Lyophilization of Pharmaceuticals II

High-Sensitivity Resistance Bridge for Low-Conductivity Measurements at Eutectic Temperatures

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A description is presented of the circuitry, design, and operating characteristics of a temperature-conductivity bridge especially fabricated for eutectic and freezing-point temperature measurements. The resistance bridge is capable of measuring accurately from 10^3 to 10^{12} ohms over a temperature range from $-50°$ to $+50°$. A d.c. applied potential of 1, 10, or 100 v. is used as a power supply, and a solid-state operational amplifier is employed as the detecting system. By employing a high-gain amplifier with an input impedance in excess of 10^8 ohms, stable power supplies, and special insulation design, it is possible to cover the range from 10^3 to 10^{12} ohms in narrow- or wide-range decade steps. The circuitry of the temperature-conductivity plotter permits temperature measurement by either thermocouple or thermistor circuits. The information obtained is displayed on a *X-Y* recorder with variable sensitivity.

KNOWLEDGE of the eutectic temperature of a pharmaceutical substance to be lyophilized is essential for the design of accurate and optimal freeze-drying cycles. Of the several methods available for the determination of eutectic temperatures, electrical resistivity measurement is the most accurate (1). This method consists of measuring the resistance of a frozen sample as a function of temperature. The resistance of a frozen mass below the eutectic temperature is very high. Consequently, for accurate estimations of eutectic temperatures through resistivity measurements, a sensitive low-conductivity bridge capable of measuring resistance to 10^{12} ohms is required. Since the normal conductivity bridges available on the market are not capable of precise measurements of resistance in the range of 10^{11} to 10^{12} ohms, a temperature-conductivity bridge of unique capabilities was designed. This bridge is capable of measuring resistance as high as 10^{12} ohms. It is composed of four wide-range decades ranging from 0–10^6 ohms to 0–10^{12} ohms and eight narrow-range decades from 10^4–10^5 ohms to 10^{11}–10^{12} ohms. Calibration resistors are provided for use as internal standards. A thermistor or thermocouple probe is used to sense changes in the temperature of the material in the conductivity cell. An *X-Y* recorder is used for plotting the resistivity as a function of temperature. This temperature-conductivity bridge has maximum versatility in that it is possible to select the axis desired on the recorder for a particular measurement. For example, we can plot resistance *versus* thermocouple, resistance *versus* thermistor, and thermistor *versus* thermocouple on either axis.

Because it was felt that such a temperature-conductivity plotter is unique in design, versatile, and would be of considerable use to the pharmaceutical research scientist concerned with product development, full details of the circuitry and construction of this equipment will be presented in this paper. For clarity of explanation to the nonelectronically trained pharmaceutical scientist, the design and circuitry have been broken down into several components, and explanations and descriptions are given in depth as simply as possible.

POWER SUPPLY AND THERMOMETRY CIRCUITS

The circuitry for the power supply to the high-resistance bridge is given in Fig. 1. The 110-v. a.c. current supply is converted to 125 v. d.c. by the transformer and then rectified to +130 and −130 v. This voltage then passes through 4.5 Henry inductors and 16 μF. capacitors to smooth out the waveform to a pure d.c. waveform. The 1500- and 2000-ohm resistors result in a reduction of the voltage reaching the gas tube stabilizers to +100 and −75 v. The gas stabilizers further stabilize the voltage and also remove any remaining ripples from the d.c. supply, giving a very smooth and constant voltage input.

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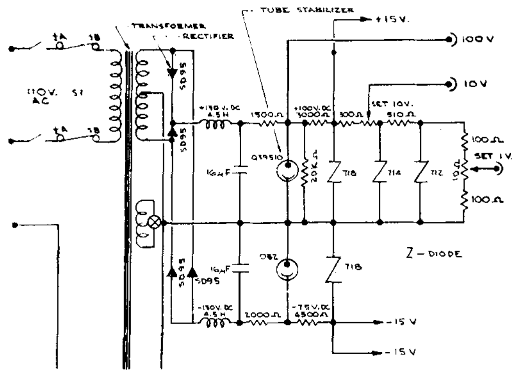

Fig. 1.—Circuitry for power supply to high resistance bridge. (Larger-scale drawings are available from the authors upon request.)

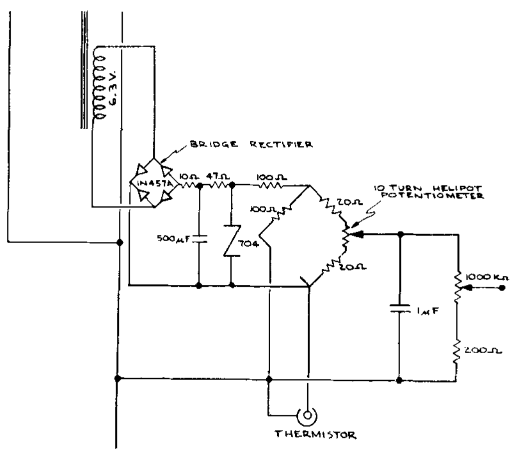

Fig. 2.—Thermistor bridge power supply circuitry. (Larger-scale drawings are available from the authors upon request.)

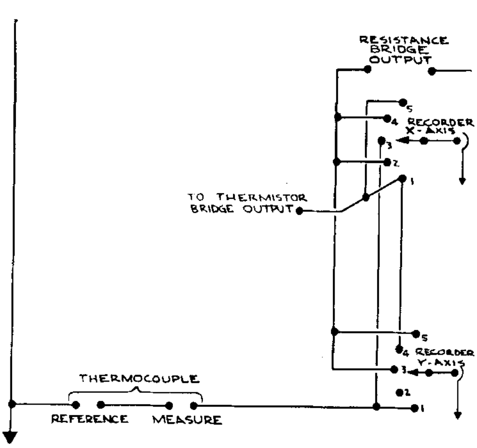

Fig. 3.—Switching circuitry for resistance bridge, thermocouple, and thermistor. (Larger-scale drawings are available from the authors upon request.)

The additional resistors and Zener diodes in the circuitry provide stabilized voltages of +15 and −15 v. to the amplifier and 1, 10, or 100 v. to the resistance bridge. Since the amplifier in the bridge circuit requires approximately 15 mamp., nearly constant loading on the circuit and constant input results in greater stability of the voltage from the Zener supplying the amplifier. To enhance the stability of the voltage supplied to the resistance bridge, each Zener diode is supplied from the voltage stabilized at the previous Zener. This results in each stage having less variation from the original input voltage. The absolute values from the 10- and 1-v. supply to the resistance bridge can be adjusted to exact values by preset potentiometers.

The thermistor bridge circuitry is presented in Fig. 2. The 110 v. a.c. is fed through a transformer and then through a bridge rectifier to give 6.5 v. d.c. A 10-ohm surge resistor and a capacitor smooth the waveform. The 47-ohm resistor reduces the voltage being supplied to the thermistor bridge to 4 v., and the Zener diode that follows stabilizes this voltage supplied to the thermistor bridge. A 10-turn Heliopot potentiometer is provided for balancing the bridge. Across the output of the bridge, a 1-μF. capacitor reduces any noise that is picked up from the thermistor circuit. The switching circuitry for taking the individual outputs from the resistance bridge, thermocouple, and thermistor to an X-Y recorder is presented in Fig. 3.

Figure 4 shows the complete circuit diagram for the power supply providing 1, 10, and 100 v. d.c. to the resistance bridge, ±15 v. d.c. to the amplifier, 4 v. d.c. to the thermistor bridge and the thermocouple and switching circuitry to the X-Y recorder. All the low-voltage circuits are grounded at a common point.

RESISTANCE BRIDGE CIRCUITRY

In designing this resistance measuring equipment, a decision was required as to whether to employ a.c. or d.c. applied potential to the bridge. It is recognized in the area of electrochemistry that when a d.c. potential is applied to an electrolyte, polarization will occur, giving a resistance reading somewhat higher than the true value. However, in the event a.c. potentials are used, the waveform is distorted by polarization at each half-cycle, preventing precise measurements. Another disadvantage in using a.c. potentials is the difficulty in shielding out electrical interference when frequencies of 60 c.p.s. are used.

Because of the small currents induced by the d.c. applied potential, the polarization effect is not particularly marked. This is especially true when potentials of more than 2 or 3 v. are applied. Consequently, the bridge to be described employs a d.c. applied potential detected by a high input impedance operational amplifier which is arranged to give a cut-off frequency of 4 c.p.s. This frequency cutoff largely eliminates any electrical noise problem which could be caused by adjacent power equipment which are primarily of 60 and 120 cycles.

Since it was felt that the resistance bridge circuitry may appear complex if introduced at this point, it was decided to explain the operation of this low-resistivity bridge through simplified versions of the circuitry for both the wide- and narrow-range decades. The circuitry involved in using the wide-

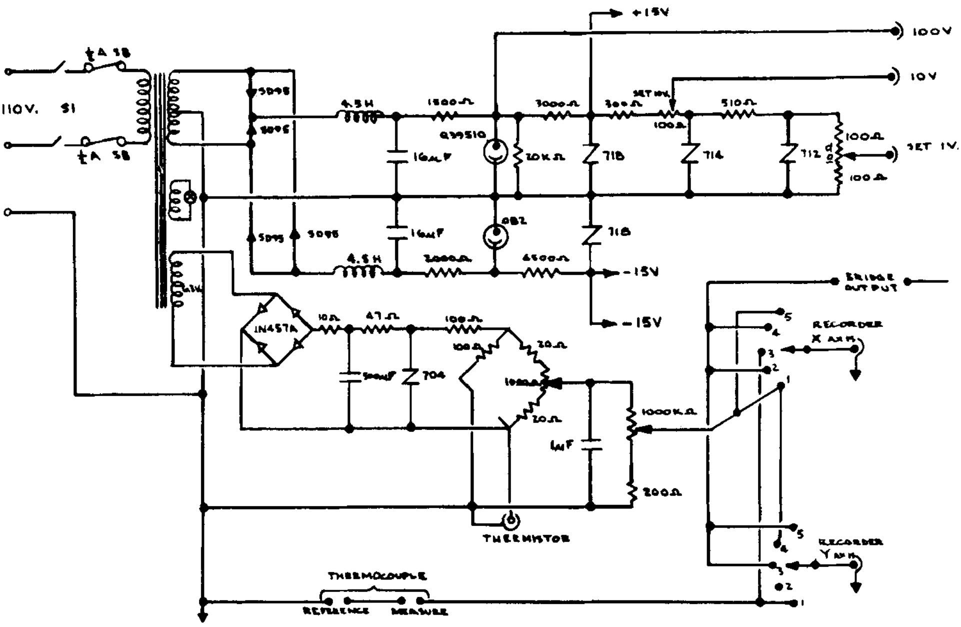

Fig. 4.—Composite circuit diagram for power supply to resistance bridge, thermistor, thermocouple, and switching circuitry. (Larger-scale drawings are available from the authors upon request.)

range resistors will be demonstrated by the diagram in Fig. 5. The voltage to be applied for measurement is selected and travels by means of a shielded cable from the high-voltage IPC connector to the electrode in the cell. The resistance of the material in the cell is measured through the other electrode entering the circuitry by shielded cable at the HN connector. This unknown resistance is placed in series with one of the range resistors A. The voltage at the junction between the two range resistors A and B provides the input to the amplifier. The gain of the amplifier is adjusted so that with no external resistance the meter will read full-scale. The input at the amplifier is determined by the resistance of the material being measured and is proportional to the applied voltage. Therefore, the gain in the amplifier must be changed when the applied voltage is changed. This is accomplished by the switching mechanism for the voltage which

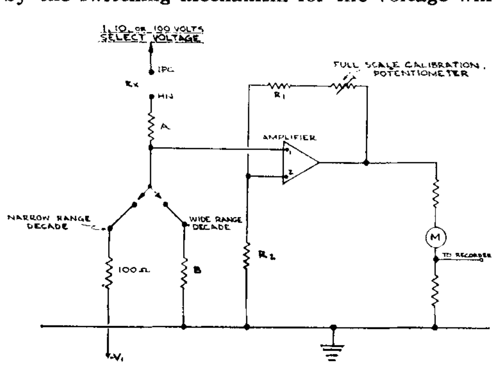

Fig. 5.—Simplified version of circuitry for resistance bridge. Key: R_1, feedback resistor; R_2, gain selector; R_x, unknown resistance. (Larger-scale drawings are available from the authors upon request.)

selects the correct gain when the change in voltage is made. Calibration of the bridge (at a preset voltage) for the wide-range decades is achieved by placing into the circuit a standard resistor having a value two orders below that of the upper level of the decade and equal in resistance to range resistor A for the particular wide-range decade. Since this doubles the total resistance, the amperage put out by the amplifier is reduced by one-half, causing the meter to read half-scale. Fine adjustment of the half-scale reading is accomplished by the calibrating potentiometer 1–4 for the wide-range decades.

For example, if the 0–10^8 ohm decade range is selected, a resistance of 10^6 ohms will correspond to half-scale on the meter, 10^7 ohms will correspond to 10%, and 10^8 ohms will correspond to 1% deflection from zero. On the other hand, 10^5 ohms will correspond to 10%, 10^4 ohms to 1%, and 10^3 ohms to 0.1% deflection from full-scale on the meter. For wide-range decades from 0–10^8 ohms and above, full-scale reading of the meter can be set by using the 10^3-ohm standard resistor. The lower-range resistor for all wide-range circuitry is taken to ground potential.

Where the narrow-range circuitry is involved for measurement, the lower-range resistor B is taken to a negative voltage so selected that the input to the amplifier is zero when the external resistance is equal to the upper limit of the decade range chosen. The input to the amplifier will vary in an almost linear manner from this value to one decade below. As in the case of the wide-range measurements, the amplifier gain is selected by the voltage selection switch. The negative voltage must be changed when the applied voltage is changed; this is also selected by the switching mechanism for the voltage. Calibration of a narrow-range decade is accomplished by selecting the lower of the two resistors in the decade range on the internal resistance stand-

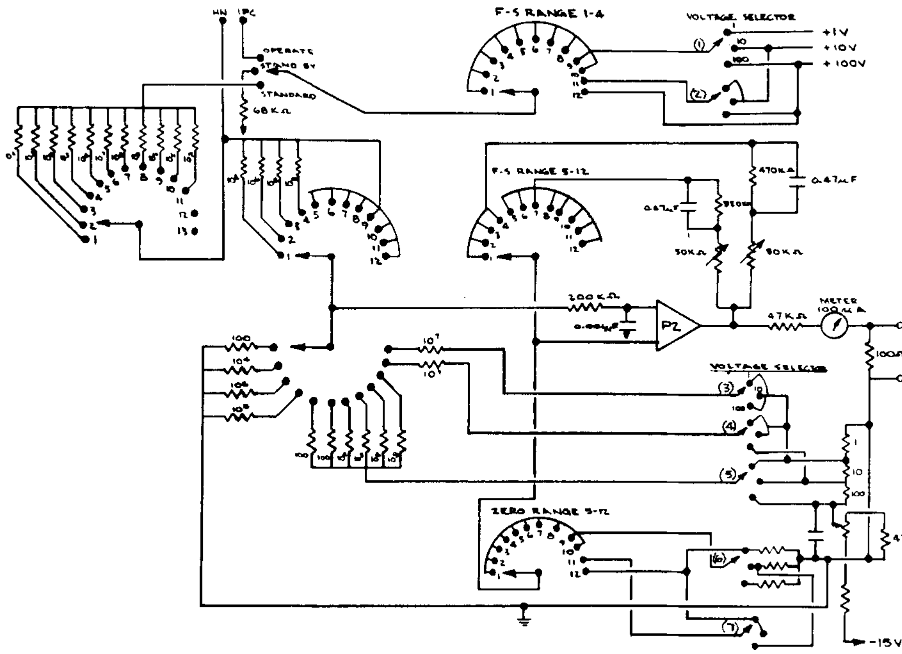

Fig. 6.—A schematic drawing of the actual resistance bridge circuitry. (Larger-scale drawings are available from the authors upon request.)

ard and setting full-scale using the full-scale calibrating potentiometer 5–15. A standard resistor one order higher corresponding to the upper level of the narrow-decade range is then selected and the meter adjusted to zero using the zero calibrating potentiometer 5–12. The output of the amplifier can now be displayed on the meter. In addition, an output corresponding to 10 mv. related to full-scale on the meter is supplied for recording purposes.

The resistance bridge circuitry described by the simple diagram in Fig. 5 is now shown in Fig. 6 as it really appears for this equipment. This diagram has been labeled wherever possible for ease in comprehension. Internal calibration resistors are provided covering the entire range of the bridge in decade steps. These resistors are selected by switching from the front panel of the instrument, as will be shown shortly when a run through of a eutectic determination on this equipment will be illustrated.

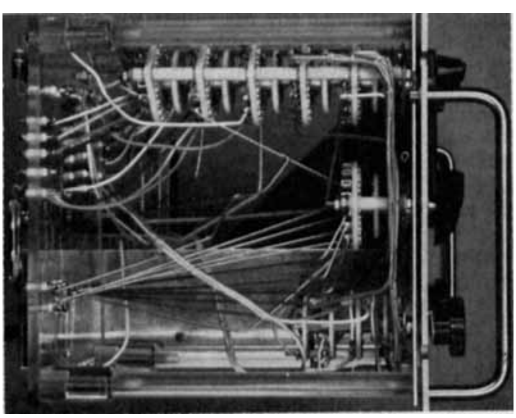

Fig. 7.—Resistor and wiring insulation and steatite switches.

The insulation methods employed in the switching and resistor mounting are of paramount importance if an accuracy of 1% is to be maintained at a resistance of 10^{12} ohms. In order to accomplish this, the insulation must be better than 10^{14} ohms. As shown by Fig. 7, this is accomplished by the use of lucite panels with Teflon inserts for mounting the resistors, and all high-resistance wiring is air insulated with switching done by heavy steatite switches. The Teflon inserts are good to about 10^{14} ohm insulation, while lucite insulation alone could develop surface crazing with subsequent leakage if voltage is continually applied. Separate shielded leads are used for applied potential to the cell and the read-out from the cell. Ground connections are provided for these leads to prevent voltage leakage into the amplifier. A steel cabinet is used to house this resistance bridge in order to reduce the effect of magnetic fields.

TEMPERATURE MEASUREMENT

The temperature change of a sample undergoing eutectic-point determination is followed by measurement with either a chromel/alumel thermocouple or a thermistor bridge circuit. Internal provision is made for calibrating the thermistor circuit against the chromel/alumel thermocouple with an X-Y plotter which is used as the read-out instrument for both temperature and resistance measurements. Such a graph is illustrated in Fig. 8. The temperature scale may be expanded when using the thermistor bridge circuit so that full-scale on the recorder may be as little as 10°, and the center of the scale may be preset to any temperature between $-50°$ and $+50°$.

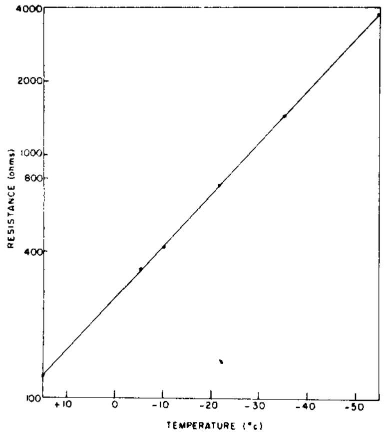

Fig. 8.—Calibration curves for thermistor against thermocouple.

EUTECTIC-POINT MEASUREMENT

Up to this point, an attempt was made to familiarize the reader with the construction and circuitry of the temperature-conductivity plotter. The use of this equipment for determining eutectic points of pharmaceutical substances will now be described. A composite photograph of the arrangement of the equipment employed for eutectic measurements which include the Plexiglas cabinet that housed the conductivity cell, the resistance–thermometry bridge, and the X-Y plotter was presented in a previous publication of this series (1).

For eutectic-point measurement, a solution of the material to be evaluated is placed into the conductivity cell (Fig. 9), and then the Teflon cap is placed onto the cell which holds the two platinum electrodes, a grounded thermocouple, and a thermistor. A vent is provided in the cap to maintain the pressure balance within the cell. The cell is placed in the cavity in the center of the Plexiglas housing and liquid CO_2 is passed through this cavity to freeze the liquid in the cell. Samples are cooled to approximately $-50°$ in about 5 min. by this approach.

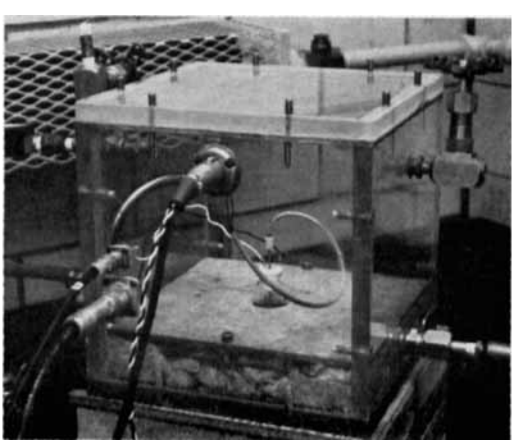

Fig. 9.—Plexiglas chamber for housing the conductivity cell during freezing and thawing.

The most convenient means for measuring resistance *versus* temperature was to use the resistance–thermistor station selected by switch J and to record the resistance on the Y axis and temperature on the X axis of the X-Y plotter. The sensitivity of the thermistor circuitry was set so that full-scale on the temperature axis of the plotter was altered to read 70° full-scale instead of 100° by the coarse H and fine I sensitivity adjustors.

Calibration of the termistor and temperature scale was accomplished by means of battery-operated solid-state direct-reading electrical thermometer.[1] A secondary calibration was made with carefully prepared ethylene glycol solutions. Using the thermistor probe, the temperature is not a linear function of the thermistor resistance on a rectilinear plot. However, as illustrated in Fig. 10, by plotting the logarithm of temperature *versus* the logarithm of the reading in millimeters, the temperature can be represented by the following expression:

$$[-]t°\text{C.} = 0.1428\,(\text{mm.})^{1.102}$$

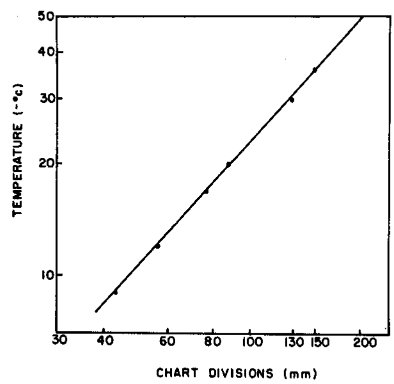

Fig. 10.—Calibration of temperature scale for the thermistor probe as a function of chart divisions.

Prior to freezing a sample, the decade range desired is selected and zero- and full-scale adjustments are made using the standard bridge circuitry. The wide-range decades have proved to be most convenient since switching is eliminated, and both the freezing and thawing curves can be used as plotted. With the narrow-range decades, the operator must repeatedly switch from one decade to the next during the course of freezing or warming; and since the recording is a series of lines each covering full-scale, it is necessary to replot the data.

The front panelling of the resistance–thermometry bridge is shown in Fig. 11. The switching mechanisms for the various operational components of the circuitry is presented on this panel. Power supply to the resistance bridge is obtained by switching the voltage selector A to 1, 10, or 100 v.

A 1- or 10-v. supply to the resistance bridge can be used for measurements in the 10^4 to 10^{10} ohm range. However, errors due to polarization are more significant at 1-v. applied potential for measurements above 10^8 ohms. Consequently, a 10-v.

[1] Model RFL 212 Radio Frequency Laboratories, Inc. Boonton, N. J.

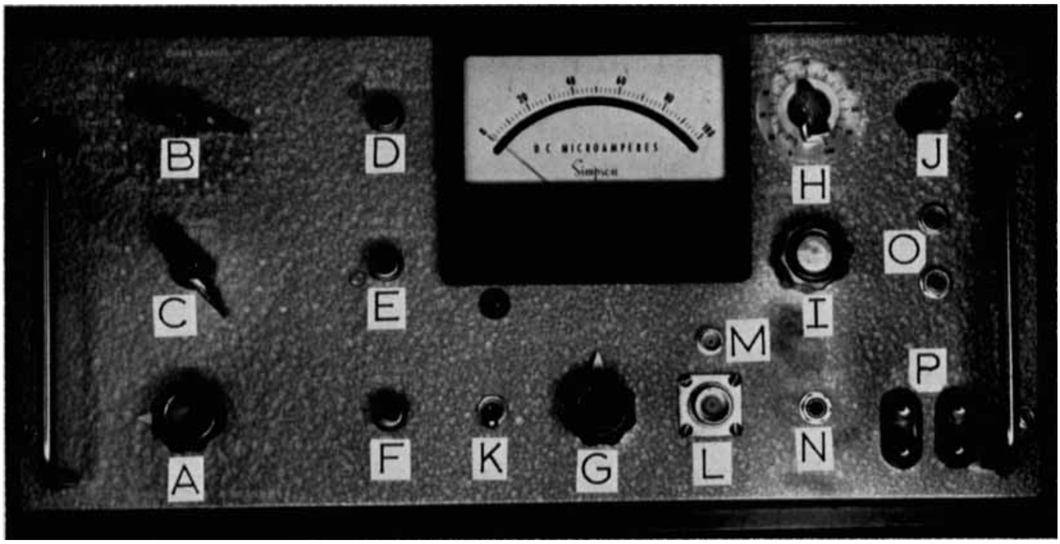

Fig. 11.—Front paneling of the resistance–thermometry bridge showing the switches and connectors for the various operating components.

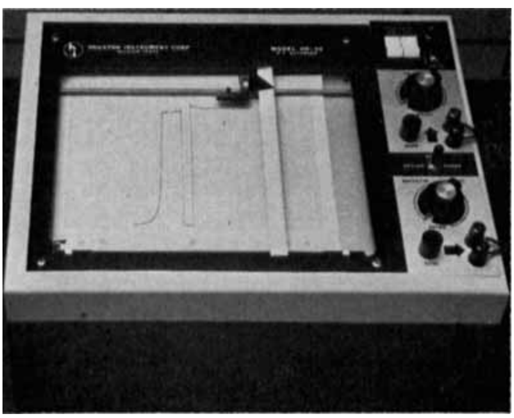

Fig. 12.—X-Y recorder plotting the resistance as a function of temperature during the warming of a frozen sample in the conductivity cell.

supply has been found most suitable for measurements in the 10^4 to 10^{10} ohm range and was generally employed for eutectic temperature measurements. Although a 10-v. supply can be employed for resistance measurements above 10^{10} ohms, it is advisable to use the 100-v. supply in the 10^{11}–10^{12} ohm range. However, the disadvantage that exists in using high voltages is the possibility of decomposition taking place due to local heating as a result of sparking across the polarized layer between electrodes.

The wide-range decade is selected on the basis of the solution under study using ohm range selector B. For high conducting solutions, such as electrolytes or compounds that completely dissociate in solution, the lower wide-range decades, 0–10^6 or 0–10^8 ohms, are used. For nonelectrolytes and poorly dissociating compounds, the higher wide-range decades, 0–10^{10} or 0–10^{12} ohms, are employed.

After the wide-range decade is selected and the voltage to be applied chosen, the meter values and X-Y recorder readings are adjusted with the standard internal bridge C and the wide-decade range calibrating potentiometer D. With this accomplished, the operating switch G is switched from the standard to the operating position. This now places the unknown resistance of the sample to be tested into the resistance bridge circuit for measurement. The sample in the conductivity cell is now frozen and permitted to thaw while resistance measurements are being made as demonstrated by the graph on the X-Y plotter (Fig. 12).

These graphs give a permanent record of the conductivity behavior of the frozen solutions as a function of temperature. From these curves, accurate estimates of the freezing and eutectic temperatures could be obtained.

SUMMARY

A detailed description of the circuitry, design, and operation of a temperature conductivity bridge permitting accurate determinations of the eutectic- and freezing-point temperatures of pharmaceutical compounds was presented. The versatility of this equipment lends itself for use in investigations requiring precise measurements over a wide range of conductivities as a function of temperature or time.

REFERENCE

(1) DeLuca, P. P., and Lachman, L., *J. Pharm. Sci.*, **54**, 617(1965).