

Lyophilization of Pharmaceuticals III

Programming of a Mathematical Expression for Estimating Eutectic Temperatures from Melting Point and Solubility Parameters

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Manipulation of the Clapeyron-Clausius equation for solubility and freezing point depression resulted in a mathematical expression for the calculation of eutectic temperatures. Using this expression, the numerical estimation of the eutectic temperature in the implicit function was programmed in Fortran II on an IBM 1401 (8K) computer. Since the eutectic temperature is a function of the differential heat of solution, Lf' , and melting point of a material, the program was written in a more general form to include values of Lf' from 100 to 6000 cal. and melting points from 10 to 300°. With this program, tables of eutectic temperatures in this region were printed.

DURING an investigation to determine the effect of certain physical-chemical properties, such as eutectic temperature and solubility, on the lyophilization of pharmaceuticals, a mathematical expression for the numerical estimation of eutectic temperature was developed. This mathematical expression utilizes the common physical-chemical parameters of melting point and differential heat of solution. It was felt that such a relationship would be extremely useful to the research pharmacist who does not have at his disposal the sensitive conductivity equipment necessary to obtain accurate measurements of eutectic points. Through a simple computer program of this mathematical expression, an accurate determination of eutectic temperatures for inorganic and organic compounds can be rapidly obtained. In fact, tables of eutectic values for a series of hypothetical compounds of varying melting points and differential heats of solution can be constructed. With this information available, it would only be necessary to have a knowledge of the melting point and differential heat of solution of the pharmaceutical compound intended for lyophilization in order to obtain an estimate of the eutectic temperature of the compound.

The objectives of this paper are to describe the programming of the mathematical expression for the estimation of the eutectic temperature and to discuss the errors associated with this expression and program.

THEORETICAL

The eutectic for a simple two-component system of a salt in water occurs at the point of intersection, c , of the freezing point depression curve of water and the solubility curve of the salt, as shown in

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Fig. 1. Using the general form of the Clapeyron-Clausius equation to express both the depression of the freezing point and the solubility of the pure solid, an expression for eutectic temperature or concentration can be derived. The general form of the equation for eutectic temperature which was developed in a previous publication (1) is as follows:

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

where

- Lf = heat of fusion of the solvent
- R = gas constant
- T_e = eutectic temperature
- Lf' = differential heat of solution
- T_0' = melting point of the pure solid
- T_0 = melting point of the solvent

By substituting 1436 cal./mole for Lf , 273.1°K for T_0 , and 1.9864 cal./degree/mole for R , the equation for water as the solvent becomes

$$\log \left(\frac{1}{T_e} - .0036616 \right) = - \frac{Lf'}{4.576} \left(\frac{1}{T_e} - \frac{1}{T_0'} \right) - 2.859 \quad (\text{Eq. 2})$$

The Lf' value is determined from solubility measurements as a function of temperature using the expression for solubility.

$$\ln x = - \frac{Lf'}{R} \left(\frac{1}{T} - \frac{1}{T_0} \right) \quad (\text{Eq. 3})$$

where $\log x$ is plotted against $1/T$ as shown in Fig. 2. The Lf' is then calculated from the slope of the line.

PROGRAMMING

Since Eq. 2 cannot be solved analytically for the eutectic temperature, it was necessary to develop a numerical estimate of its value by an iterative technique. The procedure described below was programmed for the 1401 (8K) computer in Fortran II. Experimental values of Lf , Lf' , T_0 , and T_0' are read in, and trial values of E and the final value of the eutectic temperature are printed in degrees K and C.

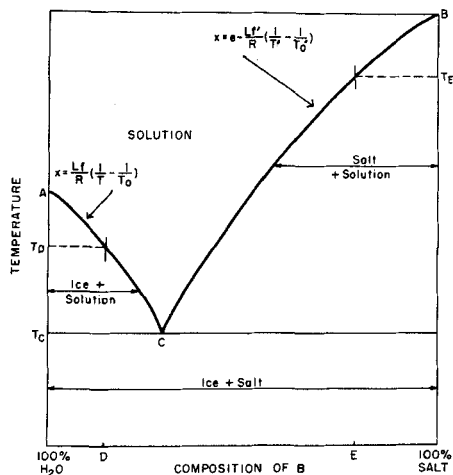


Fig. 1.—Phase diagram for a salt in water.

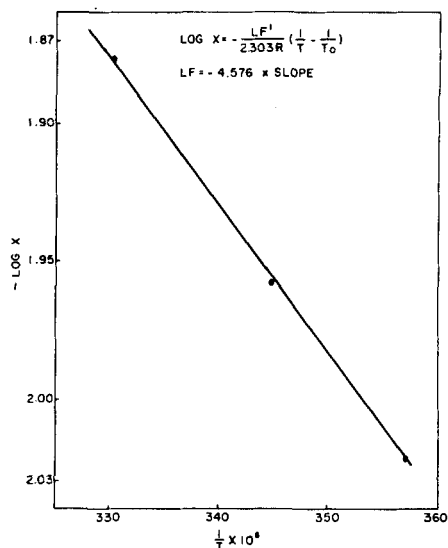


Fig. 2.—Solubility curve for methylphenidate hydrochloride as a function of temperature.

For computational convenience, the following definitions were made:

$$\begin{aligned} A &= \ln(L_f'/R) \\ B &= -(L_f'/R) \\ C &= B/(T_0 + 273.1) + A \\ D &= 1/(T_0 + 273.1) \\ E &= 1/(T_e + 273.1) \end{aligned}$$

Substitution of these definitions into Eq. 2 reduces it to the simplest form:

$$\ln(E - D) = BE - C \quad (\text{Eq. 4})$$

Since B , C , and D are constant for a given problem, what is sought is a value of E which will give the same numerical value to both sides of Eq. 4. Since the eutectic temperature will necessarily be lower than the freezing point of the solvent, its reciprocal, E , will necessarily be larger than D . An arbitrary initial value of E is chosen 1% above D , and the values of the two sides of Eq. 4 are computed separately. The difference (left side—

right side) is Δ . After two iterations, previous values are available for calculating a nonarbitrary correction to be applied to E :

$$E_n = E_{n-1} + \frac{E_{n-1} - E_{n-2}}{P - 1}$$

where

$$P = \Delta_{n-2}/\Delta_{n-1}$$

This approach usually gave convergence to a value of $\Delta = 5.0 \times 10^{-6}$ after six or seven iterations.

In a previous publication, the utility of this expression was shown for several organic compounds, and a subsequent paper of this series will demonstrate the application of this expression to inorganic salts.

The computer program was rewritten in a more general form to assume values of L_f' from 100 to 6000 cal. in increments of 100 cal., and of T_0' from 10° to 300° in increments of 10°, and to print tables of the eutectic temperatures in this region. After the first entry, the previous value of E was used as the initial value for the next entry, thereby greatly accelerating the calculations. The printed sheets of the eutectic temperatures obtained from this program are reproduced in Tables I-VI. This information should be of considerable assistance to the research pharmacist in the development of sound lyophilization cycles in the absence of highly sensitive conductivity equipment. For example, as can be seen from the data in Table III, if a compound had a melting point of 130° and a differential heat of solution of 2.5 Kcal., it will have an eutectic temperature in the neighborhood of -16.4°.

DISCUSSION OF ERRORS

Equation 2 cannot be used for an accurate prediction of eutectic temperature if the logarithm of the mole fraction (x) plotted against the reciprocal of the absolute temperature ($1/T$) is not linear. Deviation from linearity indicates that the L_f' value is not constant, but a function of the temperature.

Because of the approximation introduced in the development of the Eq. 1, in which $-x$ was substituted for $\ln(1-x)$ in the freezing point equation, deviation will occur for highly soluble salts where the mole fraction exceeds a value of 0.1. For example, the solubility of lithium chloride at 0° is 16.3 molal which is equivalent to a value for x of 0.227. Consequently, agreement between the calculated and experimental values would be expected to be poor. Data which will be presented in a subsequent paper show that over the temperature range used to determine an L_f' value for lithium chloride, the x values were between 0.20 to 0.25. Using the L_f' calculated from these solubility data, the predicted eutectic temperature was -21.7°, while the experimental value was found to be below -40°.

If the L_f' value is calculated from solubility measurements made above 0°, an erroneous estimation of eutectic temperature may occur if the solubility is not a single linear function down to the eutectic point. For example, sodium chloride undergoes phase transition to the dihydrate at 0.15°. If the differential heat of solution above 0.15° is used (101.1 cal.), the predicted value for eutectic

TABLE I.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. L_f' , cal.	M.p., °C. (T_0)									
	10	20	30	40	50	60	70	80	90	100
100	71.16	70.86	70.58	70.32	70.07	69.85	69.63	69.43	69.24	69.06
200	67.87	67.32	66.81	36.33	65.89	65.47	65.08	64.71	64.36	64.03
300	64.99	64.23	63.52	62.85	62.24	61.66	61.12	60.61	60.13	59.68
400	62.44	61.48	60.60	59.78	59.01	58.29	57.62	56.99	56.40	55.85
500	60.15	59.02	57.98	57.02	56.12	55.28	54.50	53.76	53.07	52.43
600	58.07	56.80	55.62	54.52	53.51	52.56	51.68	50.85	50.08	49.35
700	56.18	54.76	53.46	52.25	51.13	50.09	49.12	48.21	47.36	46.56
800	54.44	52.90	51.48	50.17	48.95	47.82	46.77	45.79	44.87	44.01
900	52.83	51.18	49.66	48.25	46.95	45.74	44.61	43.57	42.59	41.67
1000	51.34	49.58	47.96	46.47	45.09	43.81	42.62	41.51	40.48	39.52
1100	49.95	48.10	46.39	44.81	43.36	42.01	40.76	39.60	38.52	37.52
1200	48.66	46.71	44.92	43.27	41.74	40.34	39.04	37.83	36.71	35.66
1300	47.44	45.40	43.53	41.82	40.23	38.77	37.42	36.17	35.01	33.93
1400	46.30	44.18	42.24	40.45	38.81	37.30	35.91	34.61	33.42	32.31
1500	45.22	43.02	41.01	39.17	37.48	35.92	34.48	33.15	31.93	30.79
1600	44.20	41.93	39.86	37.96	36.22	34.61	33.14	31.78	30.52	29.36
1700	43.23	40.89	38.76	36.81	35.02	33.38	31.87	30.48	29.20	28.02
1800	42.31	39.91	37.72	35.72	33.89	32.21	30.67	29.26	27.95	26.75
1900	41.44	38.98	36.73	34.69	32.81	31.10	29.53	28.10	26.77	25.56
2000	40.60	38.09	35.79	33.70	31.79	30.05	28.45	26.99	25.65	24.42
2100	39.81	37.23	34.89	32.76	30.82	29.05	27.43	25.95	24.59	23.35
2200	39.05	36.42	34.03	31.86	29.89	28.09	26.45	24.95	23.59	22.33
2300	38.32	35.64	33.21	31.00	29.00	27.18	25.52	24.01	22.63	21.37
2400	37.62	34.90	32.42	30.18	28.15	26.30	24.63	23.10	21.72	20.45
2500	36.96	34.18	31.67	29.40	27.34	25.47	23.78	22.24	20.85	19.58
2600	36.31	33.49	30.94	28.64	26.56	24.67	22.96	21.42	20.02	18.74
2700	35.69	32.83	30.25	27.91	25.81	23.90	22.18	20.63	19.22	17.95
2800	35.10	32.20	29.58	27.21	25.09	23.17	21.44	19.88	18.47	17.19
2900	34.52	31.58	28.93	26.54	24.39	22.46	20.72	19.16	17.75	16.47
3000	33.97	30.99	28.31	25.90	23.73	21.78	20.03	18.46	17.05	15.78

TABLE II.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. L_f' , cal.	M.p., °C. (T_0)									
	10	20	30	40	50	60	70	80	90	100
3100	33.43	30.42	27.71	25.27	23.09	21.13	19.37	17.80	16.39	15.13
3200	32.92	29.87	27.13	24.67	22.47	20.50	18.74	17.17	15.76	14.50
3300	32.42	29.33	26.56	24.09	21.87	19.89	18.13	16.55	15.15	13.89
3400	31.93	28.82	26.02	23.52	21.30	19.31	17.54	15.97	14.57	13.32
3500	31.46	28.31	25.50	22.98	20.74	18.75	16.98	15.40	14.01	12.76
3600	31.01	27.83	24.99	22.45	20.20	18.20	16.43	14.86	13.47	12.24
3700	30.57	27.36	24.50	21.95	19.68	17.68	15.91	14.34	12.95	11.73
3800	30.14	26.90	24.02	21.45	19.18	17.17	15.40	13.84	12.46	11.25
3900	29.73	26.46	23.55	20.97	18.69	16.68	14.91	13.35	11.98	10.78
4000	29.32	26.03	23.10	20.51	18.22	16.21	14.44	12.89	11.53	10.33
4100	28.93	25.61	22.67	20.06	17.76	15.75	13.98	12.44	11.09	9.91
4200	28.55	25.21	22.24	19.62	17.32	15.30	13.54	12.00	10.66	9.50
4300	28.18	24.81	21.83	19.20	16.89	14.87	13.12	11.59	10.26	9.10
4400	27.82	24.43	21.43	18.79	16.48	14.46	12.71	11.18	9.87	8.73
4500	27.47	24.05	21.04	18.39	16.07	14.06	12.31	10.80	9.49	8.37
4600	27.12	23.69	20.66	18.00	15.68	13.66	11.92	10.42	9.13	8.02
4700	26.79	23.33	20.29	17.62	15.30	13.29	11.55	10.06	8.78	7.68
4800	26.46	22.98	19.92	17.25	14.93	12.92	11.19	9.71	8.45	7.36
4900	26.14	22.65	19.57	16.89	14.57	12.56	10.84	9.37	8.12	7.06
5000	25.83	22.32	19.23	16.54	14.21	12.22	10.51	9.05	7.81	6.76
5100	25.53	21.99	18.89	16.20	13.87	11.88	10.18	8.74	7.51	6.48
5200	25.23	21.68	18.57	15.87	13.54	11.55	9.86	8.43	7.22	6.21
5300	24.94	21.37	18.25	15.54	13.22	11.24	9.56	8.14	6.95	5.95
5400	24.66	21.07	17.94	15.23	12.91	10.93	9.26	7.86	6.68	5.70
5500	24.38	20.78	17.63	14.92	12.60	10.63	8.97	7.58	6.42	5.46
5600	24.11	20.49	17.34	14.62	12.30	10.34	8.69	7.32	6.18	5.23
5700	23.85	20.21	17.05	14.33	12.01	10.06	8.42	7.06	5.94	5.00
5800	23.59	19.94	16.76	14.04	11.73	9.79	8.16	6.82	5.71	4.79
5900	23.34	19.67	16.49	13.76	11.45	9.52	7.91	6.58	5.49	4.59
6000	23.09	19.40	16.22	13.49	11.19	9.26	7.66	6.35	5.27	4.39

TABLE III.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. <i>Lf'</i> , cal.	M.p., °C. (<i>T_e'</i>)									
	110	120	130	140	150	160	170	180	190	200
100	68.89	68.72	68.57	68.42	68.29	68.15	68.03	67.91	67.79	67.68
200	63.72	63.43	63.15	62.89	62.64	62.40	62.17	61.96	61.75	61.55
300	59.25	58.85	58.47	58.11	57.77	57.44	57.13	56.83	56.55	56.28
400	55.32	54.83	54.36	53.91	53.49	53.09	52.71	52.35	52.01	51.68
500	51.82	51.24	50.70	50.19	49.70	49.24	48.80	48.38	47.98	47.60
600	48.67	48.02	47.42	46.84	46.30	45.78	45.29	44.83	44.39	43.97
700	45.81	45.11	44.44	43.82	43.22	42.66	42.13	41.63	41.15	40.69
800	43.21	42.45	41.74	41.06	40.43	39.83	39.26	38.73	38.21	37.73
900	40.82	40.01	39.26	38.55	37.88	37.24	36.64	36.08	35.54	35.03
1000	38.62	37.77	36.98	36.23	35.53	34.87	34.25	33.65	33.10	32.57
1100	36.58	35.70	34.87	34.10	33.37	32.68	32.04	31.43	30.85	30.30
1200	34.68	33.77	32.92	32.12	31.37	30.66	30.00	29.37	28.78	28.22
1300	32.92	31.98	31.11	30.28	29.51	28.79	28.11	27.47	26.87	26.30
1400	31.27	30.31	29.41	28.58	27.79	27.05	26.36	25.71	25.10	24.52
1500	29.73	28.75	27.83	26.98	26.18	25.44	24.74	24.08	23.46	22.88
1600	28.28	27.29	26.36	25.49	24.68	23.93	23.22	22.56	21.94	21.35
1700	26.92	25.91	24.97	24.09	23.28	22.52	21.80	21.14	20.52	19.93
1800	25.64	24.62	23.66	22.78	21.96	21.20	20.48	19.82	19.19	18.61
1900	24.43	23.40	22.44	21.55	20.73	19.96	19.25	18.58	17.96	17.38
2000	23.29	22.25	21.28	20.39	19.57	18.80	18.09	17.43	16.81	16.23
2100	22.21	21.16	20.19	19.30	18.47	17.71	17.00	16.34	15.73	15.16
2200	21.19	20.13	19.16	18.27	17.45	16.69	15.98	15.33	14.72	14.16
2300	20.22	19.16	18.19	17.30	16.48	15.72	15.03	14.38	13.78	13.23
2400	19.29	18.24	17.27	16.38	15.57	14.82	14.13	13.49	12.90	12.35
2500	18.42	17.36	16.40	15.52	14.71	13.97	13.28	12.65	12.07	11.54
2600	17.59	16.53	15.57	14.70	13.90	13.16	12.49	11.87	11.30	10.77
2700	16.80	15.75	14.79	13.92	13.13	12.40	11.74	11.13	10.57	10.06
2800	16.04	15.00	14.05	13.19	12.41	11.69	11.04	10.44	9.89	9.39
2900	15.32	14.29	13.35	12.49	11.72	11.02	10.38	9.79	9.25	8.76
3000	14.64	13.61	12.68	11.84	11.07	10.38	9.75	9.18	8.66	8.18

TABLE IV.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. <i>Lf'</i> , cal.	M.p., °C. (<i>T_e'</i>)									
	110	120	130	140	150	160	170	180	190	200
3100	13.99	12.96	12.04	11.21	10.46	9.78	9.17	8.61	8.10	7.63
3200	13.37	12.35	11.44	10.62	9.88	9.22	8.61	8.07	7.57	7.12
3300	12.77	11.77	10.87	10.06	9.33	8.68	8.09	7.56	7.08	6.64
3400	12.20	11.21	10.32	9.53	8.82	8.18	7.60	7.08	6.61	6.19
3500	11.66	10.68	9.80	9.02	8.33	7.70	7.14	6.64	6.18	5.77
3600	11.14	10.17	9.31	8.55	7.86	7.25	6.70	6.21	5.77	5.38
3700	10.65	9.69	8.84	8.09	7.42	6.83	6.30	5.82	5.39	5.01
3800	10.18	9.23	8.40	7.66	7.01	6.43	5.91	5.45	5.04	4.67
3900	9.72	8.79	7.97	7.25	6.61	6.05	5.55	5.10	4.70	4.35
4000	9.29	8.38	7.57	6.86	6.24	5.69	5.20	4.77	4.39	4.05
4100	8.88	7.98	7.19	6.50	5.89	5.35	4.88	4.47	4.10	3.77
4200	8.48	7.60	6.82	6.15	5.56	5.04	4.58	4.18	3.82	3.51
4300	8.10	7.23	6.48	5.82	5.24	4.74	4.30	3.91	3.57	3.26
4400	7.74	6.89	6.15	5.50	4.94	4.45	4.03	3.65	3.32	3.04
4500	7.39	6.56	5.83	5.20	4.66	4.19	3.78	3.42	3.10	2.82
4600	7.06	6.24	5.53	4.92	4.39	3.94	3.54	3.19	2.89	2.62
4700	6.74	5.94	5.25	4.65	4.14	3.70	3.32	2.98	2.69	2.44
4800	6.44	5.65	4.98	4.40	3.90	3.48	3.11	2.79	2.51	2.27
4900	6.15	5.38	4.72	4.16	3.68	3.26	2.91	2.60	2.34	2.11
5000	5.87	5.12	4.48	3.93	3.46	3.07	2.73	2.43	2.18	1.96
5100	5.61	4.87	4.24	3.71	3.26	2.88	2.55	2.27	2.03	1.82
5200	5.35	4.63	4.02	3.51	3.07	2.70	2.39	2.12	1.89	1.69
5300	5.11	4.40	3.81	3.31	2.89	2.54	2.24	1.98	1.76	1.57
5400	4.87	4.19	3.61	3.13	2.72	2.38	2.09	1.85	1.64	1.46
5500	4.65	3.98	3.42	2.96	2.56	2.24	1.96	1.72	1.52	1.35
5600	4.44	3.79	3.24	2.79	2.41	2.10	1.83	1.61	1.42	1.25
5700	4.23	3.60	3.07	2.63	2.27	1.97	1.71	1.50	1.32	1.16
5800	4.04	3.42	2.91	2.49	2.14	1.85	1.60	1.40	1.23	1.08
5900	3.85	3.25	2.75	2.35	2.01	1.73	1.50	1.30	1.14	1.00
6000	3.67	3.09	2.61	2.21	1.89	1.62	1.40	1.21	1.06	0.93

TABLE V.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. <i>Lf'</i> , cal.	M.p., °C. (<i>T₀'</i>)									
	210	220	230	240	250	260	270	280	290	300
100	67.58	67.47	67.38	67.28	67.19	67.11	67.02	66.95	66.87	66.79
200	61.36	61.18	61.01	60.84	60.68	60.53	60.38	60.23	60.10	59.97
300	56.02	55.78	55.54	55.31	55.10	54.89	54.69	54.50	54.31	54.13
400	51.36	51.06	50.78	50.50	50.24	49.98	49.74	49.51	49.28	49.06
500	47.24	46.90	46.57	46.25	45.95	45.66	45.38	45.11	44.86	44.61
600	43.57	43.18	42.82	42.47	42.13	41.81	41.51	41.21	40.93	40.66
700	40.26	39.85	39.45	39.07	38.71	38.37	38.04	37.72	37.42	37.13
800	37.27	36.83	36.41	36.01	35.63	35.26	34.91	34.58	34.26	33.95
900	34.55	34.09	33.65	33.23	32.83	32.45	32.09	31.74	31.40	31.08
1000	32.06	31.59	31.13	30.70	30.29	29.89	29.52	29.16	28.81	28.49
1100	29.79	29.29	28.83	28.38	27.96	27.56	27.18	26.81	26.46	26.12
1200	27.69	27.19	26.71	26.26	25.83	25.42	25.03	24.66	24.31	23.97
1300	25.76	25.25	24.77	24.31	23.88	23.47	23.07	22.70	22.34	22.00
1400	23.98	23.47	22.98	22.52	22.08	21.67	21.27	20.90	20.54	20.20
1500	22.33	21.81	21.33	20.86	20.43	20.01	19.62	19.24	18.89	18.55
1600	20.80	20.28	19.80	19.33	18.90	18.48	18.09	17.72	17.37	17.03
1700	19.38	18.87	18.38	17.92	17.49	17.08	16.69	16.32	15.97	15.64
1800	18.06	17.55	17.07	16.61	16.18	15.78	15.39	15.03	14.69	14.36
1900	16.84	16.33	15.85	15.40	14.98	14.58	14.20	13.84	13.51	13.19
2000	15.69	15.19	14.72	14.27	13.86	13.47	13.10	12.75	12.42	12.11
2100	14.63	14.13	13.67	13.23	12.82	12.44	12.08	11.74	11.41	11.11
2200	13.64	13.15	12.69	12.26	11.86	11.49	11.13	10.80	10.49	10.20
2300	12.71	12.23	11.78	11.36	10.97	10.61	10.26	9.94	9.64	9.35
2400	11.85	11.38	10.94	10.53	10.15	9.79	9.46	9.15	8.85	8.58
2500	11.04	10.58	10.15	9.75	9.38	9.04	8.71	8.41	8.13	7.86
2600	10.29	9.84	9.42	9.03	8.67	8.34	8.03	7.73	7.46	7.21
2700	9.58	9.15	8.74	8.36	8.02	7.69	7.39	7.11	6.85	6.60
2800	8.93	8.50	8.11	7.74	7.41	7.09	6.80	6.53	6.28	6.05
2900	8.31	7.90	7.52	7.17	6.84	6.54	6.26	6.00	5.76	5.54
3000	7.74	7.34	6.97	6.63	6.32	6.03	5.76	5.51	5.28	5.07

TABLE VI.—EUTECTIC VALUES (NEGATIVE)

Diff. Heat of Soln. <i>Lf'</i> , cal.	M.p., °C. (<i>T₀'</i>)									
	210	220	230	240	250	260	270	280	290	300
3100	7.21	6.82	6.46	6.13	5.83	5.55	5.30	5.06	4.84	4.64
3200	6.71	6.33	5.99	5.67	5.38	5.12	4.87	4.64	4.43	4.24
3300	6.24	5.88	5.55	5.24	4.97	4.71	4.48	4.26	4.06	3.88
3400	5.81	5.46	5.14	4.85	4.58	4.34	4.11	3.91	3.72	3.54
3500	5.40	5.06	4.76	4.48	4.22	3.99	3.78	3.58	3.40	3.24
3600	5.02	4.70	4.40	4.14	3.89	3.67	3.47	3.28	3.11	2.96
3700	4.67	4.36	4.07	3.82	3.59	3.38	3.18	3.01	2.85	2.70
3800	4.34	4.04	3.77	3.53	3.31	3.10	2.92	2.76	2.60	2.46
3900	4.03	3.74	3.49	3.25	3.04	2.85	2.68	2.52	2.38	2.25
4000	3.74	3.47	3.22	3.00	2.80	2.62	2.46	2.31	2.18	2.05
4100	3.48	3.21	2.98	2.77	2.58	2.41	2.25	2.11	1.99	1.87
4200	3.23	2.98	2.75	2.55	2.37	2.21	2.07	1.93	1.81	1.71
4300	2.99	2.76	2.54	2.35	2.18	2.03	1.89	1.77	1.66	1.56
4400	2.78	2.55	2.35	2.17	2.01	1.87	1.74	1.62	1.51	1.42
4500	2.58	2.36	2.17	2.00	1.85	1.71	1.59	1.48	1.38	1.29
4600	2.39	2.19	2.00	1.84	1.70	1.57	1.46	1.35	1.26	1.18
4700	2.22	2.02	1.85	1.70	1.56	1.44	1.33	1.24	1.15	1.07
4800	2.06	1.87	1.71	1.56	1.44	1.32	1.22	1.13	1.05	0.98
4900	1.91	1.73	1.58	1.44	1.32	1.21	1.12	1.03	0.96	0.89
5000	1.77	1.60	1.45	1.32	1.21	1.11	1.02	0.94	0.87	0.81
5100	1.64	1.48	1.34	1.22	1.11	1.02	0.94	0.86	0.79	0.74

will be -64.76° which is considerably lower than the experimental value of -21.6° . However, as will be illustrated in the subsequent paper of this series where the solubility data below 0.15° are used, the agreement between the calculated and experimental value is much better.

For values of Lf' above about 5400 cal. for compounds having a melting point above 280° , the computer program sometimes fails to converge. This also occurs when the eutectic point is within about half a degree of the melting point of the solvent.

SUMMARY

Using the IBM 1401 (8K) computer, a program was written for the numerical estimation of the eutectic temperature from an equation which could not be solved analytically.

A second program was written in a more general form to print tables of eutectic temperatures over a range of Lf' values from 100 to 6000 cal. and melting points from 10 to 300°.

The errors inherent in the eutectic expression and the program were elucidated.

This study demonstrates one of the several possible applications of computers in pharmaceutical research and development.

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Evaluation of the Physical Properties of Compressed Tablets I

Tablet Hardness and Friability

By JAMES A. SEITZ and GERALD M. FLESSLAND

Studies were conducted to evaluate what changes occurred in the physical properties of compressed tablets as the operation of a rotary tableting machine was varied. Thin large-diameter tablets showed a capping tendency that was not apparent in smaller-diameter or thicker tablets. The crushing strength of tablets stored at 71 per cent R.H. for 28 days was unchanged, but the tablets became more friable. Increasing the compressional speed reduced the crushing strength and increased the capping tendency, but did not affect the friability of compressed tablets. At the higher compressional rates, the tablets showed a greater elastic response than at the slower speeds. Compressing the tablets at various depths in the die had no effect on the physical properties of the compressed tablets.

IN THE evaluation of the physical properties of compressed tablets, many test procedures have been developed in an attempt to study the mechanical strength of compressed tablets (1-10). Tablet hardness is the nonspecific term routinely applied to several tablet parameters: (a) resistance to bending or breaking, (b) crushing strength (axial or radial), (c) impact strength, and (d) resistance to attrition or abrasion.

In addition to the above-indicated properties, it is desirable to have a testing procedure capable of assessing tablet flaws—capping, splitting, chipping—under controlled experimental conditions. The phenomenon of capping has been studied by several investigators (11-15), but the relationship between this tablet flaw and the mechanical strength of a tablet has received little attention.

In previous studies where tablet hardness was critically evaluated, single-punch tableting machines or rotary compressors operating at a slow rate were employed (16, 17). These studies re-

vealed some valuable data, but additional information was needed to determine the influence of the various rotary tableting machine operations on the crushing strength, friability, and capping tendency of compressed tablets. The purpose of the present investigation was to elucidate the role played by rotary tableting machines on influencing the physical properties of the resulting compressed tablets.

In addition, the effect of storage conditions, tablet size, tablet density, and tablet thickness on the physical properties of compressed tablets was assessed.

EXPERIMENTAL

The tablets were compressed on a Stokes B-2 rotary compressing machine. The tableting machine was run at 36 r.p.m. with $1\frac{13}{32}$ -in. standard concave punches unless otherwise indicated. The tablets were individually weighed on a Mettler balance to the nearest 0.1 mg., and the thickness was measured with a micrometer to the nearest 0.001 in. The crushing strength was determined on an air-pressure operated Strong-Cobb hardness tester to the nearest $\frac{1}{4}$ of a scale reading.

The friability assessment was conducted on 20 tablets in an apparatus similar to the Roche friabilator (9). The tablets were tumbled in the friabilator

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