Investigation of Factors Influencing Release of Solid Drug Dispersed in Inert Matrices

By S. J. DESAI*, A. P. SIMONELLI, and W. I. HIGUCHI

A number of factors controlling the rate of drug release from plastic matrices were investigated. It was found that the choice of plastic, weight of drug incorporated in matrix, solubility of drug used, matrix additives, and solvent could markedly affect the release rate. The changes in experimental drug release behavior as a function of these variables were determined and compared to the expected results determined from theory. The matrix tortuosity factor was studied by leaching drug from tablet and then resaturating the porous matrix with a 5 per cent sodium salicylate solution. The release rate of sodium salicylate from these resaturated matrices were determined, and relative tortuosities were calculated.

RECENTLY, Higuchi proposed that the rate of release of drug from one surface of an insoluble matrix would be governed by the following relationship (1):

$$Q = \left(\frac{D\epsilon C_s}{\tau}(2A - \epsilon C_s)t\right)^{1/2}$$

where Q is the grams of drug released per unit area of surface at time, t, D is the diffusion coefficient of drug in release medium, ϵ is the porosity of the matrix, C_s is the solubility of drug in release medium, τ is the tortuosity of the matrix, and A is the concentration of drug in tablet expressed as Gm./ml.

This report will discuss the results of a preliminary investigation of its applicability to the study of release rates of drugs from matrices. The importance of this study need not be emphasized as this has been adequately discussed in recent publications (2–4). Theoretically, any variable in the equation could be utilized to govern the rate of release, providing its variability can be controlled. Before this can be accomplished, however, there must be available a method by which each variable can be measured.

The method of attack was simple. The equation predicts a straight-line relationship if the amount of drug released per unit area is plotted *versus* the square root of time. A series of experiments would be designed in such a way as to vary only one variable in a predetermined manner and hopefully keep all other variables constant. The slopes of the various curves obtained would be compared, and in this way the effect of the controlled variation on the rate of release could be determined. This result would then be compared with the theoretical effect predicted by the equation.

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EXPERIMENTAL

Tablets were made by compressing 500 mg. of a uniform drug–plastic mixture using a Carver press at a force of 10,000 lb. with a 0.5-in. flat-face die and punch. The weight and dimensions of each tablet were accurately determined.

The tablets were embedded in wax by coating the lateral and one of the flat sides with molten beeswax, thereby exposing only one flat surface of the tablet for drug release. Excess wax on the sides was removed using a proper size cork borer. After the waxed tablet was pushed into a glass tube which was slightly smaller than the cork borer used, additional melted wax was added from the open end of the tube to insure proper sealing.

The apparatus used for this study is shown in Fig. 1. The apparatus consists of a jacketed glass beaker containing 500 ml. of the solvent maintained at 30° by circulation of water through the jacket. The beaker was closed on the top by a

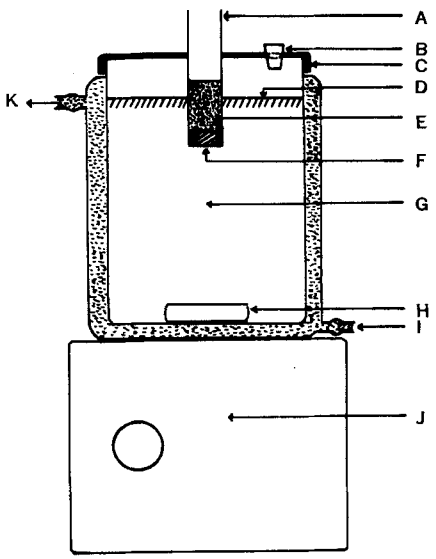

Fig. 1.—Schematic diagram of the apparatus used to study release rates. Key: A, glass tube; B, removable cork for sampling; C, container cover; D, solvent level; E, wax; F, tablet imbedded in wax; G, solvent; H, magnetic stirring bar; I, inlet for the water jacket; J, stirring motor; K, outlet for the water jacket.

tightly fitting Petri dish with two holes to prevent excessive evaporation. The tablet mounted in the glass tube was introduced into the solvent through a hole in the center of the dish and clamped to a ring stand so that the water level was above the top edge of the tablet to insure water penetration. Stirring of the solution was achieved by the use of a magnetic stirring bar. Samples were withdrawn at various times through the smaller hole in the Petri dish, which otherwise was kept closed by a cork. These were assayed spectrophotometrically. The wavelengths used for various drugs investigated were: sodium salicylate (294 mμ), salicylic acid (296 mμ), benzocaine (282 mμ), caffeine (276 mμ), benzoic acid (274 mμ).

The experimental procedure was modified as follows in the study investigating the effects of drug type and particle size on apparent tortuosity. The tablets were leached in water for a period of 2 to 3 weeks, and the leached matrix thus obtained was saturated with 5% sodium salicylate solution for another period of 2 to 3 weeks. These tablets were then removed from the glass tube along with its wax coating, and the sides were thoroughly washed to remove any sodium salicylate solution adhering to the sides. The leaching surface was also quickly rinsed to remove any excess sodium salicylate solution. The tablet was then immersed in new solvent and its rate of release studied as described for matrices containing solid drug.

RESULTS AND DISCUSSION

Choice of Matrix.—For a study of this type, it was necessary to obtain a matrix which would satisfy certain minimum requirements. It should be inert, insoluble, should remain intact during experiment, provide a sustained release over a reasonable length of time, and most important, yield a reproducible straight line when the amount of drug released is plotted *versus* the square root of time. For the above reasons, it was felt that a plastic matrix would be preferable to one consisting of fats and waxes.

Tablets containing 5% sodium salicylate were made utilizing polyvinyl chloride homopolymer,[1] linear polyethylene high density homopolymer,[1] and halogenated fluorocarbon homopolymer[2] as matrices. They will be subsequently referred to as PVC, polyethylene, and Plaskon, respectively. The release of sodium salicylate in water as a function of the square root of time for each of these plastics is shown in Fig. 2. These curves indicate that polyethylene would provide an ideal matrix for these studies since its curve was linear and passed through the origin. In addition, it remained intact during the entire experiment without flaking and measurements showed no sign of swelling. As a further check, the polyethylene plastic was added to a saturated solution of sodium salicylate, agitated overnight, filtered, and the solution assayed. The results showed no sodium salicylate interaction with polyethylene.

All graphs contained in this report utilize the square root of time as the abscissa, but it should be emphasized that plots of the amount released *versus* time have definite curvature. This is illustrated by Fig. 3.

[1] The Dow Chemical Co., Midland, Mich.
[2] Allied Chemical Corp., Plastic Division, Morristown, N. J.

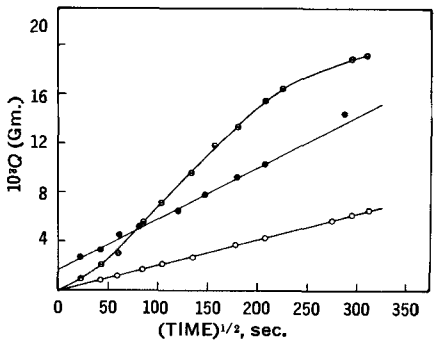

Fig. 2.—Comparison of release rates of various plastic matrices containing 5% sodium salicylate. Key: ⊖, polyvinyl chloride-III; O, Plaskon-3200; ●, experimental plastic QX-2187 (polyethylene).

Effect of A Factor.—The effect of varying the concentration of sodium salicylate in tablet was investigated utilizing tablets containing 5, 10, and 20% sodium salicylate in polyethylene. Plots of the amount of drug released *versus* the square root of time as a function of per cent sodium salicylate are shown in Fig. 4.

This can be a very important factor, as frequently it is desirable to produce several tablet concentrations of the same drug and matrix to provide a variety of dosage schedules. To do this, the tablet concentration dependency must first be determined.

The rate equation may seem to indicate that the slope of the release curve should be proportional to the square root of the amount of drug in tablet as it appears raised to the first power under the square root sign. Closer examination (1) would reveal a direct relationship. Assuming that increasing the amount of sodium salicylate in tablet would also increase the porosity by the same factor, but would not affect the other variables, it is evident from the rate equation that the slope also should increase by the same factor. Comparing the experimental results, the slope of the 10% tablet was only 1.3 times greater than the 5% tablet, and the 20% tablet was 2.9 times greater than the 5% tablet. If the above assumption were correct, the factor should have been 2 and 4 times greater. This may indicate that the other factors in the equation are

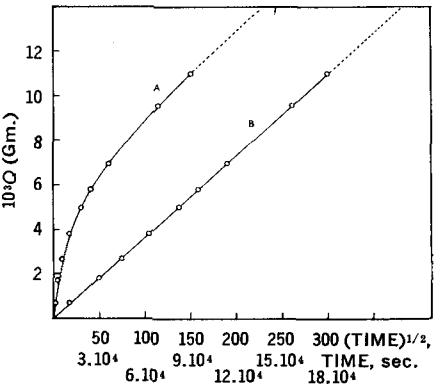

Fig. 3.—Comparison of the amount released per unit area as a function of time and (time)$^{1/2}$.

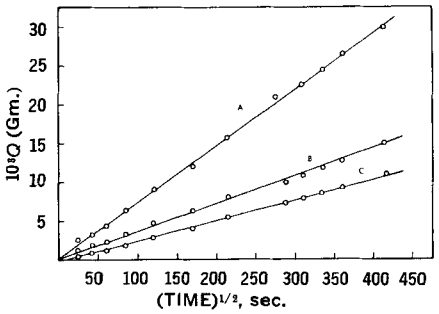

Fig. 4.—Sodium salicylate release as a function of its concentration in polyethylene tablet. Key: A, 20% w/w; B, 10% w/w; C, 5% w/w.

changing with the amount of sodium salicylate or that porosity was not proportional to A.

Effect of C_s Factor.—Very often it has been found that a matrix which provided a desired release profile for one drug was unsuitable when used to incorporate another drug. As predicted by the rate law, the solubility of the drug is an important factor one must consider when attempting to use the same matrix for more than one drug.

In order to study the effect of drug solubility, tablets containing 20% of sodium salicylate, caffeine, benzoic acid, and benzocaine were investigated, and the results are shown in Fig. 5. They all contain the same A, same solvent, but different solubilities, *i.e.*, C_s.

It can be assumed that variation of their respective diffusion coefficients should not appreciably affect the slope of their respective curves. Their variation in size should not be an important factor, as the Stokes-Einstein equation for diffusion predicts that the diffusion coefficient is inversely proportional to the cube root of its molecular weight; as a result, the slope of the curve would be inversely proportional to the sixth root of the molecular weight. The range of molecular weights for the above compounds is only from 122 to 194.

Correcting for the effect of density variation on porosity and assuming that the tortuosity is not appreciably affecting slopes, the approximate ratio of the sodium salicylate slope as compared to the caffeine slope should be 4, to the benzoic acid slope should be 11, and to the benzocaine slope should be 35. Experimentally, Fig. 5 yields results of about 6, 13, and 17, respectively. This means that the sodium salicylate–caffeine slope ratio was 1.5 times its expected value, benzocaine was one half of its expected value, and benzoic acid ratio was the expected value.

A possible explanation for this can be postulated on the basis of variation in tortuosity. If this is the case, the tortuosity in the caffeine tablet is 2.25 times greater, benzocaine is 4 times smaller, and benzoic acid yielded about the same tortuosity as sodium salicylate.

Tortuosity Factor.—In many cases additives are added to a matrix–drug formulation to improve its properties, such as uniform flow rates and stability. These additives, however, can significantly alter the release profile by causing one or more variables in the rate law to change.

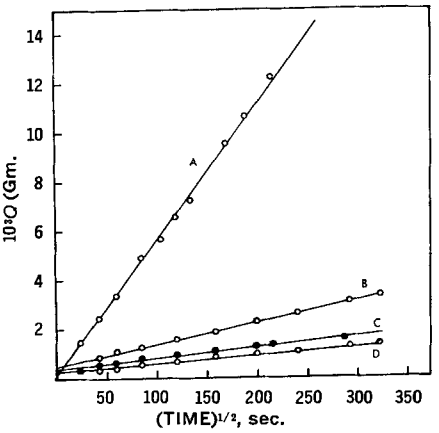

Fig. 5.—The release rates of various drugs with different solubilities, Key: A, 20% w/w sodium salicylate in polyethylene; B, 20% w/w caffeine in polyethylene; C, 20% w/w benzoic acid in polyethylene; D, 20% w/w benzocaine in polyethylene.

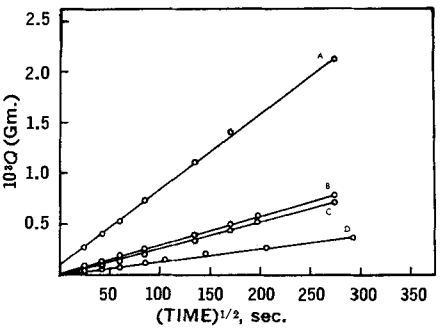

Fig. 6.—The release of sodium salicylate from polyethylene matrices made by leaching different compounds from it and then resaturating the porous matrix with 5% sodium salicylate solution. Key: A, 10% v/v sodium salicylate of <37 μ size; B, 10% v/v lactose of <37 μ size; C, 10% v/v sodium chloride or potassium chloride of <37 μ size; D, 10% v/v spray-dried lactose of <37 μ size.

In this regard the effect of various solutes upon tortuosity was investigated using sodium salicylate, sodium chloride, potassium chloride, lactose, and spray-dried lactose. Tablets were made, completely leached of solute, resaturated with 5% sodium salicylate solution, and then the release of sodium salicylate from them studied.

It is important that the volume rather than weight of solute be controlled in this experiment, as the volume of solute will determine the porosity of the leached matrix. Solute particle size was controlled by passing all solutes through a standard No. 400 mesh sieve which should provide a more uniform distribution when mixed with polyethylene. This restricted drug particle size to less than 37 μ. If the above assumptions are true, any variation in the release of the resaturated sodium salicylate matrices should be predominantly due to tortuosity differences.

The results were plotted and are shown in Fig. 6. Slopes were calculated and are reported in column 1 of Table I.

TABLE I.—COMPARISON OF SLOPES

Drug	Slope <37 μ	Slope Ratio (Sod. Sal./Drug) <37 μ	Slope 125 to 177 μ	Slope Ratio <37 μ/125 to 177 μ	Slope Ratio (Sod. Sal./Drug) 125 to 177 μ
Sodium salicylate	7.4×10^{-6}	1.0	7.3×10^{-6}	1.01	1.0
Lactose	2.85×10^{-6}	2.59	1.142×10^{-6}	2.495	6.39
KCl	2.69×10^{-6}	2.80	1.4×10^{-6}	1.88	5.21
NaCl	2.64×10^{-6}	2.80	1.15×10^{-6}	2.29	6.340
Spray-dried lactose	1.22×10^{-6}	6.06	0.32×10^{-6}	3.812	22.81

TABLE II.—ESTIMATE OF TORTUOSITY CHANGES

Drug	$\left[\text{Slope Ratio (Sod. Sal./Drug) <37 μ}\right]^2$	$\left[\text{Slope Ratio (Sod. Sal./Drug) 125 to 177 μ}\right]^2$	$\left[\text{Slope Ratio <37 μ/125 to 177 μ}\right]^2$
Sodium salicylate	1.0	1.0	1.02
Lactose	6.708	40.83	6.225
KCl	7.84	27.14	3.534
NaCl	7.84	40.19	5.244
Spray-dried lactose	36.72	520.29	14.53

In this experiment, the amount of drug released per unit area does not obey the same relationship as solid drug dispersed in a matrix. The sodium salicylate solution entrapped in the matrix will release sodium salicylate according to the following rate law (5):

$$Q = 2\,\epsilon C_0 \left(\frac{Dt}{\tau\pi}\right)^{1/2}$$

where all variables are identical to the solid drug release law. This equation predicts that the tortuosity is inversely proportional to the square root of the slope. In addition, the square of the ratio of the slopes of 2 curves will yield the value of the ratio of the respective tortuosity factors. Computations given in column 1 of Table II indicate that the apparent tortuosities of sodium chloride, potassium chloride, and lactose tablets are roughly 7 times greater than that of sodium salicylate. Surprisingly, spray-dried lactose seems to yield an apparent tortuosity that is about 6 times greater than lactose and about 37 times greater than sodium salicylate.

Particle size dependency of this phenomenon was investigated by repeating the experiments but using larger particle sizes. Particles which passed through a No. 80 mesh sieve but were retained by a No. 120 mesh sieve were used to make a second series of tablets. This restricted drug particle size to a range of 125 to 177 μ. The results are shown in Fig. 7. For comparison purposes < No. 400 mesh particle curves were also included in the above graph.

With the exception of sodium salicylate, the larger particle sizes of solutes yielded higher apparent tortuosities by factors of 4 to 14 as indicated by column 3 of Table II. Column 3 indicates that larger particle sizes of solutes may exhibit considerably higher tortuosities than smaller particle sizes.

The above effects may be due to relative hardness or flow properties of solutes as compared to the polyethylene plastic. One solute may tend to flow around the plastic, whereas the opposite may predominate in the case of other solutes. Needless to say, this would alter the tortuosity factor markedly. In addition, encapsulation of drug in the latter process could appreciably decrease the effective tortuosity. The flow pattern would be a function of the hardness, average size, distribution of sizes, and shape of solute.

Effect of Additives.—The effect of additives on the release rate of solid drug imbedded in a plastic matrix was interesting. Tablets containing 5% sodium salicylate were made with 15% potassium chloride and 15% sodium chloride. The curve for

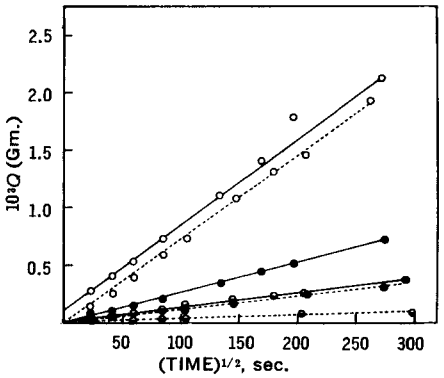

Fig. 7.—The release of sodium salicylate from polyethylene matrices made by leaching different compounds with various particle size and then resaturating the porous matrix with 5% sodium salicylate solution. Key: O—O, 10% v/v sodium salicylate <37 μ size; O- - -O, 10% v/v sodium salicylate between 125 to 177 μ size; ●—●, 10% v/v sodium chloride <37 μ size; ●- - -●, 10% v/v sodium chloride between 125 to 177 μ size; ◒—◒, 10% v/v spray-dried lactose <37 μ size; ◒- - -◒, 10% v/v spray-dried lactose between 125 to 177 μ size.

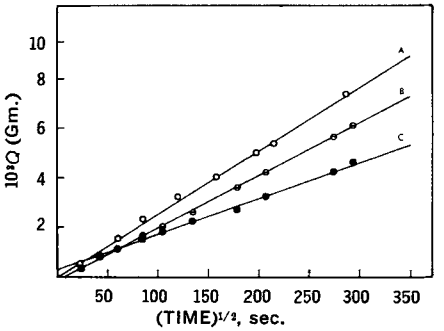

Fig. 8.—Effect of additives on release rates. Key: A, 5% w/w sodium salicylate + 15% potassium chloride w/w; B, 5% w/w sodium salicylate w/w; C, 5% w/w sodium salicylate + 15% sodium chloride w/w.

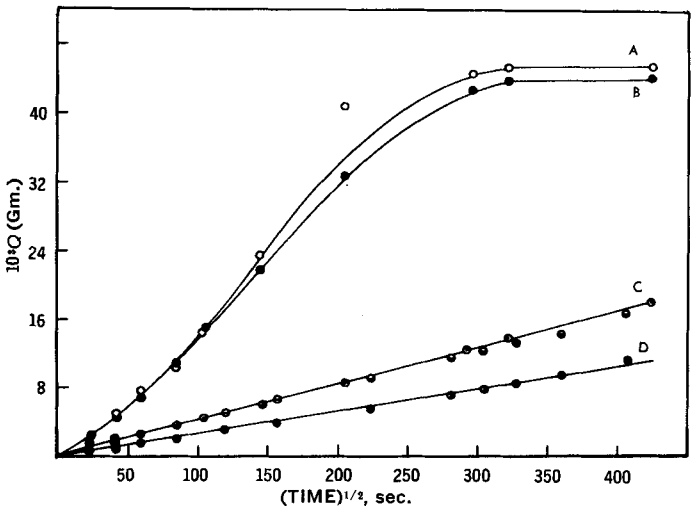

Fig. 9.—Effect of surfactants on sodium salicylate release rates. Key: A, 5% w/w sodium salicylate in polyvinyl chloride matrix using water as solvent; B, 5% w/w sodium salicylate in polyvinyl chloride matrix using 0.2% w/v benzalkonium chloride as a solvent; C, 5% w/w sodium salicylate in polyethylene matrix using the following solvents: ⊙—⊙, 0.2% benzalkonium chloride, and ⊖—⊖, 0.2% sodium lauryl sulfate; D, 5% w/w sodium salicylate in polyethylene matrix using water as a solvent.

no additives and the above curves were plotted in Fig. 8. The release rate was increased with the addition of potassium chloride. This was expected as the porosity of the tablet would be increased. The release rate was decreased, however, with the addition of sodium chloride. The porosity, tortuosity, and other variables should be the same for both salt tablets since they exhibited the same release rate in the leaching experiment illustrated in Fig. 6.

Evidently the common ion, sodium, decreases the solubility of sodium salicylate which in turn markedly decreases its release rate. Calculations using the rate law equation indicate that the magnitude of the observed change in release rate can be caused by a decrease in sodium salicylate solubility of 200 mg./ml. Approximate solubility product calculations show that sodium salicylate solubility can be decreased as much as 300 mg./ml. in the presence of sodium chloride. These calculations support the common ion effect. Needless to say, it is important that this effect be taken into consideration when selecting inert material for a new formulation or introducing changes in existing formulation.

Effect of Surfactants.—If 0.2% benzalkonium chloride or sodium lauryl sulfate was added to water, the rate of release of 5% sodium salicylate tablets increased. The magnitude was the same for both surfactants as shown in Fig. 9.

It is believed that this effect is due to surface tension lowering of the solvent. Since the same result was obtained using two different surfactants in separate experiments, it is reasonable to assume that there was no appreciable change in solubility due to sodium salicylate–surfactant interaction. Solubility studies confirmed this, as the solubility of sodium salicylate remained unchanged with addition of surfactant. In addition, the absorption spectrum did not change, and Beer's law plots yielded the same absorptivity in surfactant and nonsurfactant solutions.

The above data suggest that a surfactant may make available more channels for diffusion, and in this way increase the effective porosity of the matrix.

This experiment was repeated using PVC as the matrix in place of polyethylene. No surfactant effect was observed in this case as shown by PVC

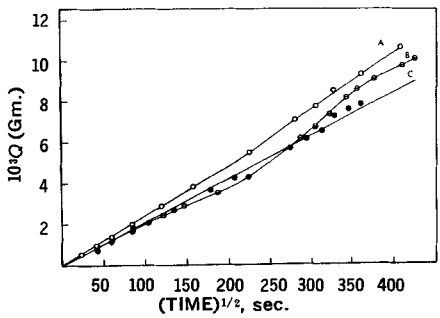

Fig. 10.—Buffer effects on release rates. Key: A, water; B, 1 *M* hydrochloric acid; C, 1 *M* potassium phosphate buffer (pH = 6.85).

curves in Fig. 9. If the assumption that surfactant releases more channels for diffusion is true, it would indicate that essentially all channels of PVC are available to water.

Since the surface tension of gastric and intestinal fluids varies widely, the above effect must be considered when selecting a matrix for a particular formulation.

Effect of Buffers.—Tablets containing 5% sodium salicylate in a matrix of polyethylene were made and their release studied in water, 1 *M* hydrochloric acid, and 1 *M* potassium phosphate buffer (pH 6.8).

It was felt that the hydrochloride solution would convert the sodium salt to the free acid and markedly decrease the release rate as compared to water and phosphate media. The results are shown in Fig. 10. These curves indicate that significant conversion did not occur and that the release rate in gastric and intestinal fluids would be the same. It should be noted, however, that the hydrochloride solution gave an S-shaped curve which was reproducible.

SUMMARY

Results of experiments showed that the rate of drug release from a plastic matrix can be described by the Higuchi equation. An attempt was made to determine the effect of varying conditions on the various parameters of the equation. The release rates were significantly changed if: (*a*) different

plastics were used as a matrix, (*b*) the amount of drug in matrix was varied, (*c*) drug solubility was changed, (*d*) additives were used, (*e*) different solvents were used.

Analysis of results shows that the above factors not only altered release rates directly as predicted by theory, but also indirectly by altering apparent porosities and tortuosities. Because of the latter effect, quantitative correlations were difficult to obtain. It is apparent that the porosity and tortuosity parameters must be accurately determined if the equation is to be applied quantitatively. This aspect of the study will be discussed in another paper (5).

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Gas Chromatographic Method of Moisture Determination

By J. H. MARTIN and A. M. KNEVEL

The acid-catalyzed reaction between 2,2-dimethoxypropane (DMP) and water to form acetone and methanol was investigated to determine the applicability of the reaction in the quantitative determination of water by gas chromatography. An 8-ft. column packed with 30 per cent Theed (tetrahydroxyethyl ethylenediamine) was found to give a satisfactory separation of the DMP and the reaction products, acetone and methanol. An equation relating the heights of the peaks observed on the chromatogram to the moisture content of the sample was derived. The accuracy of the method was determined using samples of known water content, and a comparative study using the Karl Fischer titrimetric method was performed. The gas chromatographic method gave better accuracy and precision than the Karl Fischer method. The method was applied to two common solvents, and a general procedure for moisture determination was developed.

SINCE its introduction, gas chromatography has found applications in a wide variety of separations and analytical techniques. Until recently, however, gas chromatographic methods have found very limited use in the field of moisture determinations, and few were reported prior to 1959. The principal reason for this is that water exhibits a very long, flat, tailing peak upon elution from a gas chromatographic column. Most of the studies involving moisture prior to 1959 were simply attempts to eliminate the tailing effects of water so that other substances could be assayed without interference (1–4). The first attempt at using gas chromatography as a means of determining moisture quantitatively was reported by Smith (5) in 1959. In the same year, Elvidge and Proctor (6) reported the use of gas chromatography in the determination of water in some pharmaceutical formulations, while more recently Bennett (7) used a Teflon support to eliminate the tailing of water in a quantitative method.

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The utilization of the reaction between 2,2-dimethoxypropane (DMP) and water was first reported by Erley (8) in 1957. He used the reaction as a convenient means of rendering samples intended for infrared analysis moisture free. The reaction was also utilized by Bousquet *et al.* (9) for the removal of water from biological samples and extracts. Critchfield and Bishop (10) reported the use of DMP as a reagent suitable for moisture determination. In their procedure the acetone formed in the reaction is determined by infrared analysis.

During the course of this study a paper was presented by Hager and Baker (11) in which the use of DMP in a gas chromatographic method of moisture determination was suggested. Their paper was concerned primarily with the feasibility of such a method. They presented no data and drew no conclusions.

THEORETICAL CONSIDERATIONS

A derivation of the equation relating peak heights to molar concentration of water is presented.

In the following derivation, let a = number of moles of acetone in sample, d = number of moles