Resolution of Binary Mixtures by Partial Extraction and Specialized Spectrophotometric Techniques

By M. PERNAROWSKI and V. A. PADVAL†

One of the most common procedures in analytical chemistry is the separation of two substances by solvent–solvent extraction. Complete separation of the two ingredients in the binary mixture is, however, unnecessary for quantitative assay purposes. Simultaneous analysis of the ingredients is possible by using the relationship that exists between measured partition coefficients and the relative concentration of one of the substances in the binary mixture. The method is based on the distribution of the pure substances between two immiscible solvents and on specialized spectrophotometric techniques.

ONE OF THE FIRST steps in the analysis of a pharmaceutical is the separation of one or more of the ingredients from the bulk form of the dosage unit. This is most often carried out by the solvent–solvent extraction process based on the distribution law. Analytical conditions are usually so fixed that at the completion of the extraction process only one of the ingredients is present in one of the phases of the two-phase system. If these conditions are altered in such a way that both ingredients in a binary system are present in both phases, then a relationship is established between the measured partition coefficient of the mixture and the relative concentration of one of the ingredients in such a mixture. Furthermore, simultaneous analysis does not require the total separation of the ingredients but only partial separation under controlled conditions. This technique is thus analogous to the absorbancy ratio method of analysis described in previous publications (1, 2). The principles of controlled partial extraction are outlined in the literature (3, 4) but the procedures described therein differ from those in this paper in the types of measurements used to evaluate total concentrations and in the mathematical manipulations required in the analysis.

It is not the intention of the authors to discuss or elaborate on the subject of partition coefficients. The fundamentals inherent in the distribution law and the pitfalls associated with the determination of partition coefficients are set forth in textbooks on physical pharmacy (5) or physical chemistry (6). Factors such as temperature, phase volumes, association, dissociation, or chemical reaction of the component with one or both of the solvents must be considered in any investigation involving distribution between two immiscible solvents.

The spectrophotometric terminology and symbology used in this paper shall be that suggested by the National Bureau of Standards (7). Thus, absorbancy (A_s) is equal to the product of the absorbancy index (a_s), the cell length (b), and the concentration (c).

THEORY

When component X is distributed between two immiscible phases, the equilibrium state may be expressed mathematically in the following way

$$K_x = \frac{C_{xu}}{C_{xl}} \qquad \text{(Eq. 1)}$$

K_x, the partition coefficient, is thus equal to the ratio of the concentration of the X component in the upper layer (C_{xu}) to that in the lower layer (C_{xl}). Similarly, the partition coefficient for component Y, K_y, distributed between the same two solvents under similar experimental conditions, is defined as

$$K_y = \frac{C_{yu}}{C_{yl}} \qquad \text{(Eq. 2)}$$

The concentrations of Y in the upper and lower phases are equal to C_{yu} and C_{yl}, respectively. If the distribution of X is not influenced by Y and vice versa, the partition coefficient for the mixture (K_m) containing X and Y may be defined as

$$K_m = \frac{C_{xu} + C_{yu}}{C_{xl} + C_{yl}} \qquad \text{(Eq. 3)}$$

Received April 10, 1962, from the Pharmaceutical Chemistry Section, Food and Drug Directorate, Ottawa, Canada.
Accepted for publication June 7, 1962.
† Present address: New Custom House, Ballard Estate Bombay 1, India.

However, the sum of the concentrations in the two layers is equal to the total concentration of X, C_x, and Y, C_y, in the binary mixture. The concentration of X in the upper layer is thus equal to $C_x - C_{xl}$. This latter value is now substituted for C_{xu} in Eq. 1

$$K_x = \frac{C_x - C_{xl}}{C_{xl}} \qquad \text{(Eq. 4)}$$

Eq. 4 is rearranged

$$C_{xl} = \frac{C_x}{K_x + 1} \qquad \text{(Eq. 5)}$$

Using similar mathematical manipulations, Eq. 1 is defined in terms of C_x and C_{xu}

$$C_{xu} = \frac{K_x C_x}{K_x + 1} \qquad \text{(Eq. 6)}$$

In exactly the same way as shown in Eqs. 5 and 6, C_{yu} and C_{yl} are defined in terms of C_y. All of these quantities are substituted into Eq. 3

$$K_m = \frac{\frac{K_x C_x}{K_x + 1} + \frac{K_y C_y}{K_y + 1}}{\frac{C_x}{K_x + 1} + \frac{C_y}{K_y + 1}} \qquad \text{(Eq. 7)}$$

K_1 is equal to $K_x/(K_x+1)$, K_2 to $K_y/(K_y+1)$, K_3 to $1/(K_x+1)$, and K_4 to $1/(K_y+1)$. Each term in Eq. 7 is divided by $C_x + C_y$. $C_x/(C_x + C_y)$ is now equal to F_x, the fraction of X component in the binary mixture, and $C_y/(C_x + C_y)$ is equal to F_y, the fraction of Y component in the binary mixture

$$K_m = \frac{K_1 F_x + K_2 F_y}{K_3 F_x + K_4 F_y} \qquad \text{(Eq. 8)}$$

However, the sum of F_x and F_y is equal to 1. F_y is, therefore, equal to $1 - F_x$. This latter quantity is substituted for F_y above and the equation is rearranged

$$K_m = \frac{F_x (K_1 - K_2) + K_2}{F_x (K_3 - K_4) + K_4} \qquad \text{(Eq. 9)}$$

A plot of K_m *vs.* the fraction of X in the binary mixture is thus a curve, the extremities of which are equal to the partition coefficients of X, K_x, and Y, K_y. To use this equation K_m, K_x, and K_y must be assigned numerical values during the course of an analysis. This can be conveniently carried out by using the appropriate spectrophotometric techniques.

The determination of partition coefficients by carrying out absorbancy measurements on the two phases of the system has been previously described in the literature (8). Such measurements are usually carried out at those wavelengths at which the pure substance exhibits maximum absorption. Such a technique cannot be used to determine K_m since the phases contain two substances. The total concentration in any one phase can, however, be determined by carrying out absorbancy measurements at an isoabsorptive point, that is, that wavelength at which the two substances have the same absorbancy index value. Methods for locating such a point have been described in a previous publication (2).

At the isoabsorptive point, the following equations are valid

$$C_{xu} + C_{yu} = A_u/a \qquad \text{(Eq. 10)}$$

$$C_{xl} + C_{yl} = A_l/a \qquad \text{(Eq. 11)}$$

The absorbancy index value at the isoabsorptive point is equal to a. A_u is equal to the *total* absorbancy at the isoabsorptive point in the upper phase and A_l is equal to the *total* absorbancy at the isoabsorptive point in the lower phase.

The right-hand members of Eqs. 10 and 11 may now be substituted for K_m in Eq. 3

$$K_m = \frac{A_u/a}{A_l/a} = \frac{A_v}{A_l} \qquad \text{(Eq. 12)}$$

Therefore, a plot of A_u/A_l *vs.* F_x, the fraction of X in the binary mixture, is a curve, the extremities of which are equal to K_x and K_y. A binary mixture may now be analyzed by distributing the pure substances and the binary mixture between two immiscible solvents under controlled conditions.

Eq. 9 can yield only relative quantities but absolute analysis can be carried out by utilizing the above mathematical principles in a slightly different form. From Eqs. 1 and 2, C_{xu} is equal to $K_x C_{xl}$ and C_{yu} to $K_y C_{yl}$. The appropriate terms are substituted for C_{xu} and C_{yu} in Eq. 3

$$K_m = \frac{K_x C_{xl} + K_y C_{yl}}{C_{xl} + C_{yl}} \qquad \text{(Eq. 13)}$$

K_m is, however, equal to A_u/A_l and $C_{xl} + C_{yl}$ to A_l/a. C_{yl} is thus equal to $A_l/a - C_{xl}$. These quantities are substituted into Eq. 13

$$\frac{A_u}{A_l} = \frac{K_x C_{xl} + K_y (A_l/a - C_{xl})}{C_{xl} + (A_l/a - C_{xl})} \qquad \text{(Eq. 14)}$$

The equation is rearranged, each term is multiplied by a and divided by A_l

$$\frac{A_u}{A_l} = \frac{C_{xl}}{A_l}(aK_x - aK_y) + K_y \qquad \text{(Eq. 15)}$$

However, the total concentration of X, C_x, in the binary mixture is equal to $C_{xu} + C_{xl}$. Therefore, C_{xu} is equal to $C_x - C_{xl}$. This latter quantity is substituted into Eq. 1

$$C_{xl} = \frac{C_x}{K_x + 1} \qquad \text{(Eq. 16)}$$

The right-hand member of the above equation is substituted for C_{xl} in Eq. 15

$$\frac{A_u}{A_l} = \frac{C_x}{A_l} \cdot \frac{aK_x - aK_y}{K_x + 1} + K_y \qquad \text{(Eq. 17)}$$

A plot of A_u/A_l *vs.* C_x/A_l results in a straight line with a slope value of

$$\frac{aK_x - aK_y}{K_x + 1}$$

and an intercept value of K_y. Eq. 17 may now be used to determine the quantity of X component in the binary mixture.

An acetophenetidin-caffeine system was investigated to illustrate the method described herein.

EXPERIMENTAL

Apparatus.—(*a*) Beckman model DU spectro-

photometer; (*b*) Eberbach automatic shaker; (*c*) Thomas-Hoover capillary melting point apparatus.

Reagents and Solutions.—(*a*) Acetophenetidin, recrystallized from ethanol, the sample melted between 134.5 and 135.5°; (*b*) caffeine, recrystallized from ethanol, the melting point of the substance was 235.0–236.0°; (*c*) water, saturated with *n*-butanol: add 100 ml. of reagent grade *n*-butanol to 250 ml. of water, shake well, and allow to stand at room temperature for 30 min., filter the aqueous layer through Whatman No. 1 filter paper; (*d*) *n*-butanol, saturated with water: add 100 ml. of water to 250 ml. of reagent grade *n*-butanol, shake well, and allow to stand at room temperature for 30 min., filter the butanol layer through Watman No. 1 filter paper.

Spectral Characteristics of Acetophenetidin and Caffeine.—In water, acetophenetidin absorbs ultraviolet radiant energy most strongly at 245 mμ. Caffeine exhibits maximum absorption at 273 mμ. An isoabsorptive point occurs at 261.5 mμ. Methods for locating isoabsorptive points were described in a previous publication (2).

Solutions were prepared by dissolving the substance in 25.00 ml. of ethanol and diluting to 1 L. with water. Aliquots of such stock solutions were diluted with water to give final concentrations of approximately 8–10 mg. of substance per liter of solution.

Determination of Partition Coefficients.—To a weighed sample of either acetophenetidin or caffeine, add 25.00 ml. of *n*-butanol and 50.00 ml. of water. (References to *n*-butanol and water in the text of this paper imply the solutions described in the second part of this section.) Shake for 1 hour at room temperature. Allow the layers to separate, withdraw suitable aliquots, dilute to 1 L. with water, and determine absorbancy values. The *total* absorbancy in the butanol phase divided by the *total* absorbancy in the aqueous phase is equal to the partition coefficient for the substance.

The partition coefficient for caffeine was found to be 0.83 ±0.01. This value represents six determinations on samples ranging in weight from 0.1990 to 0.2136 Gm. Two-milliliter aliquots of the butanol phase and 4.00-ml. aliquots of the aqueous phase were taken for the determinations. The partition coefficient for acetophenetidin was equal to 16.40 ±0.09. Six samples, ranging in weight from 0.1274 to 0.2078 Gm., were processed in the manner described above. Aliquots of 1.00-ml. (butanol phase) and 25.00-ml. (aqueous phase) were used in the determinations.

Relative Analysis of Mixtures Containing Acetophenetidin and Caffeine.—A 200-mg. sample of the mixture was accurately weighed and transferred to a 125-ml. Erlenmeyer flask. Twenty-five milliliters of butanol and 50.00 ml. of water were added to the flask. The flask was continuously agitated for 1 hour at room temperature. Suitable aliquots were then taken for absorbancy measurements. For commercial preparations containing $2^1/_2$ grains of acetophenetidin and $^1/_2$ grain of caffeine, 2.00 ml. of the butanol phase and 20.00 ml. of the aqueous phase, diluted to 1 L., will give suitable absorbancy readings. All absorbancies were determined at 261.5 mμ. The total absorbancy in the butanol phase divided by the total absorbancy in the aqueous phase is equal to K_m. Eq. 9 may now be used in the analysis of the binary mixture. The numerical form of this equation is

$$K_m = \frac{0.489\ F_x + 0.545}{-0.489\ F_x + 0.546}$$

F_x is equal to the relative concentration of acetophenetidin in the binary mixture. The relative contration of caffeine in the mixture may be determined by subtracting F_x from 1, or by using an equation similar to that above but defined in terms of caffeine. The results of the analysis of 10 mixtures of acetophenetidin and caffeine are reported in Table I.

Table I.—Results of the Analysis of Mixtures Containing Acetophenetidin and Caffeine

Mixture	Acetophenetidin Present, %	Acetophenetidin Found, %	Caffeine Present, %	Caffeine Found, %
1	90.9	90.9	9.1	9.1
2	87.7	87.7	12.3	12.3
3	85.0	84.9	15.0	15.1
4	80.0	80.2	20.0	19.8
5	78.9	79.4	21.1	20.6
6	75.1	75.5	24.9	24.5
7	69.4	68.9	30.6	31.1
8	60.0	60.3	40.0	39.7
9	50.7	51.2	49.3	48.8
10	39.4	40.4	60.6	59.6

Absolute Determination of Acetophenetidin in Mixtures.—The analytical manipulations are identical to those described above. Eq. 17 must be put in its numerical form in order to complete the analysis. This was done by preparing 10 synthetic mixtures containing known quantities of acetophenetidin and caffeine, subjecting the mixtures to the above procedure, and substituting the appropriate numbers for A_u and A_l in Eq. 17. The data were plotted as shown in Fig. 1 and subjected to the method of least squares (9). The numerical form of Eq. 17 is

$$K_m = A_u/A_l = \frac{30.99\ C_p}{A_l} + 0.88$$

In the analysis of unknown mixtures, the total

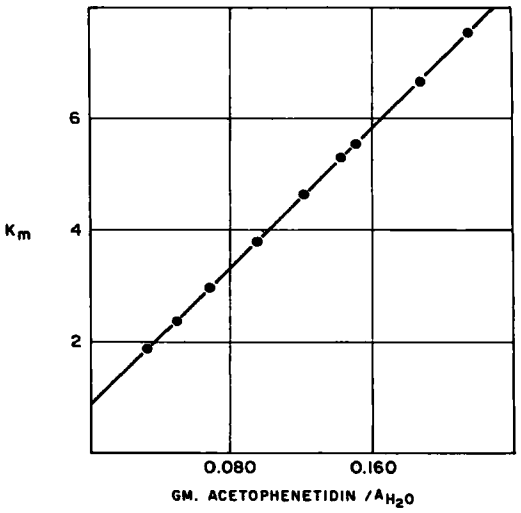

Fig. 1.—Calibration curve for the determination of acetophenetidin in the presence of caffeine.

absorbancy in the butanol phase (A_u) and the total absorbancy in the aqueous phase (A_l) are knowns. C_p, the concentration of acetophenetidin in the sample taken in the analysis, can then be calculated from the above equation. The results of the analysis of acetophenetidin in synthetic mixtures are shown in Table II.

TABLE II.—RECOVERY OF ACETOPHENETIDIN FROM MIXTURES CONTAINING ACETYLSALICYLIC ACID, ACETOPHENETIDIN, AND CAFFEINE

Acetophenetidin Present, Gm.	Acetophenetidin Recovered, Gm.	Recovery, Per Cent
0.1556	0.1531	98.4
0.1497	0.1512	101.0
0.1600	0.1597	99.8
0.1606	0.1606	100.0
0.1607	0.1609	100.1
0.1642	0.1641	99.9
0.1711	0.1732	101.2
0.1619	0.1603	99.0
0.1618	0.1617	99.9
0.1610	0.1603	99.6
Average Recovery		99.9
Standard Deviation		±0.8

Determination of Acetophenetidin in APC Tablets.—Add 50 ml. of chloroform to an amount of sample equivalent to one tablet. Shake to dissolve as much of the powdered material as possible and then add 10 ml. of 5% sodium bicarbonate solution. Shake, draw off the chloroform layer, and wash with 15 ml. of distilled water. Extract the combined bicarbonate and wash solutions with 2 × 15-ml. portions of chloroform. Wash the chloroform with 10 ml. of water, combine the chloroform extracts, filter through a pledget of cotton wool, wash the cotton wool with a few ml. of chloroform, and evaporate the organic solvent. To the residue, add water and butanol and continue as indicated above. The results of the analysis of a number of commercial preparations are shown in Table III.

TABLE. III.—RESULTS OF THE ANALYSIS OF COMMERCIAL PREPARATIONS CONTAINING ACETYLSALICYLIC ACID, ACETOPHENETIDIN, AND CAFFEINE

Product	Acetophenetidin per Tablet, mg. Label Claim	Found
A	129.6	125.8
		127.1
B	162.0	157.7
		154.8
C	162.0	156.0
		157.5
D	162.0	162.5
		160.5
E	162.0	166.6
		165.4

DISCUSSION

This method of analysis is based on a single but controlled extraction and on specialized spectrophotometric measurements. Although this confers a degree of specificity to the technique, it also limits its applicability to those binary mixtures which meet the conditions implied by the mathematical derivations. These limitations are mostly those associated with the distribution law and with the spectrophotometric measurements required by the assay.

Eq. 9 yields relative concentrations but places no limitations on the procedures used to determine K_m, K_x, and K_y. Eq. 12, on the other hand, specifies absorbancy measurements at an isoabsorptive point. Consequently, the two components in the binary mixture must characteristically absorb ultraviolet radiant energy and, more important, must show the presence of an isoabsorptive point when the absorbancy index–wavelength curves are superimposed. The exact nature of the spectrophotometric curves is not too important but if the spectrophotometric differences between the two substances are optimal, then some other method of analysis may prove to be faster and more accurate. This method of analysis is, therefore, applicable to those substances which have essentially similar spectral characteristics.

Eq. 9 implies that a plot of K_m *vs.* the relative concentration of one of the substances in the binary mixture should result in a curve. This was found to be experimentally true and such a curve is shown in Fig. 2. This curve is based on the data obtained by subjecting known mixtures of acetophenetidin and caffeine to the procedure described in the previous section. An examination of this figure indicates one of the limitations of this method of analysis. Even though the partition coefficients of the pure substances differ significantly, the rate of change of K_m with relative concentration is small in the 0 to 60% acetophenetidin region. Mixtures having concentrations defined by the above limits will not lend themselves to accurate analysis and consequently this method becomes inoperative. The reason for choosing the binary mixture containing acetophenetidin and caffeine to illustrate the applicability of this technique is thus almost self-evident.

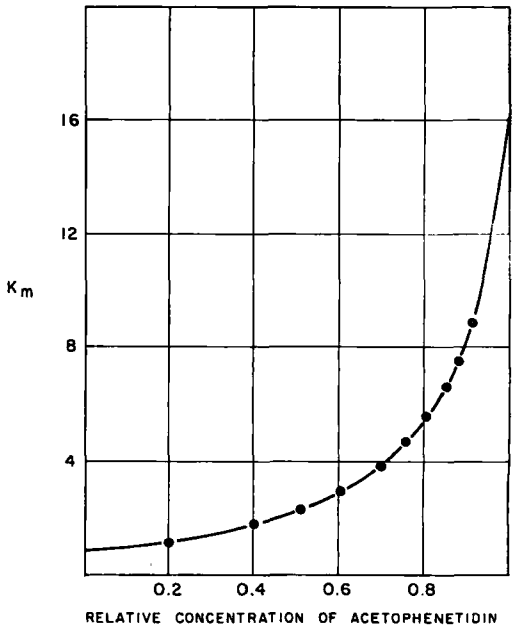

Fig. 2.—Partition curve for acetophenetidin and caffeine.

Commercial preparations usually contain 85 parts of acetophenetidin and 15 parts of caffeine. Fig. 2 shows that mixtures containing 85% acetophenetidin can be analyzed with good accuracy because the rate of change of K_m with respect to relative concentration is now considerably greater than that for lesser concentrations. A curve such as that shown in Fig. 2 must, therefore, be constructed in order to assess the relative accuracy of the method. If the particular mixture under investigation does not fall in an optimal range then some other method of analysis must be used.

The equations derived in the previous section imply that no spectrophotometric constants or partition values are required prior to analysis. Necessary data can be accumulated by analyzing synthetic mixtures or mixtures in which the absolute concentration of only one of the two substances is known. For example, the calibration curve illustrated in Fig. 1 can be constructed from data obtained by subjecting weighed quantities of acetophenetidin and unknown quantities of caffeine to the distribution process described in the previous section. The direct approach is to determine K_x, K_y, and a separately and then substitute the appropriate values into Eq. 17. This was done for the mixture investigated herein. When the determined partition and absorbancy index values at 261.5 mμ were substituted into Eq. 17, certain discrepancies between the numerical form so calculated and that reported in the previous section were observed. The slope value was found to be 31.59 and the intercept value 0.83. The latter value differs from that reported in the previous section by approximately 2%, a not unacceptable error. The discrepancy between intercept values is somewhat greater (that is, 0.83 as compared to 0.88). This discrepancy is not too significant provided the relative concentration of acetophenetidin is 60% or more and is probably due to the factors cited in the previous paragraph. It is preferable, therefore, to obtain the numerical form of Eq. 17 by the method of least squares from data obtained by analyzing actual mixtures of the two substances. This not only avoids a tedious, direct determination of constants but also serves as a check on the validity of Eq. 17.

The general shape of Fig. 2 is governed by the partition coefficient values of the two components and these, in turn, are governed by the volumes of the two phases used in the first step of the determination. By changing the ratio of one solvent to the other, the partition coefficient values will change and hence alter the accuracy of the method. For example, initial investigations on the acetophenetidin-caffeine mixture were carried out by using 50.00 ml. of *n*-butanol and 50.00 ml. of water. The results obtained under such circumstances were not as satisfactory as those shown in Table 1. The volumes were then changed to 25.00 ml. of *n*-butanol and 50.00 ml. of water in order to provide a more favorable distribution of the two components between the two immiscible solvents. This might be considered as one of the advantages of the method, that is, by altering volumes, the conditions of assay and hence the accuracy can be easily changed. On the other hand, it is somewhat difficult to determine optimal conditions for the most accurate analysis of the binary mixture. As a general rule, conditions should be so fixed that there is a maximal difference between the partition coefficient values of the pure substances. Substance solubility and ease of handling of smaller quantities of solvent will limit the applicability of this rule.

Any two immiscible solvents can be used in this type of analysis provided the two components of the mixture show complete solubility when subjected to the distribution procedure. The limitation here is the temperature coefficients of the particular solvents used in the analysis. All the determinations described in this paper were carried out at room temperature and because this temperature varied only slightly from day to day, the accuracy of the method was found to be excellent. This, of course, may not always occur (and, in fact, certain solvents are more susceptible to slight varations in temperature) and, consequently, a more accurate control of temperature would be necessary. This in itself is a disadvantage and implies a criticism of the method. There is yet a second factor to consider. Partition coefficient values depend not only on the volumes of the two phases but also on the inherent characteristics of the solvents. Although this was not investigated, changes in pH, for example, will alter the solubility of a particular substance in one of the phases and thus change the numerical value of the partition coefficient.

If the total weight of the mixture being analyzed is known, then relative concentrations can be easily converted to absolute quantities. Even though most methods of analysis begin with a weighing, the sample often contains substances other than those being analyzed. There is thus no way of determining the total weight of the active ingredients unless some secondary step is introduced into the method. The simplest approach is to carry out a complete isolation of the two components, determine the total weight, and then subject the mixture to the procedure described in the previous section. Another possible approach is to determine the absorbancy index value at the isoabsorptive point. The total absorbancy in both phases divided by the absorbancy index value is equal to total quantity of mixture present. The absolute concentrations of the two components can then be calculated. Both approaches suffer from a number of inherent errors. The gravimetric approach is tedious and does not guarantee that the isolated material being weighed is actually composed of only two substances. The spectrophotometric approach involves the determination of absorbancy index values at an isoabsorptive point. While this is feasible (2), the necessary manipulations are sufficiently involved to make this approach undesirable.

Eq. 17 provides an alternative approach. Since this is the equation of a straight line, it can be used in its numerical form, a form that can be easily calculated from data obtained on a restricted number of synthetic mixtures. Concentrations are now in absolute terms and are more meaningful when comparing the analytical result with the quantity claimed on a label or manufacturing ticket.

This method of analysis has an accuracy of approximately one per cent under ideal conditions. If secondary steps are introduced into the procedure in order to isolate the two substances being analyzed, the precision and accuracy of the method will be somewhat less than that shown in Tables I and II. There is no indication, however, that such

errors become excessive since the agreement between duplicate analyses of commercial preparation containing acetophenetidin is generally satisfactory.

CONCLUSION

Eq. 9 is fundamental to this general type of analysis. All the basic advantages and disadvantages associated with this method are found therein. It is important, therefore, to prepare a plot of K_m *vs.* relative concentration before attempting an analysis based on controlled partial separation. The importance of this is evident from Fig. 2. If such a curve shows that a simultaneous analysis of the components of a particular binary mixture is possible, then the method commends itself to the analyst. This method is particularly useful in those cases where the usual spectrophotometric methods of simultaneous analysis are not possible because of the similarity of the spectrophotometric curves of the components and where the usual solvent–solvent extraction techniques are not capable of completely separating the two components. Table I shows that the method is accurate and precise. The method, therefore, provides another approach to the basic problem of the analysis of complex pharmaceuticals.

REFERENCES

(1) Pernarowski, M., Knevel, A. M., and Christian, J. E., THIS JOURNAL, 50, 943(1961).
(2) Pernarowski, M., Knevel, A. M., and Christian, J. E., THIS JOURNAL, 50, 946(1961).
(3) Morton, C., and Tinley, E. H., *J. Pharm. Pharmacol.*, 8, 967(1956).
(4) Bontemps, R., *Svensk Farm. Tidskr.*, 61, 203(1957).
(5) Martin, A. N., "Physical Pharmacy," Lea & Febiger, Philadelphia, 1960.
(6) Moore, W. J., "Physical Chemistry," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1955.
(7) U. S. Dept. Commerce, National Bureau of Standards, LC 484, September 1949.
(8) Garrett, E. R., and Woods, O. R., THIS JOURNAL, 42, 736(1953).
(9) Wallis, W. A., and Roberts, H. V., "Statistics A New Approach," The Free Press, Glencoe, 1956, p. 252.

Investigation of the Sedimentation Behavior of Dispersions

By AMY MOORE† and A. P. LEMBERGER

Using a modification of the method of Greiner and Vold, suspension isotherms were obtained for dispersions of zinc oxide, calcium carbonate, and bismuth subcarbonate in sodium lauryl sulfate, dioctyl sodium sulfosuccinate and sodium-salts of polymerized alkylnaphthalenesulfonic acids (Daxad 11) solutions. For zinc oxide and bismuth subcarbonate systems maximum suspendability was reached at surfactant concentrations somewhat beyond the critical micelle concentration and extended over a relatively short concentration range. In the case of calcium carbonate, limited suspendability was observed with all three surfactants. Previous workers attribute the reduction in suspendability at higher surfactant concentrations to a reduction in zeta potential, thus permitting increased aggregation. Suspension isotherms obtained at constant and varying ionic strengths of sodium chloride indicate that aggregation is facilitated by the presence of excess surfactant through some additional mechanism.

THE SEDIMENTATION behavior exhibited by a dispersion has long been recognized as being of interest and importance pharmaceutically. Separation of phases in a polyphase pharmaceutical product can result in failure to provide uniform doses of the drug or drugs suspended.

One phenomenon which may occur and contribute to increased rates of sedimentation in these dispersions is aggregation (1). Thus, a number of investigations of sedimentation or creaming rates have been made and aggregation behavior deduced in a qualitative or semiquantitative fashion (1–5).

Further interest in the phenomenon of aggregation arises from the observation that in addition to the effect on physical stability, aggregation may also contribute to the flow properties exhibited by emulsions and suspensions (6). Recently, W. I. Higuchi, Okada, and Lemberger (7) reported on the reversible aggregation-deaggregation of hexadecane-in-water emulsions containing dioctyl sodium sulfosuccinate (AOT). In this study a procedure involving rapid counting and sizing of droplets as a function of time was employed, thus permitting direct determination of aggregation in the system.

Received March 27, 1962, from the School of Pharmacy, University of Wisconsin, Madison.
Accepted for publication July 7, 1962.
This work was supported in part by grant A2649 from the National Institutes of Health, Bethesda, Md.
† Present address: Mead Johnson & Co., Evansville, Ind.