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Short communication

Rapid, small-scale determination of organic solvent solubility using a thermogravimetric analyzer

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Abstract

A rapid gravimetric method for determining drug candidate solubility in organic solvents has been developed. The scale, speed, precision, and accuracy of the method make it ideal for solubility screening of pharmaceutical compounds during early development. The method utilizes a thermogravimetric analyzer to automate drying and weighing. Results for model compounds compare favorably with literature values.

Keywords: Thermogravimetric analysis; Organic solvent solubility; Solubility determination; Solubility screening; Gravimetric solubility

1. Introduction

Drug solubility in organic solvents plays a key role in many processes throughout pharmaceutical development. The measurement of organic solvent solubility is typically the first step in crystallization process development as the solubility is a primary determinant of the crystallization rate, polymorphic outcome, and overall yield [1]. Also, knowledge of the solubility greatly helps to identify the most appropriate solvents for polymorph screening [2,3], analytical method development, and drug formulation. For these reasons, a rapid and reliable method for determining organic solvent solubility early in the drug development process is desired.

The gravimetric method, or residue weight method, is the oldest and simplest method for determining solubility [4]. In comparison to other methods such as spectroscopy, calorimetry, refractometry, and polarimetry, the gravimetric method is more straightforward in that detection requires only a reliable microbalance. Moreover, the gravimetric method does not require the measurement of standard solutions and a large solubility range (ca. 0.1–300 mg/mL) can be achieved without dilution. Gravimetry is ideal for solubility determinations in volatile organic solvents as they are easily removed by evaporation. A downside to the gravimetric method is that it can be quite arduous when solvent evaporation and weighing are carried out manually.

In this work, TGA has been used as a tool for automating solvent evaporation and weighing, thus enabling rapid gravimetric determination of organic solvent solubility on a small-scale. In order to evaluate the reliability of the method, solubility values determined by TGA for several model compounds are compared to literature values determined using other methods.

2. Experimental

2.1. Instrumentation

All experiments were performed on a Mettler-Toledo (Columbus, OH) thermogravimetric analyzer model TGA/SDTA851/SF equipped with TSO801RO robotic autosampler and Mettler-Toledo STAReSW software. Inert

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gas (N_2) was purged through the TGA at 40 mL/min. An internal furnace and a Julabo (Seelbach, Germany) circulating water bath were used to control the temperature of the TGA. Mettler-Toledo 100-μL aluminum crucibles were used for all determinations.

2.2. Materials

Nimesulide, (±)-thalidomide, and riboflavin were purchased from Sigma–Aldrich (St. Louis, MO). Paracetamol and carbamazepine were purchased from Aldrich (Milwaukee, WI). 4-Aminophenylacetic acid was purchased from Fluka (Milwaukee, WI). Meloxicam was purchased from LKT Laboratories (St. Paul, MN). All compounds were of the highest available quality and were used as received. All organic solvents were of purity ≥99%.

2.3. Sample preparation and TGA solubility measurement

Saturated solutions of the test compounds were prepared in the organic solvents and at the temperature specified in the literature. Samples with excess solid were stirred at approximately 500 rpm on a stir plate using magnetic stir bars coated with poly(tetrafluoroethylene) (PTFE, Teflon). The temperatures of the solutions were maintained at their respective literature values using a circulating water bath (Julabo, Seelbach, Germany). The temperatures used for each compound were as follows: paracetamol (30 °C), riboflavin (30 °C), (±)-thalidomide (32 °C), carbamazepine (25 °C), nimesulide (25 °C), meloxicam (25 °C), and 4-aminophenylacetic acid (20 °C). The solutions were stirred for 3 days to allow for equilibration. At the three-day time point, the solutions were filtered through a 0.45-μm PTFE filter. To avoid precipitation in the filtered saturated solutions, filtrates were maintained at their corresponding literature temperature until aliquots were pulled for analysis.

Although a fully automated routine is easily conceived, for this work the concentrations of the saturated solutions were determined semi-automatically. While pipetting was done manually, all weighing and evaporation steps were automated on the Mettler-Toledo TGA instrument. The procedure consisted of (1) taring the pans, (2) delivering a known volume of saturated solutions (40–80 μL aliquot) into the pans, (3) evaporating the solvent by holding the samples isothermally (80–180 °C) until a constant weight was achieved (5–20 min) and (4) determining the residual weight in the pans at 25 °C. The drying time and temperature were chosen based on the volatility of the solvent and the thermal stability of the compound. The solubility of the compound in each solvent was calculated by dividing the mass of the residual solid by the aliquot volume of the saturated solution. All solubility values were determined in triplicate from the same stock solution.

3. Results and discussion

Sample thermograms ($n = 3$) from the drying step of the solubility determination of paracetamol in 1-hexanol are shown in Fig. 1. The sample volume was 40 μL and three different aliquots were dried at an isothermal temperature of 140 °C. The thermograms clearly show when the solvent has completely evaporated and the sample weight has become constant after approximately 4 min.

Table 1 compares the solubility values determined by TGA to literature values obtained under the same conditions using a variety of methods. The data were grouped into solubility ranges of 0–1, 1–10, 10–100, and 100–300 mg/mL to assess the precision and accuracy of the method (Table 2). The accuracy of the method was expressed as the average absolute % difference from literature solubility values and the precision of the method was expressed as the average % relative standard deviation (% R.S.D.) for three determinations. In general, the precision and accuracy of the gravimetric method improved as the solubility values increased. The lowest solubility range (0–1 mg/mL) showed the highest average % R.S.D. (51.7%) and average % difference (66.3%). This is because the residual weights for these low solubilities approach the limit of detection of the microbalance. However, the average absolute difference was only 0.11 mg/mL for the lowest solubility range, which is accurate enough for early stage screening purposes. In the 1–10 mg/mL range, the average % R.S.D. and average % difference improved to 8.6% and 24.5%, respectively. Excellent precision and accuracy were achieved in the 10–100 and 100–300 mg/mL solubility ranges with average % R.S.D. <4% and average % difference <10% in these ranges.

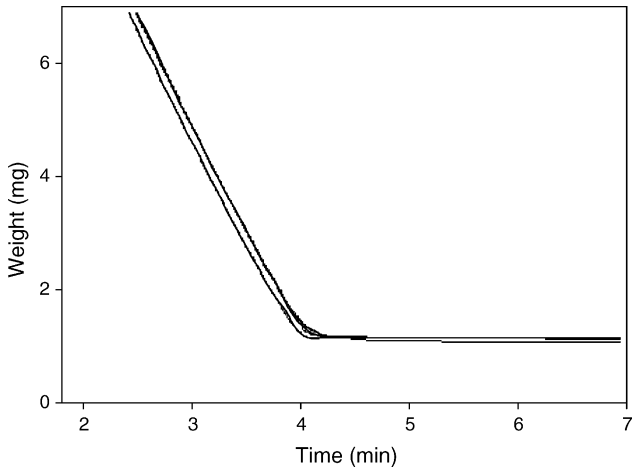

Fig. 1. TGA thermograms ($n = 3$) from the drying step of the solubility determination of paracetamol in 1-hexanol using 0.040-mL aliquot volumes. The samples were dried isothermally at 140 °C until a constant weight was achieved.

Table 1
Comparison of solubility values ($n = 3$) determined by TGA to literature values

Compound	Solvent	Solubility (mg/mL)		Difference (mg/mL)
		Experimental	Literature[a]	
Riboflavin	Methanol	0.11 ± 0.05	0.03	0.08
Riboflavin	Acetone	0.03 ± 0.02	0.04	−0.01
Thalidomide	1-Octanol	0.10 ± 0.04	0.07	0.03
Thalidomide	1-Heptanol	0.26 ± 0.08	0.09	0.17
Thalidomide	1-Hexanol	0.24 ± 0.24	0.12	0.12
Thalidomide	1-Pentanol	0.09 ± 0.08	0.16	−0.07
Thalidomide	1-Butanol	0.07 ± 0.07	0.19	−0.12
Thalidomide	1-Propanol	0.15 ± 0.14	0.26	−0.11
Meloxicam	1-Butanol	0.07 ± 0.04	0.29	−0.22
Paracetamol	Toluene	0.16 ± 0.05	0.29	−0.13
Meloxicam	Ethanol	0.21 ± 0.06	0.35	−0.14
Meloxicam	Methanol	0.31 ± 0.19	0.38	−0.07
Thalidomide	Ethanol	0.49 ± 0.16	0.40	0.09
Paracetamol	Dichloromethane	0.48 ± 0.03	0.42	0.06
4-Aminophenylacetic acid	2-Propanol	0.74 ± 0.03	0.47	0.27
4-Aminophenylacetic acid	Ethyl acetate	0.73 ± 0.01	1.08	−0.35
4-Aminophenylacetic acid	Ethanol	1.76 ± 0.11	1.10	0.66
Thalidomide	Methanol	1.18 ± 0.19	1.13	0.05
Paracetamol	Carbon tetrachloride	0.15 ± 0.07	1.42	−1.27
4-Aminophenylacetic acid	4-Methyl-2-pentanone	1.64 ± 0.07	1.76	−0.12
Nimesulide	1-Butanol	2.07 ± 0.12	2.12	−0.05
Paracetamol	Chloroform	0.59 ± 0.09	2.28	−1.69
Nimesulide	Ethanol	3.18 ± 0.08	3.32	−0.14
4-Aminophenylacetic acid	Methanol	3.95 ± 0.22	3.40	0.55
4-Aminophenylacetic acid	Acetone	5.85 ± 0.06	6.95	−1.10
Nimesulide	Methanol	8.58 ± 0.23	8.81	−0.23
Carbamazepine	2-Propanol	9.95 ± 0.72	9.23	0.72
Paracetamol	Ethyl acetate	9.84 ± 0.09	9.66	0.18
Carbamazepine	Ethyl acetate	10.7 ± 0.4	10.5	0.2
Paracetamol	4-Methyl-2-pentanone	14.0 ± 0.1	14.3	−0.3
Carbamazepine	Acetone	12.0 ± 0.3	17.1	−5.1
Carbamazepine	1-Propanol	18.3 ± 0.8	18.1	0.2
Carbamazepine	2-Butanone	27.6 ± 0.9	22.4	5.2
Carbamazepine	Ethanol	24.4 ± 0.3	25.4	−1.0
Paracetamol	Acetonitrile	22.4 ± 0.4	25.8	−3.4
Paracetamol	1-Heptanol	28.0 ± 0.6	30.8	−2.8
Carbamazepine	Acetonitrile	40.4 ± 1.3	38.3	2.1
Riboflavin	Dimethyl sulfoxide	39.6 ± 1.0	39.7	−0.1
Paracetamol	1-Hexanol	38.6 ± 0.9	40.5	−1.9
Paracetamol	1-Pentanol	50.8 ± 3.5	55.0	−4.2
Paracetamol	2-Butanone	54.6 ± 1.9	56.3	−1.7
Carbamazepine	Methanol	76.8 ± 1.2	75.9	0.9
Paracetamol	1-Butanol	73.6 ± 4.1	75.9	−2.3
Paracetamol	Acetic acid	83.7 ± 1.7	86.8	−3.1
Paracetamol	Acetone	81.1 ± 3.9	88.2	−7.1
Paracetamol	2-Propanol	110 ± 2	107	3
Paracetamol	1-Propanol	110 ± 5	107	3
Paracetamol	THF	133 ± 2	138	−5
Paracetamol	Ethylene glycol	141 ± 3	161	−20
Carbamazepine	Chloroform	169 ± 2	183	−14
Paracetamol	Ethanol	152 ± 13	184	−32
Carbamazepine	Dichloromethane	158 ± 9	204	−46
Paracetamol	Methanol	274 ± 3	294	−20

[a] References for literature solubilities are: paracetamol [5], riboflavin [6], (±)-thalidomide [7], carbamazepine [8], nimesulide, meloxicam [9], and 4-aminophenylacetic acid [10].

Table 2
Precision and accuracy of the TGA method as a function of solubility range

Solubility range (mg/mL)	*n*	Average absolute values			
		Difference (mg/mL)	Difference (%)	S.D. (mg/mL)	R.S.D. (%)
0–1	15	0.11	66.3	0.08	51.7
1–10	13	0.55	24.5	0.16	8.6
10–100	17	2.5	7.13	1.4	3.0
100–300	8	18	9.58	5	3.4

4. Conclusions

In this work, we have reported a method for rapid determination of drug solubility in organic solvents on a small scale using TGA. The precision and accuracy of the method were assessed by comparing 53 solubility values determined by TGA to literature values for seven model compounds. The method achieved optimal precision and accuracy when the solubility was >10 mg/mL, although solubility values <10 mg/mL were precise and accurate enough for early stage screening purposes. The results reported here indicate that the TGA method is most suitable for solubility screening of pharmaceutical compounds during early development.

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