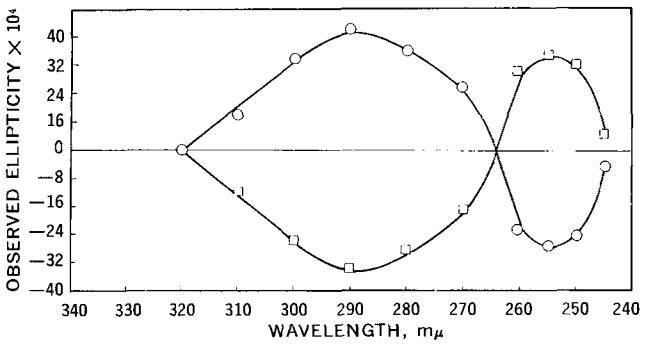


**Figure 1**—*Extrinsic circular dichroism curves for 7.0 × 10⁻⁴ M SETD in an 8.9 × 10⁻² M aqueous betaine solution. Key:* O, D-*betaine;* □, L-*betaine; and S/N ratio = 20:1. All measurements were made in a 0.1-cm. cell.*

CMC's, measured by optical rotatory dispersion and circular dichroism, have been found to be approximately $1 \times 10^{-2}$ *M* at 25° (6, 7). Sulfaethidole (SETD) was used as the optically inactive molecule; this drug has been found to become optically active when bound to bovine serum albumin (8), giving peaks in ellipticity at 280 (negative) and 257 mμ (positive) which are consistent with the UV spectra.

All measurements were made in a 6002 attachment to a Cary 60 spectropolarimeter[1] at 25°. Under the experimental conditions, the betaine showed no optical activity above 240 mμ (7), and the SETD alone showed no activity at any wavelengths. Figure 1 shows the optical activity induced in the SETD molecules by the L- and D-betaines at concentrations considerably above their CMC. Peaks of opposite sign are seen at wavelengths of 288 and 255 mμ. We have not observed any induced optical activities at concentrations of betaine below the CMC.

Figure 2 shows the effect of betaine concentration on the ellipticity at 285 mμ with the SETD concentration constant. These ellipticities are small, as is the signal–noise (S/N) ratio, but it appears that the plot cuts the betaine concentration axis at approximately the CMC. At a concentration of $6.0 \times 10^{-2}$ *M*, the ellipticity seems to have reached a plateau. This is probably the result of all the SETD being solubilized by the micellar betaine, so that subsequent additions of betaine can cause no further interaction. These extrinsic effects probably are due to the interaction of the hydrophobic core of the micelle with the hydrophobic portion of the drug molecule. It is possible that the extrinsic effects observed in aqueous macromolecular solutions are also predominantly hydrophobic in origin.

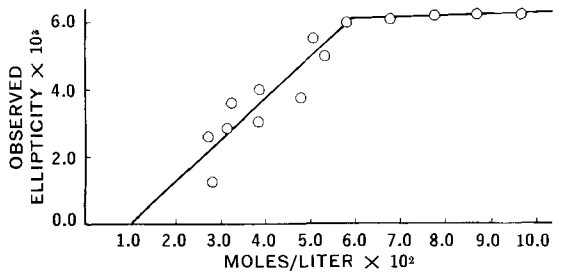


**Figure 2**—*Plot of observed ellipticity at 285 mμ against* D-*betaine concentration for a constant SETD concentration of 7.0 × 10⁻⁴ M. S/N ratio = 20:1 at largest ellipticities and 4:1 at the lowest. All measurements were made in a 0.2-cm. cell.*

[1] Cary Instruments, Monrovia, Calif.

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## Macromolecular Dissolution: Temperature Effects on Polymer–Drug Preparation

**Keyphrases** □ Macromolecular dissolution—temperature of product formation effect □ Polyethylene maleic anhydride–phenylpropanolamine interaction temperature—effect on dissolution rate □ Temperature of preparation, polymer–drug system—physicochemical properties

*Sir:*

Polymer–drug interaction systems have been a source of study for application toward the design of prolonged-release dosage forms (1–3). The general method of preparing these systems has differed from investigator to investigator and between the types of polymers and drugs. However, at no time has the effect of preparation temperature on dissolution and/or drug release from the polymer been investigated.

This report concerns the effects of preparation tem-

**Table I**—Dissolution Rates as Effected by Preparation Temperature

| Temperature | Dissolution Rate, × $10^{-1}$, Δ Refractometer Scale Units/min. |
|---|---|
| 27° | 4.14 |
| 40° | 3.36 |
| 45° | 3.82 |
| 50° | 3.83 |
| 55° | 2.89 |
| 60° | 0.24 |
| 80° | 0.26 |
| 100° | 0.09 |

Table II—Bound Moisture as a Function of Reaction and Drying Temperature

| Temperature | Dried Polymer–Drug, mg. | Bound Moisture, mg. | Bound Moisture, % |
|---|---|---|---|
| 40° | 182.6 | 20.3 | 12.52 |
| 45° | 179.7 | 17.4 | 10.72 |
| 50° | 178.6 | 16.3 | 10.04 |
| 55° | 174.6 | 12.3 | 7.58 |
| 60° | 173.2 | 10.9 | 6.72 |
| 80° | 173.0 | 10.7 | 6.59 |
| 100° | 162.0[a] | — | — |

[a] Polymer–drug sample used as reference containing essentially no moisture.

perature on the dissolution of a polyethylene maleic anhydride–phenylpropanolamine interaction system that was recently devised (4). Samples of the interaction system were prepared at 27, 40, 45, 50, 55, 60, 80, and 100°; aqueous solutions of the polymer and drug were mixed in a 1:1 stoichiometric ratio at each indicated temperature. The solutions were evaporated to dryness, and the powder was compressed into 1-g. nondisintegrating disks on a laboratory press using a 1.6-cm. (0.63-in.) punch and die set. Dissolution studies were then performed using a refractometric method previously described (5). In addition, 10-ml. samples from a stock solution containing 16.40 mg./ml. of polymer–drug in a 1:1 ratio were oven dried to constant weight at the stated temperatures to determine bound moisture.

The results of these experiments are summarized in Tables I and II. It is apparent from an examination of Table I that the dissolution rates of the polymer–drug are essentially the same between the temperature range of 27–55°, with the higher rate at 27°. However, an abrupt, approximately 10-fold, decrease in rate is shown at 60 and 80°, with another significant drop in rate at 100°. These results clearly indicate that temperature has a pronounced effect on some physicochemical property of the polymer–drug system during preparation.

The data in Table II summarize the temperature effect on bound moisture in the polymer–drug system. There is a continuous decrease in bound moisture with an increase in drying temperature, the percent being approximately equal from 40 to 50° and from 55 to 80°. This table shows a rank order correlation with the data in Table I, because both dissolution rate and bound moisture decrease with an increase in temperature. In both studies, 55° appears to be the inflection point at which temperature has the most pronounced effect on dissolution and bound moisture.

Moisture, it appears, is a factor contributing to this dissolution phenomenon. Therefore, water associated with the molecules of the polymer–drug system influences the dissolution mechanism of this polymeric material. Prior to polymer dissolution, solvent imbibition and hydration must occur to form a swollen gel; subsequently, gel disintegration must occur for dissolution to proceed. This situation suggests a dynamic system which encompasses several rate phenomena such as solvent penetration, hydration, swelling, and gel disintegration, all of which determine the dissolution rate of the polymer. The state of hydration, therefore, has an apparent influence on the dynamics of polymer–drug dissolution as suggested by this report.

Other factors, which may contribute to a change in dissolution characteristics when a polymer–drug system is prepared at different temperatures, are stability of the individual components comprising the system and the type of interaction system formed.

The effect of preparation temperature on dissolution could not be attributed to instability of the components of the system studied. The integrity of the pure polymer was confirmed, since no change in dissolution rate was found when a solution of pure polymer was dried at 27 and 100° and then tested. In addition, polyethylene maleic anhydride was reported by the supplier to be stable to any rupture of molecules and does not break down into smaller units at temperatures below 200° (6). The spectra for phenylpropanolamine did not change when a solution of the drug at the concentration used for interaction system preparation was heated at 100° for 2 days, the time required for preparation of the polymer–drug systems.

Ethylene maleic anhydride hydrolyzes in water to form the free acid, each monomer containing two carboxyl groups. Dicarboxylic acids form salts or amides with amines depending upon the reaction temperature (7). It is, therefore, proposed that the polymer and drug may interact at the lower and intermediate temperatures to form a salt. As the temperature increases, a greater proportion of the interaction system formed may be the amide form. The salt form, being more hydrophilic, would have a greater affinity than the amide for bound water. The amide, being more hydrophobic, would show a lesser degree of attraction for moisture. One would, therefore, have a lower rate of hydration and subsequent dissolution, which are consistent with the experimental data.

I am presently engaged in studies to elucidate further the mechanism of this dissolution phenomenon and to determine the effect of preparation temperature on drug release from the polymer.

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