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A SOLID SAMPLING DEVICE FOR USE IN BATCH SOLUTION CALORIMETRY

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ABSTRACT

A stainless steel ampul has been designed which greatly facilitates batch solution calorimetric analyses. The device has been validated by measurement of the enthalpy of solution of potassium chloride in water at 298.15 K. Ampul-to-ampul reproducibility of measurements has been demonstrated by determination of the enthalpy of solution of two polymorphic forms of chloramphenicol palmitate dissolving in 95% ethanol.

INTRODUCTION

Solution calorimetry is an important experimental tool in the investigation of many processes which involve enthalpy changes. Operating in the batch mode, isoperibol calorimeters have been used for the measurement of heat effects associated with complexation reactions [1,2], the measurement of enthalpies and heat capacities of transfer of solutes from one solvent to another [3,4], the calorimetric determination of the hydrogen bond enthalpy of some alcohols [5], the determination of the enthalpy of solvate formation [6], the determination of heats of immersion [7], the determination of degree of crystallinity [8], the evaluation of heats of solution of polymorphs [9–11], and the quantitation of binary mixtures of polymorphs and of solvated and non-solvated forms [11].

In batch solution calorimetry, mixing of two reactants is accomplished by breaking a bulb and allowing the reactants to mix, by displacing a seal separating the two reactants in the calorimeter reaction vessel, or by rotating the reaction vessel and allowing the reactants to mix [12]. Although batch solution calorimetry simplifies data analysis, there are design problems in arranging for the mixing of reactants. The glass ampuls currently used in conjunction with ampul crushing devices suffer from a number of shortcomings. They are typically spherical glass bulbs which are filled through narrow

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glass stems. The bulbs are fragile, and it is difficult to completely transfer powdered sample into them without having some sample adhere to the stem. Larger crystals must be crushed prior to insertion into the ampul, and it has been observed that some samples undergo polymorphic transformation on grinding. The stems must be removed by flame sealing the ampul, which can cause problems with samples which are heat sensitive, e.g. compounds which are susceptible to polymorphic transformation, or to loss of solvent of crystallization. Furthermore, when the ampuls are crushed to liberate their contents, curved shards of glass are sometimes produced which entrap air and solid sample, preventing complete dissolution of the sample. These shards can also alter the stirring characteristics of the system.

The challenge of designing a capsule which is simple to construct, easy to use, has a negligible heat of opening, and does not appreciably change the stirring power has caused practitioners of calorimetry to seek alternative techniques for mixing the reactant components [12]. However, the devices which have been proposed are often complicated and costly to produce.

We have developed a reusable stainless steel ampul which can be employed with isoperibol calorimeters, including the Tronac Model 450 isoperi-

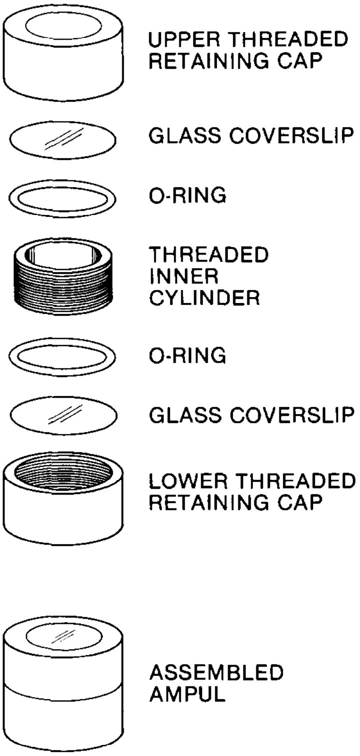

Fig. 1. Components of a stainless steel ampul for batch solution calorimetry.

bol calorimeter and its automatic batch ampul adapter. The ampul (Fig. 1) consists of three parts fabricated from Type 316 stainless steel: the upper and lower threaded retaining caps (14 mm diameter × 6 mm height) and a threaded inner cylinder (12 mm diameter × 7 mm height). The retaining caps have an aperture 11 mm in diameter. It is through these apertures that the spring loaded plunger of the ampul crushing device passes.

To seal the ampul, a microscope cover slip (12 mm diameter) is fitted into each of the retaining caps, and is held in place by an O-ring (12 mm). Rings are fabricated from a variety of materials which can be selected to be resistant to the solvent employed. In these experiments the O-rings (Kontes 758292) used were composed of an ethylene–propylene elastomer. Samples can be weighed directly into the tared cup formed from the lower threaded retaining cap, glass cover slip, O-ring and threaded inner cylinder. Then the upper threaded retaining cap (with coverslip and O-ring) is screwed into position. The ampul is placed in the automatic batch ampul adapter, and when the device is activated, the plunger passes through the upper and lower glass coverslips, liberating the contents of the ampul to solvent. The glass shards which are produced are flat, and there is little change in the stirring power.

To evaluate the performance of the ampuls, three experiments were devised: (1) estimation of the "enthalpy of ampul breaking" in water; (2) determination of the enthalpy of solution of a reference compound, potassium chloride in water; and (3) evaluation of the reproducibility from one ampul to the next of the results obtained from two ampuls constructed according to the same specifications, by determination of the enthalpy of solution of chloramphenicol palmitate in 95% ethanol.

EXPERIMENTAL

Enthalpy of ampul breaking in water

To obtain a precise measure of the enthalpy of solution of a compound, it is necessary to correct for the extraneous heat effects which accompany ampul breaking. Samples of NBS Reference Standard potassium chloride (SRM 1655) previously dried for 4 h at 800 K, and weighing between 13.69 and 26.77 mg (Sartorius Model 1712 MP balance) were used for this determination. Sample weights were corrected to vacuum by use of a buoyancy factor, 1.000455 [13]. The calorimeter used for all measurements was the Tronac Model 450 isoperibol calorimeter.

The steel ampul containing the sample was sealed and placed in the ampul crushing/stirring device. A Dewar flask containing 50.00 g of glass-distilled water served as the reaction vessel. The bath temperature was 25.000 °C, checked against an NBS certified thermometer. The temperature of the bath was monitored throughout the runs by use of a Hart Microtherm Model 1006 digital thermometer, and was found to remain constant at a nominal reading of 25.0000 ± 0.0004 °C. The stirrer was operated at 900 rpm. An operational heat capacity calibration, to determine the energy equivalent of the system, was performed when the reaction vessel temperature reached a predetermined value near the set point of 25 °C. After preliminary baseline collection, the sample run was initiated, and following total dissolution of the sample and resumption of the baseline, a final heat capacity calibration was performed. The average value of the heat capacity before and after ampul breaking was employed in the calculation of the heat effect associated with dissolution of the sample. The calorimeter was interfaced with an Apple II+ computer through an ADALAB analog–digital converter and accompanying signal amplifier. Details of the method of data collection and analysis have been reported elsewhere [11,14].

Enthalpy of solution of potassium chloride in water

Performance of the Tronac Model 450 isoperibol calorimeter and the software for acquisition and reduction of the results was tested at 298.15 K by determination of the enthalpy of solution of NBS certified potassium chloride (SRM 1655). Samples of the Standard Reference Material, calculated to yield a solution with molality $m = 0.111$ mol kg^{-1}, previously dried for 4 h at 800 K, were weighed on a Sartorius Model 1712 MP balance. Experimental procedures were as described in the previous section.

Demonstration of ampul-to-ampul reproducibility

For convenience in experimental work, it was important to demonstrate that the ampuls could be fabricated reproducibly, and that there was essentially no difference in results obtained from one ampul to the next. The enthalpy of solution for the dissolution of chloramphenicol palmitate polymorphs in ethanol (45.00 g) was evaluated for samples of mass ranging from 3.655 to 30.95 mg. Two ampuls were used for these determinations, and a record was kept of which ampul was used for each determination. Form A chloramphenicol palmitate and authentic U.S.P. Reference Standard samples of Form A and Form B chloramphenicol palmitate were generously provided by Warner-Lambert Pharmaceutical Company. Additional Form B was prepared by a previously reported method [15]. A Cahn Model 2100 electrobalance was employed for the weighings. Calorimetric analyses were performed as described for the potassium chloride experiments.

Identification of the polymorphic forms was performed by use of Fourier transform infrared spectrophotometry (FTIR), differential scanning calorimetry (DSC), and powder diffraction analysis. FTIR spectra were obtained as

Nujol mulls between sodium chloride plates using 0.025 mm lead spacers. The instrument used for these analyses was a Nicolet Model 5DXB, operating at 2 cm^{-1} resolution. DSC thermograms were obtained on the Perkin–Elmer DSC-2 instrument interfaced with a Model 3600 Thermal Analysis Data Station. Analyses were performed under nitrogen purge at 1.25 deg min^{-1} on samples contained in crimped aluminum pans. The temperature and energy axes were calibrated using ultrapure (Alfa M6N) indium. Powder patterns were obtained using a Philips APD Model 3500 automated diffractometer, with monochromatized Cu K_α ($A = 1.5418$ Å) radiation. The diffractometer is equipped with a 2θ compensating slit and a graphite monochromator. It was calibrated to within 2° (2θ) using the quartz peak at 26.66°. Patterns were scanned from 2 to 62° (2θ) at a scanning speed of 2.4° (2θ) min^{-1}. The minimum peak/background ratio was 2.5; the count mode fixed time was 0.5.

RESULTS AND DISCUSSION

Enthalpy of ampul breaking in water

When the ampul used in solution calorimetric measurements is broken, there is a small but reproducible heat effect which arises from the mechanical energy associated with breaking of the two glass coverslips, the enthalpy of wetting of the inside surface of the ampul and of the O-rings, and the change in the level of solvent in the reaction vessel as liquid displaces air in the ampul. Since this effect is small, it can best be approximated by performing a series of determinations on small samples of solute, with subsequent extrapolation of the plot of heat absorbed or evolved vs. sample mass. The intercept of such a plot represents the apparent "enthalpy of ampul breaking". In the case of the potassium chloride samples dissolving in

TABLE 1

Data used to determine enthalpy of ampul breaking. Enthalpy of solution, KCl in water at 273.15 K

Sample mass (mg)	Enthalpy (J)
13.70	3.1695
14.56	3.3703
17.12	3.9674
19.42	4.4990
21.45	4.9929
23.29	5.4274
26.78	6.2295

distilled water, the apparent "enthalpy of ampul breaking" was obtained from the intercept of the linear plot of the data shown in Table 1.

Linear regression ($r^2 = 0.99998$) of these data yields a slope of 234.56 ± 0.68 J g^{-1} ($n = 7$), which corresponds to 17,487 ± 51 J mol^{-1}. This provides an estimate of the enthalpy of solution of KCl at infinite dilution ($m \simeq 3.67$ to 7.18×10^{-3} mol kg^{-1}). The value reported by Sanahuja and Cesari [16] for ΔH, 17,206 ± 92 J mol^{-1}, was obtained by extrapolation from higher concentrations ($m = 6 \times 10^{-2}$ mol kg^{-1}). The intercept of the plot, −0.046 ± 0.014 J, represents the apparent "enthalpy of ampul breaking" in water. Thus, the heat effect of ampul breaking is small and slightly exothermic.

Enthalpy of solution of potassium chloride in water

Data obtained in five analyses are shown in Table 2. The mean enthalpy of solution obtained for KCl in water at 298.15 K ($m = 0.111$ mol kg^{-1}) was 235.23 ± 0.71 J g^{-1} ($n = 5$). This result is within 0.25% of the value reported in the National Bureau of Standards Certificate [13], 235.86 ± 0.23 J g^{-1}.

Enthalpy of solution of chloramphenicol palmitate in 95% ethanol

Chloramphenicol palmitate is an antibiotic whose polymorphic forms exhibit significantly different bioavailabilities. Because of this, the United States Pharmacopeia [17] requires that the suspension dosage form contain not more than 10% of polymorph A. Infrared spectroscopic data for Forms A and B used in this study are comparable to those obtained by Kaneniwa and Otsuka [18]. These data are shown in Table 3, as are results of DSC analyses performed on six samples of chloramphenicol palmitate Form A and Form B. These results are in good agreement with data reported by Borka [19] and by Kaneniwa and Otsuka [18].

Qualitatively, the powder patterns obtained correspond to those previously reported by Aguiar et al. [20], by Suzuki et al. [21], and by Kaliszan [22]. The lattice spacings (d, Å) and relative intensities (% I/I_1) of the three

TABLE 2

Enthalpy of solution, KCl, 0.111 mol kg^{-1} in water at 273.15 K

Sample mass (g)	Heat effect (J)	Corrected heat (J)	Enthalpy of solution (J g^{-1})
0.41395	97.300	97.346	235.16
0.41394	97.830	97.875	236.45
0.41392	97.056	97.102	236.59
0.41397	97.355	97.401	235.38
0.41398	97.191	97.237	234.88

TABLE 3

Infrared and DSC data, chloramphenicol palmitate polymorph A and B

Infrared data		Data of Kaneniwa and Otsuka [18]	This work
Form A	Amide NH stretch	3410 cm^{-1}	3407 cm^{-1}
	OH stretch	3270	3263
	Ester C=O stretch	1737	1741
	Amido C=O stretch	1668	1671
		1628 sh	1634 sh
	NO_2 asymmetric stretch	1603	1606
		1594	1597
Form B	Amide NH stretch	3325	3316
	OH stretch	3490	3479
	Ester C=O stretch	1727	1734
	Amido C=O stretch	1700	1705
		1675	1680
	NO_2 asymmetric stretch	1605	1608
		1594	1601

DSC data		Data of Borka [19]	Data of Kaneniwa and Otsuka [18] [a]	This work [b]
Form A	Peak onset (K)		363.5	364.38 ± 0.17
	Peak maximum (K)			366.32 ± 0.19
	Heat of fusion (kJ mol^{-1})	64.0	65.7 ± 2.2	64.27 ± 0.53
Form B	Peak onset (K)		359.9	361.25 ± 0.04
	Peak maximum (K)			362.10 ± 0.06
	Heat of fusion (kJ mol^{-1})	43.5	46.36 ± 0.88	45.53 ± 0.13

[a] $n = 3$; [b] $n = 6$.

most intense lines in the powder patterns of Form A were 26.35, 100; 8.77, 37; and 4.38, 20. For Form B, the corresponding values were 4.49, 100; 3.98, 98; and 3.92, 68.

The enthalpy of solution of chloramphenicol palmitate Form A, determined in 95% ethanol at 298.15 K ($m = 1.45$ to 12.2×10^{-4} mol kg^{-1}) was 63.24 ± 0.32 kJ mol^{-1} ($n = 16$), and for Form B, the value was 55.69 ± 0.35 kJ mol^{-1} ($n = 16$). These values were obtained from the slopes of plots of heat absorbed vs. sample mass shown in Fig. 2. Correlation coefficients for these plots were 0.9996 (Form A) and 0.9994 (Form B). The upper plot (broken line, open symbols) was obtained using Form A. The lower plot (continuous line, closed symbols) was obtained using Form B.

The intercepts of the plot correspond to the apparent "enthalpy of ampul breaking" in ethanol. Data for the enthalpy of ampul breaking for the individual ampuls, and the combined data are collected in Table 4.

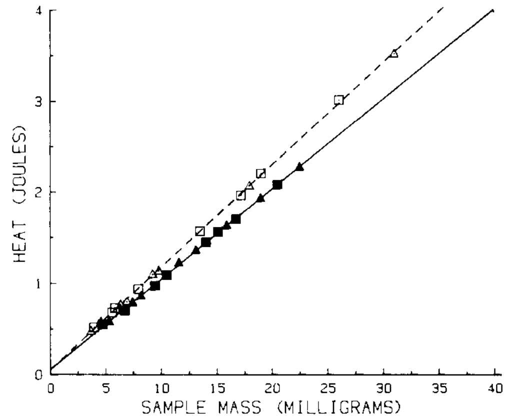

Fig. 2. Data obtained from 2 ampuls (ampul No. 1, squares; No. 2, triangles). Data for enthalphy of solution of chloramphenicol palmitate polymorph A [63.24 ± 0.32 kJ mol^{-1} (broken line, open symbols)] and polymorph B [55.69 ± 0.35 kJ mol^{-1} (continuous line, closed symbols)].

The data for chloramphenicol palmitate were also used to evaluate the reproducibility of the results obtained with different ampuls. This evaluation was accomplished using multiple regression techniques [23,24] in conjunction with Student's t-distribution. When the same polymorph (either A or B) was analyzed, and the ampul was varied, two-sided hypothesis tests at the 95% confidence level indicated that both the slopes and intercepts of each pair of regression lines were statistically indistinguishable. In three out of four comparisons the null hypothesis of no difference could not be disproved at the 50% confidence level (the lowest tabled value listed), while in the remaining comparison it could not be disproved at the 80% confidence level. On this basis, the results from both ampuls were combined for each polymorph, and the resulting regression lines for the two polymorphs were compared. The two slopes were statistically different at the 99.9% confidence level, while the two intercepts were statistically indistinguishable even at the 50% confidence level.

The y-intercepts of all regression lines were found to be statistically different from zero at confidence levels of 99% or greater. The enthalpy of

TABLE 4

Enthalpy of ampul breaking, chloramphenicol palmitate in 95% ethanol at 298.15 K

	Form A	Form B
Ampul No. 1	0.0521 ± 0.013 J ($n = 8$)	0.0528 ± 0.014 J ($n = 8$)
Ampul No. 2	0.0540 ± 0.009 J ($n = 8$)	0.0561 ± 0.009 J ($n = 8$)
Both ampuls	0.0538 ± 0.008 J ($n = 16$)	0.0546 ± 0.009 J ($n = 16$)

ampul breaking in ethanol, as determined from these *y*-intercepts, is positive but small in comparison to the enthalpy of solution of chloramphenicol palmitate.

A number of evaluations of the heat of solution of chloramphenicol palmitate have appeared in the literature. In these published reports the enthalpy of solution has been estimated from van't Hoff plots, plots of the logarithm of solubility or the logarithm of dissolution rate vs. the reciprocal of the temperature. The assumption is made that such plots are linear; however it is found in many instances that there is pronounced curvature in van't Hoff plots. This is particularly true if solubility studies are performed over a wide temperature range. Aguiar and Zelmer [25] estimated the enthalpy of solution of Form A (in 35% t-butanol–water mixtures) to be 21.8 kcal mol^{-1}, and that of Form B, to be 15.4 kcal mol^{-1}. From solubility measurements in water, Muramatsu et al. [15] obtained estimates of the enthalpy of solution for Forms A and B of 20.0 and 13.7 kcal mol^{-1}, respectively. From dissolution rate determinations at several temperatures, performed in 80% aqueous ethanol, Wadke and Reier [26] estimated the difference in heats of solution between the two forms to be approximately 5.31 kcal mol^{-1}.

The difference in the enthalpies of solution of the two forms obtained in this study was smaller. Apart from the dangers associated with the assumption of linearity in van't Hoff plots, it is possible that other factors might contribute to the smaller difference in enthalpies observed in solution calorimetric determinations. It is known that there are differences in the surface characteristics of polymorphs A and B of chloramphenicol palmitate. For example, there is evidence that crystalline particles of polymorph A exhibit higher zeta-potential values when compared with polymorph B [22]. Such differences in surface properties might be reflected in differences in the enthalpy of wetting. Enthalpy of wetting differences would not be expected to influence the enthalpy of solution determined by the van't Hoff method.

REFERENCES

1 T.F. Bolles and R.L. Drago, J. Am. Chem. Soc., 87 (1965) 5015.
2 P. Rohdewald, G. Elmahrouk and G. Wesselmann, Thermochim. Acta, 49 (1981) 101.
3 R.V. Jasra and J.C. Ahluwalia, J. Chem. Soc. Faraday Trans. 1, 79 (1983) 1303.
4 M. Goffredi and V.T. Liveri, J. Solution Chem., 10 (1981) 693.
5 A. Kolbe, C. Zimmermann and R. Wilke, Adv. Mol. Relax. Interact. Processes, 19 (1981) 107.
6 R.W. Carling, A.T. Wondolowski and D.C. Macmillan, J. Chem. Thermodyn., 14 (1982) 125.
7 M. Hattori and T. Tamamoto, Thermochim. Acta, 63 (1983) 51.
8 M.J. Pikal, A.L. Lukes, J.E. Lang and K. Gaines, J. Pharm. Sci., 67 (1978) 767.
9 W. Beckman, Thermochim. Acta, 66 (1983) 295.
10 S. Lindenbaum and S.E. McGraw, Pharm. Manuf., 2 (1) (1985) 26.

11 J.K. Guillory and D.M. Erb, Pharm. Manuf., 2 (9) (1985) 28.
12 L.D. Hansen, E.A. Lewis and D.J. Eatough, in J.K. Grime (Ed.), Analytical Solution Calorimetry, Wiley, New York, 1985, p. 57.
13 G.A. Uriano, N.B.S. Certificate for Standard Reference Material 1655, National Bureau of Standards (1981).
14 D.M. Erb, Ph. D. Dissertation, The University of Iowa, Iowa City, December, 1984.
15 M. Muramatsu, M. Iwahashi and K. Masumoto, J. Chem. Eng. Data, 20 (1975) 6.
16 A. Sanahuja and E. Cesari, J. Chem. Thermodyn., 94 (1984) 1195.
17 The United States Pharmacopeial Convention, The United States Pharmacopeia, Mack, Easton, PA, 1985, p. 192.
18 N. Kaneniwa and M. Otsuka, Chem. Pharm. Bull., 33 (1985) 1660.
19 L. Borka, Acta Pharm. Suec., 7 (1970) 1.
20 A.J. Aguiar, J. Krc, Jr., A.W. Kinkel and J.C. Samyn, J. Pharm. Sci., 56 (1967) 847.
21 E. Suzuki, K. Chihara and K. Sekiguchi, Chem. Pharm. Bull. Jpn., 31 (1983) 632.
22 R. Kaliszan, J. Pharm. Sci., 75 (1986) 187.
23 J. Neter, W. Wasserman and M.H. Kutner, Applied Linear Statistical Models, 2nd edn., R.D. Irwin, Inc., Homewood, IL, 1985, p. 328.
24 Minitab, Release 82.1, Statistics Dept., Pennsylvania State Univ., State College, PA, 1985.
25 A.J. Aguiar and J.E. Zelmer, J. Pharm. Sci., 58 (1969) 983.
26 D.A. Wadke and G.E. Reier, J. Pharm. Sci., 61 (1972) 868.