.3144 J mol^{-1} K^{-1}
T = temperature, K
M_{meas} = solute amount used in the experiment
$M_{lit.}$ = solute amount calculated from the literature value

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