Effect of pH on the Micellar Properties of a Nonionic Surfactant

J. R. BLOOR*, J. C. MORRISON, and C. T. RHODES†

Abstract □ The effect of change in pH on the critical micelle concentration of a nonionic surfactant (Tween 40) has been investigated by surface tension and light-scattering methods. It is shown that a linear relationship exists between the free energy of micellization and pH. Significance of changes in the enthalpy and entropy of micellization are discussed. A computer program, written in Algol 803, is presented to convert raw experimental light-scattering data to micellar molecular weights. It is shown that both micellar molecular weight and the hydration per unit mass of surfactant decrease with increase in pH value. Interpretation of these results is discussed.

Keyphrases □ Nonionic surfactant—micellar properties, pH effect □ Micellar properties, nonionic surfactants—pH effect □ Surface tension method—pH effect, micelle concentration □ Turbidity method—pH effect, micelle concentration □ Refractive index—determination □ NMR—identification □ Computer program—conversion of light-scattering data to micellar molecular weights

Surfactants are widely used in pharmaceutical technology as wetting agents, solubilizers, and emulsifiers. Thus, studies of the properties of surfactants are of assistance in placing pharmaceutical formulation on a rational rather than an empirical basis (1). Also, naturally occurring surfactants, as found for example in bile and gastric juice, can have a significant effect upon drug absorption rates and other aspects of drug action (2). Kakemi *et al.* have attributed the retarded absorption of sulfonamides from aqueous solutions of a nonionic surfactant to micellar entrapment of drug (3). It has also been suggested that surface-active bile salts transport lipids by micellar solubilization (4). Surfactants can therefore play an important part in the biotransport of drugs. In the present paper the effects of pH upon a number of micellar properties of a nonionic surfactant are reported. This work forms part of a study of drug diffusion in micellar solution, further results of which will be published shortly (5). In addition to the value which the results reported in this paper have for diffusion studies, the data are of use in further elucidating the micellar structure of nonionic surfactants and in identifying the forces involved in micellar aggregation.

EXPERIMENTAL

Materials—A polyoxyethylene sorbitan monopalmitate[1] was characterized by NMR spectroscopy. The solvent used was D_2O, and the sodium salt of tetramethylsilane was used as the internal reference. Mean molecular surfactant formula was estimated by the method previously described by Rhodes (6).

The water used in this investigation was double distilled from an all-glass still.

Both the sodium chloride and benzene used in this work were of AnalaR grade.

[1] Tween 40, supplied by Honeywill-Atlas Ltd., Carshalton, England.

Table I—Characterization of the Surfactant by NMR Spectroscopy

Formula Claimed by Manufacturers	Formula Calculated Using Methyl Protons as Reference	Formula Calculated Using Sorbitan Ring Protons as Reference
Alkyl protons 31	30 (.4)	31 (.1)
Polyoxyethylene protons 20	20 (.0)	19 (.5)

Surface Tension Measurements—The critical micelle concentrations (CMC) values of the surfactant at various temperatures and pH values were determined by use of a Du Nouy tensiometer (7). Experimental technique was checked by measuring the surface tension of water which was found to be 72.0 dynes cm.$^{-1}$ at 25°. This was in excellent agreement with the literature value (8). The temperature was controlled at all times to ±0.1° of that required.

Light Scattering—Turbidities were measured using a Brice-Phoenix Universal light-scattering photometer[2] using unpolarized incident light, wavelength 436 mμ, and a standard 30 × 30-mm. turbidity cell. Temperature during determination of turbidities was maintained at ±0.1° of that required. The photometer was calibrated against an opal glass diffuser as a primary reference standard. For benzene the observed Rayleigh ratio was found to be 48.8 × 10^{-6} cm.$^{-1}$ which was in good agreement with the previously reported value (9). All solutions were clarified by filtration through Millipore cellulose membrane filters (0.1 μm pore size). Dissymmetries Z (I 45°/I 135° where I is the intensity of scattered light) were determined for each solution using a standard 40 × 40-mm. semioctagonal cell.

Refractive Index Measurements—The refractive indices of surfactant solutions were determined using a Hilger and Watts interference refractometer[3] with ±0.1° temperature control. Calibration was effected using sodium chloride as standard (10).

RESULTS AND DISCUSSION

The results of the NMR characterization of the surfactant (Table I) show that the mean molecular formula determined experimentally is in good agreement with that stated by the manufacturers. Absence of signals, other than those assigned to the surfactant (5.8 p.p.m. sorbitan ring protons, 6.3 p.p.m. polyoxyethylene protons, 8.7 p.p.m. alkyl protons, and 9.1 p.p.m. terminal methyl protons), is supporting evidence for the manufacturers' formula.

Plots of surface tension and turbidity against surfactant concentration showed abrupt changes of slope at the CMC; typical results are shown in Figs. 1 and 2. Results obtained by the two methods are in good agreement with one another and literature values (11).

Table II records the CMC values for the surfactant at various pH values and temperatures. Methods for calculating the thermodynamic parameters of micellization from CMC values and solubilization data have been discussed in some detail by Molyneaux *et al.* (12) and Humphreys and Rhodes (13). Subject to activity corrections, which for a nonionic surfactant are probably small, the free energy of micellization, ΔG_m, may be calculated by use of Eq. 1:

$$\Delta G_m = -RT \ln K \qquad \text{(Eq. 1)}$$

[2] Supplied by Techmation Ltd., London, England.
[3] Supplied by Hilger and Watts Ltd., London, England.

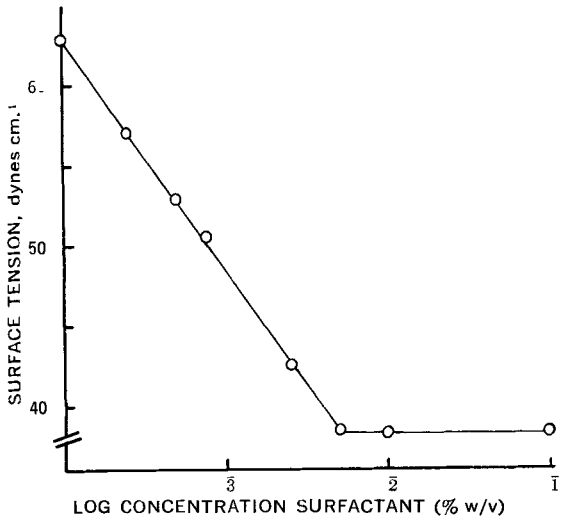

Figure 1—*Surface tension as a function of log surfactant concentration at 25°.*

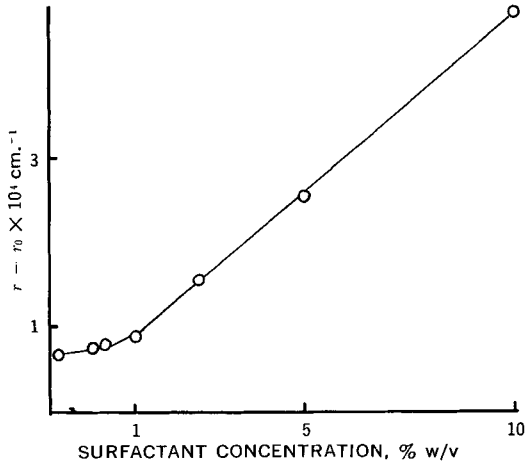

Figure 2—*Turbidity as a function of surfactant concentration at 25° and pH 2.1.*

where R is the gas constant, T the absolute temperature, and K the CMC expressed in terms of mole fraction. Figure 3 shows the ΔG_m values for the surfactant as a function of pH. A linear relationship between these two quantities is apparent. When data are available on the variation of K with temperature, it is possible to resolve ΔG_m into the enthalpic and entropic, ΔH_m and ΔS_m, factors by means of Eq. 2:

$$\Delta G_m = \Delta H_m - T\Delta S_m \qquad \text{(Eq. 2)}$$

Estimates of these quantities have been made (Table III). Because of the small temperature difference, 15°, used in this work, high-precision estimates of ΔH_m and ΔS_m are not possible. However, the values are of use for qualitative interpretation of micellar structure.

The average micellar molecular weight, $\bar{M}_w$, was determined from turbidities measured at 90° by extrapolating the Debye function to zero micellar concentration (14, 15):

$$H(C - C_0)/(\tau - \tau_0) = 1/\bar{M}_w \lim (C - C_0) \to 0 \qquad \text{(Eq. 3)}$$

where H is a constant for any given surfactant system under specified instrumental and environmental conditions, C is the surfactant concentration, C_0 is the CMC, τ is the turbidity at 90°, and τ_0 is the turbidity at 90° at the CMC. Plots of the Debye function against $(C - C_0)$ are governed by Eq. 4:

$$H(C - C_0)/(\tau - \tau_0) = 1/\bar{M}_w + 2B(C - C_0) \qquad \text{(Eq. 4)}$$

The term B, the second virial coefficient, represents the deviation from ideal behavior. The value of H is evaluated from Eq. 5:

$$H = \{32\pi^3 n^2[(n - n_0)/C]^2\}/(3\lambda^4 N) \qquad \text{(Eq. 5)}$$

where C is the solution concentration in g./ml.; n is the refractive index of the solution, n_0 is the refractive index of the solvent, λ is the wavelength of the incident light in cm., and N is Avogadro's number.

A computer program has been written in Algol 803 to substitute raw imput data, surfactant concentration, turbidities, refractive index measurements, and relevant constants into the above equations. Using least-squares procedures the program causes the determination of the best line for the refractive index against concentration plot and the plots of Debye function against concentration. Samples of imput and output data together with the program are given in the Appendix. Dissymmetry ratios were always close to unity, less than 1.03. These values confirmed the clarity of the solutions and substantiated the validity of the experimental procedure. Debye plots are shown in Fig. 4.

Figure 5 shows that a substantial change in micellar molecular weight occurs with change in pH. The values of $\bar{M}_w$ reported do not include water of hydration because the refractive index of the hydrated water is very close to that of the solvent. However, as shown in Fig. 6, the second virial coefficient shows a significant decrease in value with increase in pH. This shows that the solvent–solute interaction is greater at low pH values, indicating more micellar hydration than in alkaline solution. Thus, both the aggregation number and amount of water bound per unit mass of surfactant are greater in acid solution.

In interpreting these results the effect of pH upon water structure is probably a critical factor. There is evidence that sodium and hydroxyl ions are structure-formers which thus increase the extent of water structure around the monomeric surfactant (16).

Table II—Critical Micelle Concentrations of the Surfactant

Temperature	pH	Critical Micelle Concentration (molar) × 10^5
25	2.1	6.5
25	5.0	4.1
25	7.4	3.7
25	9.2	2.6
25	12.1	2.2
40	2.1	4.9
40	12.1	1.4

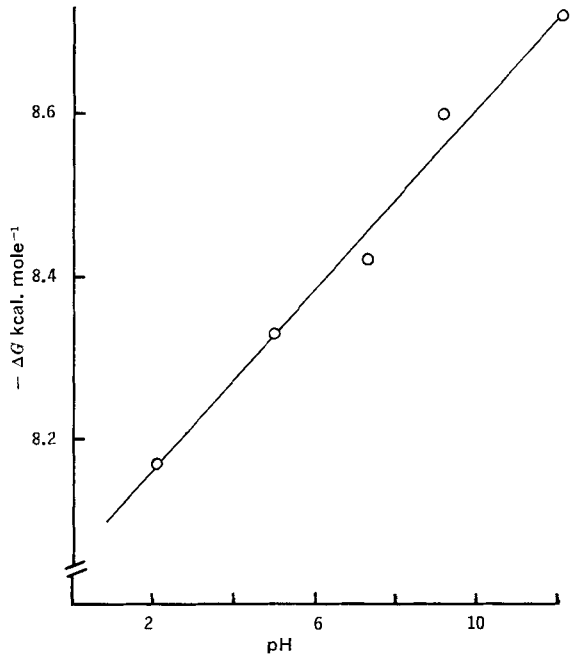

Figure 3—*Free energy of micellization at 25° as a function of pH.*

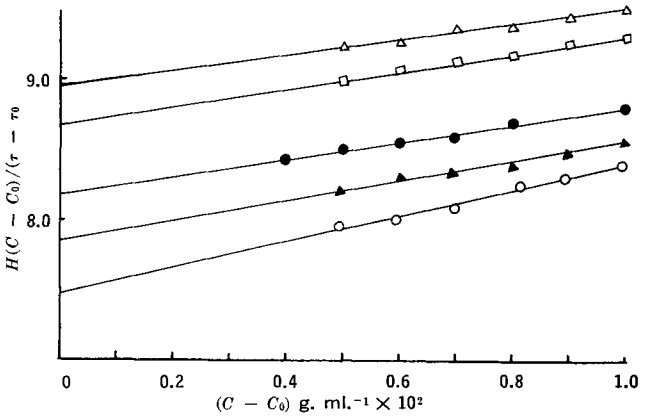

Figure 4—*Debye plots. Key: pH 2.1,* ○; *pH 5.2,* ▲; *pH 7.3,* ●; *pH 9.8,* □; *and pH 11.9,* △.

Chloride ions, however, are considered to be structure-breakers. The observed values for entropy of micellization will, of course, be greatly dependent upon the extent of water structure around the monomeric surfactant, as well as the structure and order of the micelle. Since the micelle is hydrated to a greater extent in acid solution, it is most likely that the palisade layer has a more open and flexible, and thus less ordered, structure than at high pH values. It is thus unlikely that the micelle in acid solution has a lower configurational entropy than that in alkaline solution since the structure of the hydrocarbon core is very probably independent of pH (12). This discussion is supported by the experimentally observed values of ΔS_m, 5 e.u. at pH 2.1 and 18 e.u. at pH 12.1, the larger entropy change being provisionally assigned as due to the greater degree of water structure at higher pH.

The enthalpy of micellization may be further resolved as shown in Eq. 6:

$$\Delta H_m = \Delta H_m^1 + \Delta H_m^2 \qquad \text{(Eq. 6)}$$

where ΔH_m^1 is the enthalpy change associated with the hydrophobic part of the surfactant and ΔH_m^2 is the enthalpy change associated with the head group. The difference in the estimated ΔH_m at pH values 2.1 and 12.1 which are −6.7 and −3.4 kcal. mole^{-1}, respectively, may therefore be expected to be due to several factors. Wurzshmitt (17) has suggested that nonionic surfactants are in fact weakly cationic in nature. The ionic nature of the head group and the extent of palisade layer hydration may thus be expected to be pH dependent. Since a greater amount of water structure is believed to exist around the surfactant molecules at high pH, the enthalpy change associated with the destruction of this "iceberg sheath" (18) would be expected to be greater than at low pH values. However, the enthalpy values shown in Table III are greater at low pH. Thus the other factors involved must more than compensate for this effect.

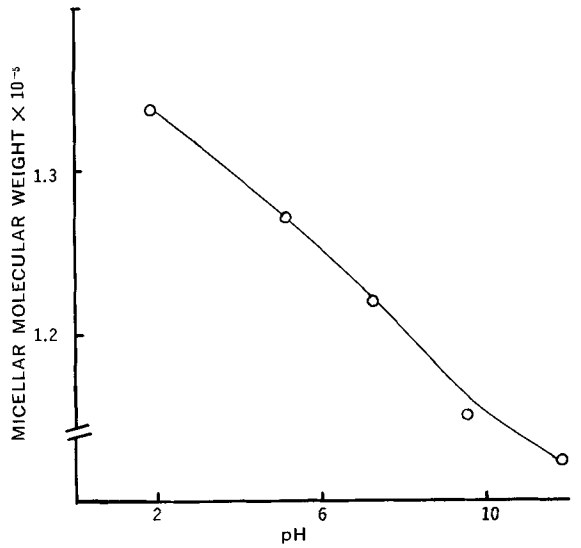

Figure 5—*Change in micellar molecular weight of surfactant with pH at 25°.*

Table III—Thermodynamic Parameters Controlling the Micellization

pH	ΔG_m kcal. mole^{-1}	ΔH_m kcal. mole^{-1}	ΔS_m cal. mole^{-1} $^0K^{-1}$
2.1	8.2	6.7	5
12.1	8.7	3.4	18

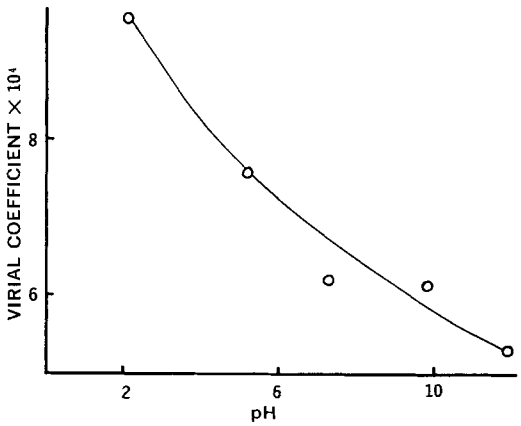

Figure 6—*Variation of second virial coefficient with pH.*

The reasons for the higher aggregation number at low pH cannot be precisely delineated at the present time. It may be that geometric limitations imposed by the differences in hydration with pH play a significant role. For a spherical micelle, changes in the hydration and thus in the size of the palisade layer must be accompanied by alteration in the aggregation number if the density of the hydrocarbon core is to remain constant.

There is no reason to suppose that the nonionic surfactant investigated in this study is unique of its type. It is therefore probable that other nonionic surfactants show similar significant changes in micellar properties with pH. Further work is necessary to see if the hypotheses outlined in this paper are of general applicability. In particular, information about the pH dependence of the interaction with drugs and the effect upon drug diffusion and transport is of considerable pharmaceutical relevance.

APPENDIX

The following computer program converts experimental light-scattering data into micellar molecular weights. The comment statement in the programs defines the symbols and explains the form of the imput data.

Imput Data

```
7
436
0.0327
1.333000
1.023
0.490   0.221   0.109   0.0336
5  4.85  4.73  4.70  4.72  4.78  0.0
5  2.55  2.53  2.57  2.52  2.55  0.0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
0.000063
1.333657  0.005
1.333788  0.006
1.333920  0.007
1.334051  0.008
1.33418   0.009
1.334314  0.010
3  5.27  5.25  5.24  0  0  0
```

```
3  4.88  4.87  4.88  0 0 0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
1  1  1  0.0336

3  5.13  5.12  5.12  0  0  0
3  4.00  4.00  3.99  0  0  0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
1  1  1  0.0336

3  5.25  5.23  5.22  0  0  0
3  3.54  3.53  3.54  0  0  0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
1  1  1  0.0336

2  5.20  5.20  0  0  0  0
2  5.00  5.00  0  0  0  0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
0.490  1  0.109  1

3  5.17  5.16  5.16  0  0  0
3  4.43  4.43  4.42  0  0  0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
0.490  1  0.109  1

3  5.21  5.20  5.20  0  0  0
3  4.08  4.07  4.07  0  0  0
1  0  0  0  0  0  0
1  0  0  0  0  0  0
0.490  1  0.109  1
```

Program

```
FMT. LIGHT SCATTERING ANALYSIS'
BEGIN
REAL R,Q,K,KI,FS,FF,Z,T,P,H,C1,C2,F1,F2,F3,F4,FS1,FS2,
  FS3,FS4,
A,B,AA,AI,BI,CCMC,TS'
INTEGER W,M,I,L,NN,J'
SWITCH S1:=LI'
READ M'
BEGIN
    REAL ARRAY S(1:4),SUM(1:4),D,C,CM,N(1:M),
      G(1:4,1:6),GS(1:4,1:6)'
    REAL PROCEDURE INNERPRODUCT (A,B,M,I)'
    REAL A,B' INTEGER M,I'
    BEGIN
        REAL SUM' SUM:=O'
        FOR I:=1 STEP 1 UNTIL M DO SUM:=SUM+
          (A*B)'
        INNERPRODUCT:=SUM'
    END OF INNERPRODUCT PROCEDURE'
    PROCEDURE F(X,Y,M,F,A,B)'
    REAL ARRAY X,Y' INTEGER M' REAL F,A,B'
    BEGIN
        REAL XBAR,YBAR' INTEGER I'
        XBAR:=YBAR:=O' FOR I:=1 STEP 1 UNTIL
          M DO
        BEGIN
            XBAR:=XBAR+X(I)'
            YBAR:=YBAR+Y(I)'
        END'
        XBAR:=XBAR/M' YBAR:=YBAR/M'
        F:=(INNERPRODUCT(X(I)-XBAR,Y(I)-YBAR,
          M,I))/
        (SQRT(INNERPRODUCT(X(I)-XBAR-X(I)
          -XBAR,M,I)*
        INNERPRODUCT(Y(I)-YBAR,Y(I)-YBAR,M,1)))'
        A:=INNERPRODUCT(X(I) -XBAR,Y(I)-YBAR,M,
        I)/INNERPRODUCT(X(I)-XBAR,X(I)-XBAR,M,I)'
        B:=(INNERPRODUCT(X(I),1,M,I)*
          INNERPRODUCT(X(I),Y(I),M,I)-
        INNERPRODUCT(Y(I),1M,I)*INNERPRODUCT
          (X(I),X(I),M,I))/
        (INNERPRODUCT(X(I),1,M,I)**2-M*
          INNERPRODUCT(X(I),X(I),M,I))'
    END OF F PROCEDURE'
COMMENT DATA IS GIVEN IN FORM
M- NUMBER OF SOLUTIONS INCLUDING SOLVENT
W- WAVELENGTH
AA- CONSTANT VARIABLE A
N(M) -REFRACTIVE INDEX OF SOLVENT
R- RW/RC, CORRECTION FACTOR
F1,F2,F3,F4- FILTERS USED FOR SOLVENT—IF NO
  FILTER USED
THEN PUT VALUE EQUAL TO 1
NN- NUMBER OF GALVO READINGS FOLLOWED BY
  GALVO READINGS FOR EACH OF
GS,GW,G45,G135,FOR SOLVENT—IF NUMBER OF
  READINGS LESS THAN 6 THEN ADD APPROPRIATE
  NUMBER OF ZEROS
CCMC-CONCENTRATION AT CMC
N- REFRACTIVE INDEX OF SOLUTION FOLLOWED BY
  CONCENTRATION C OF
SOLUTION FOR EACH OF THE M SOLUTIONS
NN - NUMBER OF GALVO READINGS FOLLOWED BY
  GALVO READINGS
FOR EACH OF GS GW G45 G135 FOR SOLUTION
  FOLLOWED BY FILTERS
USED (AS ABOVE) FOR EACH OF THE M SOLUTIONS'
READ W,AA,N(M),R,F1,F2,F3,F4' C(M):=O'
IF W=436 THEN Q:=1.25 ELSE IF W=546 THEN Q:=1.41'
K:=Q*R*AA'
KI:=(32*3.1428571**3)/(3*W**4*6.023*10**(-5))'
FOR J:=1 STEP 1 UNTIL 4 DO
BEGIN
    READ NN' S(J):=O'
    FOR I:=1 STEP 1 UNTIL 6 DO
    BEGIN
        READ G(J,I)'
        S(J):=S(J)+G(J,I)'
    END'
    S(J):=S(J)/NN'
END'
FF:=F1*F2*F3*F4' TS:=K*N(M)*N(M)*FF*S(1)/S(2)'
  READ CCMC'
FOR I:=1 STEP 1 UNTIL M-1 DO
    BEGIN
        READ N(I), C(I)'
        CM(I):=C(I)-CCMC'
    END'
F(C,N,M,C1,A,B)'
IF C1 LESSEQ 0.9 THEN
BEGIN
    PRINT £NO CORRELATION?'
    GOTO LI'
END ELSE PRINT FREEPOINT(5), £
CORRELATION RI VERSUS C= ?,SAMELINE,C1,£
AI= ?,SAMELINE,A,£ BI= ?,SAMELINE,B'
FOR L:=1 STEP 1 UNTIL M-1 DO
BEGIN SWITCH S2:=L2'
    FOR I:=1 STEP 1 UNTIL 4 DO
    BEGIN
        SUM(I):=O' READ NN'
        FOR J:=1 STEP 1 UNTIL 6 DO
        BEGIN
            READ GS(I,J)'
            SUM(I):=SUM(I)+GS(I,J)'
        END'
        SUM(I):=SUM(I)/NN'
    END'
    READ FS1,FS2,FS3,FS4'
    FS:=FS1*FS2*FS3*FS4'
    IF G(3,1)=0 AND G(4,1)=0 AND GS(3,1)=0 AND
    GS(4,1)=0 THEN GOTO L2 ELSE
    Z:=(FS*SUM(3)/SUM(2)-FF*S(3)/S(2))/
    (FS*SUM(4)/SUM(2)-FF*S(4)/S(2))'
    IF Z GREQ 0.7 AND Z LESSEQ 1.3 THEN GOTO LI'
    L2:P:=A*C(L)+B'
    T:=K*P*FS*SUM(1)/SUM(2)' T:=T-TS'
    H:=(KI*P*P*(P-N(M))**2)/(C(L)*C(L))'
    D(L):=(H*CM(L))/T'
END'
F(CM,D,M-1,C2,AI,BI)'
PRINT FREEPOINT (5),£
CORRELATION HCM/T VERSUS CM= ?, SAMELINE,C2,£
A2= ?,SAMELINE,AI,£ B2= ?,SAMELINE,BI' PRINT £
MOLECULAR WEIGHT= ?,SAMELINE,1/BI'
END'
LI:END OF PROGRAM'
```

Data Output

```
CORRELATION RI VERSUS C=1.0000
AI= .13142 BI = 1.3330
CORRELATION HCM/T VERSUS CM= .98405
A2= .00010 B2= .00001
MOLECULAR WEIGHT = 121761.14
END OF PROGRAM
```

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DRUG STANDARDS

Trifluoperazine Tablets: Alternative Methods of Analysis

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Abstract □ Procedures utilizing a direct spectrophotometric measurement (such as described in the British Pharmacopoeia) for the analysis of trifluoperazine tablets suffer from several disadvantages. The possibility of excipient interference is not precluded and this factor, coupled with use of a fixed reference absorptivity value, can sometimes lead to erroneous results. Therefore, alternative assay procedures are required to assess accurately the drug content. Two such methods are described. The first is the acid-dye type and involves the partitioning of a trifluoperazine-bromocresol purple complex between an aqueous buffer pH 6 and benzene containing 1% isoamyl alcohol and subsequent measurement of the yellow-colored organic phase at 410 mμ. Acidic and neutral compounds as well as the common excipients do not interfere. The second method employs an alkaline siliceous earth column through which the drug is eluted into a chloroform–methanol–HCl system and the absorbance measured at 259 mμ. The precision and accuracy of the alternative methods, as well as the pharmacopeial procedure are compared using commercial dosage forms and simulated drug–excipient mixtures.

Keyphrases □ Trifluoperazine tablets—analyses □ Acid-dye method—trifluoperazine analysis □ Column chromatography—analysis □ UV spectrophotometry—analysis □ Colorimetric analysis—spectrophotometer

The current BP method for the analysis of trifluoperazine hydrochloride tablets (1) involves dissolution of an aliquot sample of 20 powdered tablets and direct spectrophotometric measurement of the filtrate at 256 mμ using a fixed reference absorptivity value. Although the method is satisfactory in most cases, it suffers from the disadvantage of possible interference from excipients and also from both inter- and intrainstrumental variations. The latter variations may be considerable (2, 3) and introduce unsuspected error into the assay. Therefore, alternative assay procedures which are relatively free from interference and instrumental variation are required on occasion for products with assay results that are suspect by the pharmacopeial method.

While several methods have been reported in the literature as general procedures suitable for the analysis of piperazinyl phenothiazine drugs in pharmaceutical dosage forms and in biological media, there are virtually no data on their direct application to the analysis of trifluoperazine hydrochloride tablets. Blazek and Mares (4) determined drugs of the piperazinyl phenothiazine type gravimetrically by precipitation with silicotungstic acid or by electrochemical titration against the same reagent. Other electrochemical methods include controlled-potential coulometric analysis (5) and polarography (6), the latter being reported as having an accuracy of ±5% when applied to trifluoperazine hydro-