Fig. 5.—Comparison of Simoons' experimental data (5) with Eq. 17.

GENERAL DISCUSSION

The several solutions to the release behavior of the systems considered are believed to be essentially exact for the models employed. Experimental data available appear to substantiate these analyses (5).

In real systems, however, a number of other factors may come into play which may modify the total behavior. The models employed assume that the systems are neither surface coated, nor that their matrices undergo significant alteration in the presence of moisture. Since in real systems these play varying roles in modifying the release pattern of sustained-action dosage forms, any attempt to apply these equations must be made with this in mind.

Other serious deviations from the derived relationship may occur for systems which tend to differ significantly from the adopted models. For example, for pellets containing a relatively high percentage of drugs the leaching process would tend to weaken the matrix structure and produce erosion. This may play a significant role in altering the observed real rate. Another effect which is not considered in these treatments is the influence of solvent flow induced within the pellets by external agitation. This effect, however, will be important only with pellets of relatively high porosity.

In Fig. 5 data reported by Simoons in his interesting paper on experimental measurements of release rate of sustained-action medication (6) for relatively insoluble drug hard compressed (his Fig. 15) are plotted in the form of square of fraction released against extraction time. The extraction data show a short lag time probably corresponding to that required to wet the pellets. This is followed by a release pattern closely matching that predicted by Eq. 17, the smooth line representing the theoretical values and the points, the experimentally observed values reported by Simoons. The total theoretical curve was based on experimentally observed time for 50% release and the initial lag time.

REFERENCES

(1) Lazarus, J., and Cooper, J., THIS JOURNAL, **50**, 715 (1961).
(2) Wiegand, R. G., and Taylor, J. D., *Drug. Std.*, **27** 165(1959).
(3) Wagner, J. G., *ibid.*, **27**, 178(1959).
(4) Higuchi, T., THIS JOURNAL, **50**, 874(1961).
(5) Lazarus, J., and Cooper, J., private communication.
(6) Simoons, J. R. A., "Formulation and Experimental Evaluation of Oral Sustained Release Medication Based on the Principle of Delayed Diffusion," Drukkerij Wed. G. Van Soest N. V., Amsterdam, The Netherlands, 1962.

Dielectric Constants of Complex Pharmaceutical Solvent Systems I

Water-Ethanol-Glycerin and Water-Ethanol-Propylene Glycol

By D. L. SORBY, R. G. BITTER, and J. G. WEBB

Dielectric constants of water-ethanol-glycerin and water-ethanol-propylene glycol systems have been experimentally determined. The measured values were found to differ from values calculated according to simplification of the Onsager-Kirkwood equation, regardless of whether composition of the various solutions was expressed on the basis of weight percentage or volume percentage. Dielectric constant values presented in this paper are recommended for precise adjustment of solvent polarity in formulation work and data are presented to be of maximum use in this respect.

MOORE (1) HAS PRESENTED a method wherein manipulation of solvent dielectric constant is utilized to produce dissolution of a solute at a desired concentration and to blend pharmaceutical solvents to a predetermined degree of polarity. In this method, certain simplifying

assumptions are made, one being that the dielectric constant of a complex solvent mixture may be calculated to a good approximation by taking the sum of the products of volume composition and dielectric constant for each individual component in the mixture. This method of calculating dielectric constants of complex mixtures is based on a simplification of the Onsager-Kirkwood

equation and would theoretically be correct only if the mixture of substances exhibited properties of an ideal solution. Since most common pharmaceutical solvent systems are composed of substances which exhibit a high degree of intermolecular association and are seldom ideal in their behavior, dielectric constants of such systems would not usually be expected to be a simple additive function of the concentrations of the components as described above. In these situations, the method of obtaining the dielectric constant by calculation would be expected to give only rough approximations of the true value for the solvent mixture in question. It was also stated (1) that while more precise work would require that compositions of the solvent mixtures be stated on the basis of weight per cent, volume compositions could be substituted in the calculations for convenience in formulation work. It was

implied that as a result of expressing concentration on a volume percentage basis, the calculated values would not be as precise as when weight per cent had been used.

Decroocq and Jungers (2), however, have presented data showing that if concentrations of the individual components are expressed on the basis of volume percentage when using the simplified form of the Onsager-Kirkwood equation described above, agreement between experimental and calculated dielectric constants is better than when concentrations are expressed on the basis of mole fraction. From results of studies on binary mixtures exhibiting ideal or nearly ideal behavior, Decroocq and Jungers estimated that calculated values would usually be within 1% of experimental values when volume percentage is used as the concentration variable. Their report also presented data showing large deviations between experimental and calculated dielectric constants when the binary solutions studied were non-ideal in their behavior.

Thus one might expect that use of volume per-

TABLE I.—SUMMARY OF DATA OBTAINED FOR TEST SAMPLES IN THE WATER-ETHANOL-GLYCERIN SYSTEM AT 25°C.[a]

Ratio of Glycerin to Ethanol[c]	Water Content of Test Sample[b]				
	20% w/w	40% w/w	60% w/w	80% w/w	Other
1:0	52.4 (1.2107)	62.6 (1.1594)	68.9 (1.1024)	74.2 (1.0487)	[d]
	52.2	62.5	70.0	75.1	
4:1	45.7 (1.1266)	57.0 (1.0971)	67.3 (1.0656)	74.0 (1.0325)	[e]
	45.6	55.9	67.7	73.7	
7:3	44.4 (1.0814)	54.9 (1.0678)	64.8 (1.0479)	72.3 (1.0244)	[f]
	44.1	55.3	64.8	72.1	
1:1	38.4 (1.0027)	50.1 (1.0166)	61.6 (1.0135)	71.5 (1.0062)	
	38.5	50.1	61.7	71.1	
3:7	36.3 (0.9330)	46.0 (0.9600)	58.9 (0.9812)	70.3 (0.9917)	
	36.2	46.5	59.1	70.5	
1:4	34.5 (0.9003)	44.2 (0.9366)	57.3 (0.9640)	69.3 (0.9832)	
	34.4	44.4	57.0	69.7	
0:1	31.7 (0.8423)	54.2 (0.9351)	41.2 (0.8900)	68.1 (0.9704)	[g]
	31.6	54.0	41.4	68.1	

[a] The first figures in each section are dielectric constant values measured for the duplicate samples. The figure in parenthesis is the specific gravity of one test sample. [b] The amount of water contained in the commercial products of ethanol and glycerin was included in calculation of the water content of test samples. [c] These ratios represent the ratio of 100% glycerin to 100% ethanol. Water contained in the commercial products of ethanol and glycerin was accounted for in preparing all samples. [d] 5.0% w/w—43.0, 43.0. [e] 5.0% w/w—38.2, 38.2 (1.1397); 10% w/w—40.8, 40.7 (1.1382). [f] 10.0% w/w—38.7, 38.4 (1.0847); 15% w/w—41.2, 41.2 (1.0855). [g] 7.7% w/w 24.9, 25.2 (0.8107); 50.0% w/w—46.8, 47.0 (0 9132).

TABLE II.—SUMMARY OF DATA OBTAINED FOR TEST SAMPLES IN THE WATER-ETHANOL-PROPYLENE GLYCOL SYSTEM AT 25°C.[a]

Ratio of Propylene Glycol to Ethanol[c]	Water Content of Test Sample[b]				
	20% w/w	40% w/w	60% w/w	80% w/w	Other
1:0	38.6 (1.0742)	49.5 (1.0417)	62.4 (1.0313)	71.0 (1.0155)	
	40.1	51.5	63.2	72.0	
4:1	37.3 (0.9976)	48.6 (1.0089)	61.0 (1.0115)	70.9 (1.0049)	
	38.0	48.6	60.8	71.2	
3:2	36.2 (0.9548)	46.6 (0.9791)	59.4 (0.9918)	70.7 (0.9935)	[d]
	36.1	46.7	60.0	71.0	
2:3	33.7 (0.9135)	42.6 (0.9475)	57.3 (0.9720)	69.6 (0.9843)	[e]
	34.6	45.0	58.1	70.0	
1:4	32.5 (0.8777)	41.1 (0.9180)	54.2 (0.9532)	68.4 (0.9724)	[f]
	33.3	43.6	57.3	70.3	
0:1	31.7 (0.8423)	54.2 (0.9351)	41.2 (0.8900)	68.1 (0.9704)	[g]
	31.6	54.0	41.4	68.1	

[a] The first figures in each section are dielectric constant values measured for the duplicate samples. The figure in parenthesis is the specific gravity of one test sample. [b] The amount of water contained in the commercial samples of ethanol and propylene glycol was included in calculation of the water content of test samples. [c] These ratios represent the ratio of 100% propylene glycol to 100% ethanol. Water contained in commercial products was accounted for in preparing all samples. [d] 3.1% w/w—26.0, 25.8 (0.9302); 10% w/w—30.7, 30.7 (0.9431). [e] 5.0% w/w—25.9, 25.9 (0.8886); 12% w/w—30.0, 30.1 (0.9014). [f] 10% w/w—27.8, 27.7 (0.8566); 15% w/w—30.5, 30.5 (0.8649). [g] 7.7% w/w—24.9, 25.2 (0.8107); 50% w/w—46.8, 47.0 (0.9132).

centage in these calculations should not produce less precise results than when alternative methods, such as weight per cent or mole fraction, are used for expressing concentrations of the various components of a system.

In actual practice, precise values of dielectric constants of complex, multi-component solutions can best be obtained by direct experimental measurement. The scientific literature contains much data pertaining to dielectric constants of binary mixtures, *e. g.*, (2–5), but little information concerning the more complex mixtures utilized in pharmaceutical formulations. The objectives of this research were to (*a*) determine relationships existing between dielectric constant and composition experimentally in two common pharmaceutical solvent systems, water-ethanol-glycerin and water-ethanol-propylene glycol, (*b*) determine the accuracy of calculated dielectric constants and the method of expressing compositions (weight percentage, or volume percentage) producing the better agreement between experimental and calculated values for these complex systems. Information of this type would be useful for precise adjustment of solvent polarity in pharmaceutical formulation work and, in addition, would be of potential interest to various types of physicochemical investigations of the behavior of these complex non-ideal systems.

EXPERIMENTAL

Materials and Reagents.—Since data were desired for systems actually encountered in pharmaceutical formulation practice, the materials used in this study were of commercially available grades. The following materials were used without further purification; ethanol, 92.3% w/w; propylene

glycol, 99.5% w/w; and glycerin, 95.0% w/w. Distilled water was used in preparing all samples.

Acetone, reagent grade, was distilled over calcium chloride and stored, protected from atmospheric moisture, until needed for calibrating the instrument used to measure dielectric constants of the test mixtures.

Preparation of Test Samples and Collection of Data.—Sets of test mixtures were prepared so that in a given set all samples contained the same ratio of ethanol to glycerin or ethanol to propylene glycol. The water content of mixtures in each set was varied throughout a range of concentration, usually including samples containing 20, 40, 60, and 80% by weight of water. The amount of water present in the stock solutions of ethanol, propylene glycol, and glycerin was taken into consideration in all calculations of solvent composition. Duplicates were prepared of each different sample.

The required amount of each ingredient needed to make a 100-Gm. quantity of sample was weighed with an accuracy of ±0.05 Gm. into glass-stoppered Pyrex bottles. The bottles were then immersed in a constant temperature bath at 25.0°. When thermal equilibrium was established, the specific gravity of each sample was determined by the pycnometer method using water at 25.0° as the reference solution. The remainder of the sample was returned in the thermostat until measurement of the dielectric constant was performed.

Dielectric constants of the test mixtures were determined with a Sargent, model V, chemical oscillometer standardized with water-acetone mixtures of known dielectric constant (6). Approximately 10 ml. of the test sample was pipetted into

TABLE III.—WEIGHT COMPOSITIONS OF THE WATER-ETHANOL-GLYCERIN SYSTEM WHICH ARE EXPECTED TO GIVE IDENTICAL DIELECTRIC CONSTANT VALUES

Dielectric Constant Value	Water, % w/w	Ethanol, % w/w	Glycerin, % w/w
70	61.7	0	38.3
	67.8	6.4	25.8
	73.5	8.0	18.5
	76.0	12.0	12.0
	79.3	14.5	6.2
	80.6	15.5	3.9
	82.8	17.2	0
60	34.7	0	65.3
	45.4	10.9	43.7
	49.8	15.1	35.1
	56.2	21.9	21.9
	61.8	26.7	11.5
	64.3	28.6	7.1
	68.4	31.6	0
50	16.5	0	83.5
	28.6	14.3	57.1
	30.5	20.8	48.7
	39.6	30.2	30.2
	45.7	38.0	16.3
	48.8	41.0	10.2
	54.3	45.7	0
40	8.7	18.3	73.0
	12.8	26.2	61.0
	20.4	39.8	39.8
	29.5	49.4	21.1
	33.3	53.4	13.3
	37.5	62.5	0

TABLE IV.—WEIGHT COMPOSITIONS OF THE WATER-ETHANOL-PROPYLENE GLYCOL SYSTEM WHICH ARE EXPECTED TO GIVE IDENTICAL DIELECTRIC CONSTANT VALUES

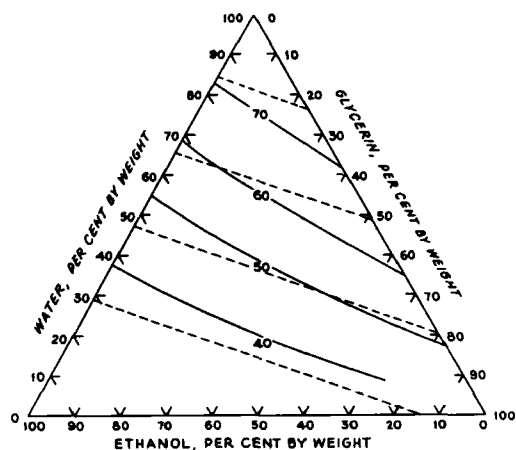| Dielectric Constant Value	Water, % w/w	Ethanol, % w/w	Propylene Glycol, % w/w
70	74.8	0	25.2
	77.7	4.5	17.8
	78.7	8.5	12.8
	79.0	12.6	8.4
	81.5	14.8	3.7
	82.8	17.2	0
60	55.8	0	44.2
	58.5	8.3	33.2
	60.5	15.8	23.7
	61.5	23.1	15.4
	66.4	26.9	6.7
	68.4	31.6	0
50	40.0	0	60.0
	41.5	11.7	46.8
	45.3	21.9	32.8
	47.5	31.5	21.0
	51.7	38.6	9.7
	54.3	45.7	0
40	21.5	0	78.5
	24.5	15.1	60.4
	28.2	28.7	43.1
	32.5	40.5	27.0
	35.2	51.8	13.0
	37.5	62.5	0
30	9.3	36.3	54.4
	12.0	52.8	35.2
	14.3	68.6	17.1
	17.0	83.0	0

Fig. 1.—Dielectric constant-weight percentage relationships for the system water-ethanol-glycerin. Key: ————, experimental; - - - - -, calculated.
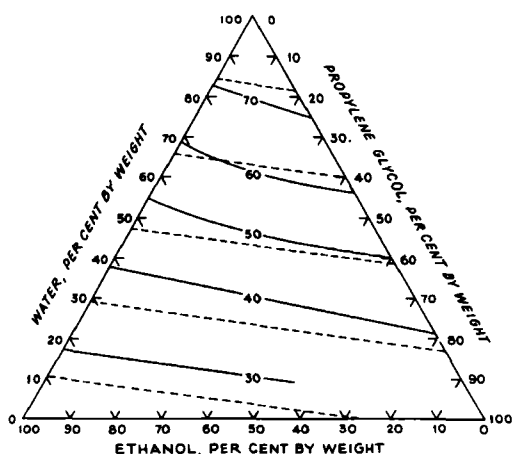

Fig. 2.—Dielectric constant-weight percentage relationships for the system water-ethanol-propylene glycol. Key: ————, experimental; - - - - -, calculated.
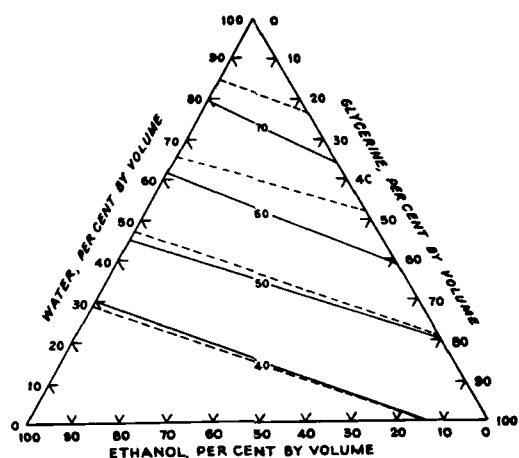
the test cell of the oscillometer and the scale reading recorded. This measurement was made in duplicate for each sample, the test cell being cleaned and dried between each reading. The dielectric constant for each test mixture was obtained by comparing the scale reading on the oscillometer to a standard curve constructed by plotting dielectric constant against scale reading for the water-acetone standards described above.

Specific gravity and dielectric constant values determined for the various samples in the two systems of solvents tested are given in Tables I and II.

Treatment of Data.—Plots of dielectric constant *versus* weight per cent water were made for each set of samples having the same constant ratio of ethanol to glycerin or ethanol to propylene glycol. Water concentrations which theoretically would have been needed to produce samples having dielectric constant values of 70, 60, 50, etc., in each set were determined from curves drawn through points representing the experimental data. The amount of ethanol and glycerin or propylene glycol in each hypothetical sample was determined from a knowledge of their ratio in the sample and the difference between the per cent water and 100%. These derived solvent compositions (Tables III and IV) were plotted on a ternary diagram and tie lines were drawn which best fitted all points representing solutions expected to exhibit the same dielectric constant (Figs. 1 and 2). The per cent by volume compositions of the test samples were calculated by the usual methods from knowledge of their weight per cent compositions and experimentally determined specific gravities. Solutions theoretically giving dielectric constants of 70, 60, 50, etc., were determined graphically and plotted on ternary diagrams as described above (Figs. 3 and 4). The values derived from the experimental data and used to prepare Figs. 3 and 4 are summarized in Tables V and VI.

Dielectric constants measured for solutions of compositions given by points picked at random from the curves in Figs. 1–4 verified the accuracy of these curves as being within ±0.5 units of the dielectric constant specified for the given curve.

Fig. 3.—Dielectric constant-volume percentage relationships for the system water-ethanol-glycerin. Key: ————, experimental; - - - - -, calculated.
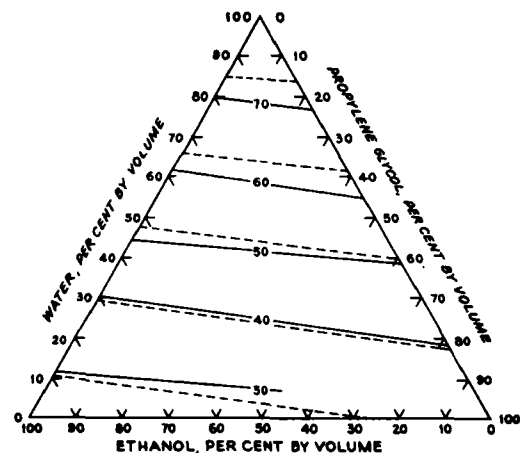

Fig. 4.—Dielectric constant-volume percentage relationships for the system water-ethanol-propylene glycol. Key: ————, experimental; - - - - -, calculated.

TABLE V.—VOLUME COMPOSITIONS OF THE WATER-ETHANOL-GLYCERIN SYSTEM WHICH ARE EXPECTED TO GIVE IDENTICAL DIELECTRIC CONSTANT VALUES

Dielectric Constant Value	Water, % v/v	Ethanol, % v/v	Glycerin, % v/v
70	66.2	0	33.8
	68.5	9.0	22.5
	74.7	10.3	15.0
	75.6	15.0	9.4
	76.5	18.5	5.0
	77.8	19.2	3.0
	79.5	20.5	0
60	38.7	0	61.3
	47.5	15.0	37.5
	48.9	20.8	30.3
	54.8	27.8	17.4
	57.5	33.5	9.0
	59.6	35.0	5.4
	61.6	38.4	0
50	18.8	0	81.2
	28.0	20.5	51.5
	29.5	28.7	41.8
	37.1	38.7	24.2
	41.2	46.4	12.4
	43.2	49.2	7.6
	47.0	53.0	0
40	7.7	26.3	66.0
	11.3	36.1	52.6
	19.6	49.5	30.9
	24.6	59.5	15.9
	26.7	63.5	9.8
	30.2	69.8	0

TABLE VI.—VOLUME COMPOSITIONS OF THE WATER-ETHANOL-PROPYLENE GLYCOL SYSTEM WHICH ARE EXPECTED TO GIVE IDENTICAL DIELECTRIC CONSTANT VALUES

Dielectric Constant Value	Water, % v/v	Ethanol, % v/v	Propylene Glycol, % v/v
70	77.0	0	23.0
	77.0	5.7	17.3
	76.5	11.0	12.5
	76.6	15.5	7.9
	77.9	18.6	3.5
	79.5	20.5	0
60	55.0	0	45.0
	56.8	10.7	32.5
	57.6	19.8	22.6
	59.8	26.7	13.5
	60.0	33.6	6.4
	61.6	38.4	0
50	38.8	0	61.2
	40.2	14.8	45.0
	41.2	27.5	31.3
	43.5	37.5	19.0
	42.4	48.4	9.2
	47.0	53.0	0
40	18.8	0	81.2
	23.3	19.0	57.7
	24.3	35.4	40.3
	25.7	49.3	25.0
	25.8	62.3	11.9
	30.2	69.8	0
30	6.8	43.6	49.6
	8.8	60.5	30.7
	10.7	75.0	14.3
	11.8	88.2	0

DISCUSSION

In Figs. 1 and 2, dielectric constants have been plotted as a function of both calculated and experi-mentally determined solvent composition. It is apparent that rather large deviations exist between theoretical and experimental values. In addition, dielectric constant is not in most cases in these systems a linear function of the weight composition. These deviations are not unexpected when one considers the strong tendencies for interaction between the molecular species involved. While data for other ternary solvent systems are lacking in the scientific literature, deviations of this magnitude are found when calculated values of dielectric constants are compared with data of other investigators (3, 5) for water-ethanol and water-glycerin systems. Values of dielectric constants reported in the literature (3, 5) are in general good agreement with the values reported here, considering differences in methodology and sample purity.

Results shown in Figs. 3 and 4 indicate that curves relating dielectric constant and volume composition of samples are linear, although agreement between experimental and calculated values is poor, except in the solutions where dielectric constants equal 40 and 50. Moore (1) noted that deviations of dielectric constant from the direct proportionality predicted by mathematical computation should be more pronounced as polarity of the mixtures increases. Such is indeed the case in the two systems studied. The nature of the curves does indicate that dielectric constants in these systems are apparently some type of linear function of the concentration of the various components expressed on a volume basis; however, because of the various complexities of these systems, no simple relationship appears to exist between dielectric constants of the mixtures and those of the pure components which would allow computation by the simplified form of the Onsager-Kirkwood equation. There seems to be no major advantage to expressing concentrations on a weight basis; in fact, use of volume percentage appears to be of some benefit in regard to ease of fitting curves through the experimental points.

It has been our experience that the dielectric constant principle of blending solvent systems as outlined by Moore (1) sometimes fails to produce the desired results when used in actual practice. It is quite possible that some of these failures have been because of the large differences which can occur between calculated and actual dielectric constant values in these complex systems. We hope that the dielectric constant–composition relationships obtained as a result of our investigation can serve to place this useful technique of solvent blending on a more reliable basis. Experimental determinations of dielectric constants of other pharmaceutical systems and other important aspects of the relationships between solubility and dielectric constants are being continued and will be reported at a later date.

REFERENCES

(1) Moore, W. E., THIS JOURNAL, **47**, 855(1958).
(2) Decroocq, D., and Jungers, J. C., *Compt. Rend.*, **252**, 1454(1961).
(3) Hall, J. L., and Phillips, H. O., *Proc. West Va. Acad. Sci.*, **26**, 26(1954).
(4) Critchfield, F. E., Gibson, J. A., Jr., and Hall, J. L., *J. Am. Chem. Soc.*, **75**, 1991(1953).
(5) Harned, H. S., and Owen, B. B., "The Physical Chemistry of Electrolytic Solutions," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1958, p. 161.
(6) Sherrick, P. H., Dawe, G. A., Karr, R., and Ewen, E. F., "Manual of Chemical Oscillometry," E. H. Sargent and Co., Chicago, Ill., 1954, p. 34.