

Modified Computer Programs for Determining Eutectic Temperatures

Sir:

In a recent publication (1), the errors associated with both an expression for calculating eutectic temperatures and the computer program for solving this expression were elucidated. The general form of the equation which was derived from freezing point depression and solubility curves (2) was as follows:

$$\log \left(\frac{1}{T_e} - \frac{1}{T_0} \right) = - \frac{L_f'}{2.303R} \left(\frac{1}{T_e} - \frac{1}{T_0'} \right) - \log \frac{L_f}{R} \quad (\text{Eq. 1})$$

where L_f and L_f' = the heat of fusion of the solvent and differential heat of solution, respectively; T_0 and T_0' = melting point of the solvent and of the solid, respectively; and T_e = the eutectic temperature.

Because of an approximation introduced in the freezing point equation during the derivation of the eutectic expression in which $-x$ was substituted for $\ln(1-x)$, deviation occurs for highly soluble salts where the mole fraction, x , exceeds a value of 0.1. However, a new program has been written in which the approximation has been eliminated in accordance with the following expression:

$$1 = \exp \left[- \frac{L_f'}{R} \left(\frac{1}{T_e} - \frac{1}{T_0'} \right) \right] + \exp \left[- \frac{L_f}{R} \left(\frac{1}{T_e} - \frac{1}{T_0} \right) \right] \quad (\text{Eq. 2})$$

To simplify the expression, the following definitions are introduced:

$$A = L_f/R \qquad A' = L_f'/R$$

$$B = L_f/RT_0 = A/T_0 \qquad B' = L_f'/RT_0' = A'/T_0'$$

Then

$$1 = \exp [-A'/T_e + B'] + \exp [-A/T_e + B] \quad (\text{Eq. 3})$$

TABLE I.^a—EUTECTIC TEMPERATURE

| Diff. Heat of Soln., cal. | M.p. °C. (T_0') | | | | | | | | |
|---------------------------|---------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| | 20 | 40 | 60 | 100 | 140 | 180 | 220 | 260 | 300 |
| 100 | 116.59 | 115.00 | 113.62 | 111.35 | 109.57 | 108.13 | 106.95 | 105.95 | 105.10 |
| 300 | 90.65 | 88.05 | 85.80 | 82.14 | 79.27 | 76.97 | 75.09 | 73.52 | 72.19 |
| 500 | 77.69 | 74.46 | 71.68 | 67.17 | 63.68 | 60.90 | 58.65 | 56.78 | 55.21 |
| 700 | 69.05 | 65.35 | 62.18 | 57.08 | 53.17 | 50.09 | 47.61 | 45.58 | 43.88 |
| 900 | 62.63 | 58.55 | 55.09 | 49.55 | 45.34 | 42.07 | 39.46 | 37.33 | 35.37 |
| 1100 | 57.55 | 53.17 | 49.47 | 43.59 | 39.18 | 35.79 | 33.11 | 30.95 | 29.18 |
| 1300 | 53.38 | 48.75 | 44.85 | 38.71 | 34.17 | 30.71 | 28.01 | 25.86 | 24.12 |
| 1500 | 49.87 | 45.02 | 40.95 | 34.62 | 29.99 | 26.51 | 23.83 | 21.72 | 20.02 |
| 1700 | 46.85 | 41.81 | 37.61 | 31.12 | 26.45 | 22.98 | 20.35 | 18.30 | 16.68 |
| 1900 | 44.21 | 39.00 | 34.69 | 28.09 | 23.41 | 19.99 | 17.43 | 15.46 | 13.91 |
| 2100 | 41.88 | 36.53 | 32.11 | 25.44 | 20.77 | 17.42 | 14.95 | 13.07 | 11.62 |
| 2300 | 39.79 | 34.31 | 29.82 | 23.10 | 18.47 | 15.21 | 12.83 | 11.06 | 9.71 |
| 2500 | 37.91 | 32.32 | 27.76 | 21.02 | 16.46 | 13.29 | 11.03 | 9.36 | 8.11 |
| 2700 | 36.21 | 30.51 | 25.90 | 19.15 | 14.67 | 11.62 | 9.48 | 7.93 | 6.77 |
| 2900 | 34.65 | 28.86 | 24.21 | 17.48 | 13.10 | 10.16 | 8.14 | 6.71 | 5.65 |
| 3100 | 33.22 | 27.35 | 22.66 | 15.97 | 11.69 | 8.89 | 7.00 | 5.67 | 4.71 |
| 3300 | 31.90 | 25.95 | 21.24 | 14.60 | 10.44 | 7.78 | 6.01 | 4.79 | 3.93 |
| 3500 | 30.67 | 24.67 | 19.94 | 13.36 | 9.33 | 6.80 | 5.16 | 4.05 | 3.27 |
| 3700 | 29.54 | 23.47 | 18.73 | 12.23 | 8.34 | 5.94 | 4.42 | 3.41 | 2.72 |
| 3900 | 28.47 | 22.36 | 17.62 | 11.20 | 7.45 | 5.19 | 3.79 | 2.88 | 2.26 |
| 4100 | 27.48 | 21.32 | 16.58 | 10.26 | 6.65 | 4.54 | 3.25 | 2.43 | 1.88 |
| 4300 | 26.55 | 20.35 | 15.62 | 9.40 | 5.94 | 3.96 | 2.78 | 2.04 | 1.56 |
| 4500 | 25.67 | 19.43 | 14.71 | 8.62 | 5.30 | 3.45 | 2.38 | 1.72 | 1.29 |
| 4700 | 24.84 | 18.58 | 13.87 | 7.89 | 4.73 | 3.01 | 2.03 | 1.44 | 1.07 |
| 4900 | 24.06 | 17.77 | 13.09 | 7.23 | 4.22 | 2.62 | 1.74 | 1.21 | 0.89 |
| 5100 | 23.32 | 17.00 | 12.35 | 6.63 | 3.76 | 2.28 | 1.48 | 1.02 | 0.73 |
| 5300 | 22.61 | 16.28 | 11.66 | 6.07 | 3.35 | 1.99 | 1.26 | 0.85 | 0.61 |
| 5500 | 21.94 | 15.60 | 11.01 | 5.56 | 2.98 | 1.73 | 1.08 | 0.72 | 0.50 |
| 5700 | 21.31 | 14.95 | 10.39 | 5.09 | 2.65 | 1.50 | 0.92 | 0.60 | 0.42 |
| 5900 | 20.70 | 14.34 | 9.82 | 4.66 | 2.36 | 1.30 | 0.78 | 0.50 | 0.34 |

^a Eutectic values are negative.

TABLE II.—EUTECTIC TEMPERATURE FOR SOME PHARMACEUTICALS AND INORGANIC ELECTROLYTES

| Compd. | Exptl. | Eutectic Temp., °C. | | Lit. Value |
|--------------------|-----------|------------------------|--------------------------|------------|
| | | Calcd. (no approx.) | Calcd. (with approx.) | |
| Methylphenidate | | | | |
| hydrochloride | -11.7 | -11.91 | -11.39 | ... |
| methanesulfonate | -10.1 | -9.07 | -8.77 | ... |
| phosphate | -4.29 | -3.97 | -3.92 | ... |
| Phentolamine | | | | |
| hydrochloride | -1.3 | -2.35 | -2.34 | ... |
| methanesulfonate | -11.0 | -8.54 | -8.28 | ... |
| phosphate | -0.75 | -0.88 | -0.88 | ... |
| Sodium chloride | -21.6 | -26.74 | -24.01 | -21.6 |
| Sodium bromide | -27.7 | -33.88 | -29.76 | -28.0 |
| Sodium iodide | -29.9 | -37.89 | -33.09 | -31.5 |
| Potassium chloride | -11.1 | -12.66 | -12.03 | -10.7 |
| Potassium bromide | -12.9 | -13.26 | -12.72 | -12.6 |
| Potassium iodide | -22.8 | -30.07 | -26.67 | -23.0 |
| Lithium chloride | below -40 | -23.70 | -21.57 | ... |
| Cesium chloride | -24.1 | -27.89 | -24.98 | ... |

An initial trial value of T_e equal to 273.1°K. is taken resulting in a value, Y , for the right hand side of Eq. 3, and Y' is calculated from $T_e' = T_e + \Delta T$, where $\Delta T = 0.01 T_e$.

Then

$$\frac{\Delta Y}{\Delta T} = \frac{Y' - Y}{T_e' - T_e} \quad (\text{Eq. 4})$$

The error in Y is $1 - Y$, which can be corrected by incrementing T_e by an amount ϕ , where

$$\frac{\Delta Y}{\Delta T} = \frac{1 - Y}{\phi} \quad \text{or} \quad \phi = (1 - Y) \frac{\Delta T}{\Delta Y} \quad (\text{Eq. 5})$$

The next trial value will be $T_e + \phi$ and this procedure is repeated until the error in Y is arbitrarily small. In this procedure, the correction ϕ to be applied to the trial value of the eutectic can be calculated immediately, not requiring two previous iterations as in the former program. The procedure converges rapidly, usually after three iterations. Furthermore, since the correction does not depend on division by previous improvements, no difficulty is encountered when these values approach zero, as occurred, for example, in the former program for large values of Lf' and T_0' .

A program was written in Fortran II, and an IBM 1401 (8K) computer was used to print a revised table of eutectic temperatures in a condensed form to include values of Lf' from 100-5900 cal. in increments of 200 cal., and melting points T_0' from 20-60° in increments of 20° and from 60-300° in increments of 40° (Table I). The maximum error involved in interpolating values from the condensed table is 0.5°.

Independently, a somewhat different program for solving Eq. 2 was written in Manchester Autocode, and an ICT 1301 computer was used to obtain a similar table of eutectic temperatures as a function of Lf' and T_0' . The results of the two methods agree within 0.01°.

Since most pharmaceuticals do not exceed a 0.1 mole fraction concentration in water, the difference in the values obtained using Eq. 2 as compared to those using the approximation given by Eq. 1 is not of practical significance as shown in Table II. The major discrepancies as would be expected occur for highly soluble salts above 0.1 mole fraction in water.

Some previously published values (2, 3) have been recalculated with the new programs and they are listed in Table II.

The deviation which occurs in calculated and experimental values was discussed in the previous papers and is presently undergoing investigation.

(1) DeLuca, P., Lachman, L., and Yost, W., *J. Pharm. Sci.*, **54**, 1348(1965).

(2) DeLuca, P., and Lachman, L., *ibid.*, **54**, 617(1965).

(3) *Ibid.*, **54**, 1411(1965).

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Received January 17, 1966.

Accepted for publication January 28, 1966.