Improved Method for Diffusion Coefficient Determinations Employing the Silver Membrane Filter

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A convenient and rapid method for determining diffusion coefficients has been developed that is based on the quasi-stationary diaphragm cell method. A silver filter membrane is used to separate two compartments of the apparatus that are stirred magnetically with synchronous motors. The advantages are the good precision of the data, running times of the experiments, and the extended repeated usability of a given membrane.

THERE RECENTLY has been much interest shown in drug dissolution rate mechanisms as well as in other diffusionally characterized transport processes. Regardless of the situation, quantification requires diffusion coefficient determination as one parameter. A method for determining the diffusion coefficient has been described by Northrup and Anson (1) and by McBain (2). Desai *et al.* (3) employed a method similar to the Northrup-McBain technique using sintered-glass disks to separate the drug solution from the "sink." Singh (4) found improvement by using organic polymer membrane filters.

Almost all membrane filters lack the physical strength required for repeated use. They would, after soaking in the drug solutions, lose their integrity, causing changes of area available for transport. One membrane filter,[1] impregnated with glass fibers, was found to maintain itself rather well for as long as 75–80 hr. of experimentation but would then slowly slough its surface. Recently, a new membrane filter was marketed, made from silver,[2] and has been used with the apparatus shown in Fig. 1. This filter has tensile strength as an advantage over the other membrane filters, and the advantage of thinness over the sintered-glass disks. This allows for faster, easier wetting of all the pores. This insures having the same porosity and tortuosity in each succeeding trial, and hence, better reproducibility. Also, the thinner the membrane, assuming all other factors are constant, the faster the rate of transport through it. This advantage, however, makes the overall diffusion rate more stirring speed dependent, due to the greater importance of the aqueous diffusion layers next to the membrane. Therefore, single speed (300 r.p.m.) synchronous motors were employed to control the hydrodynamics. To these motors, 5.6 cm. (2.25 in.) magnetic cylinders were attached, which in turn rotated Teflon-coated magnetic stir bars within each side of the cell. The silver filters, once installed in the cell, may be used over and over again, and appear to be "permanent," *i.e.*, after soaking in drug solution for more than 2 months, there were no apparent deleterious

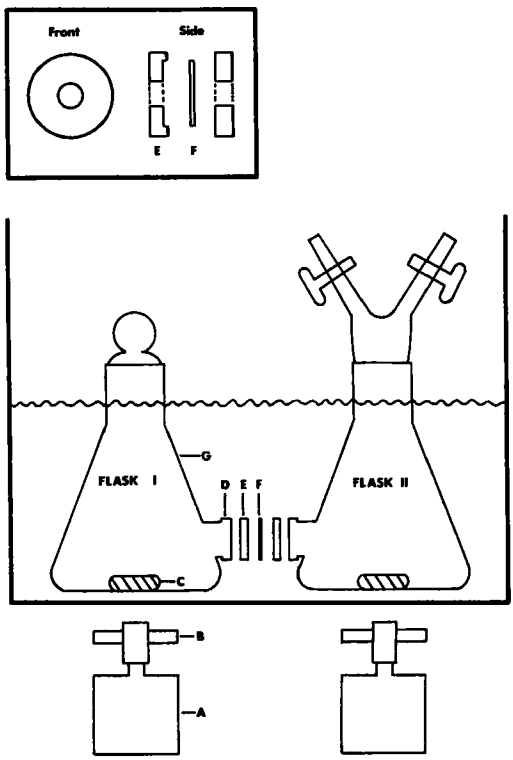

Fig. 1—Schematic diagram of cell used to determine diffusion coefficients. Inset is enlarged schematic of the Teflon washers. Key: A, *synchronous motor, 300 r.p.m.;* B, *5.6-cm. magnetic (cylindrical);* C, *5-cm. Teflon-coated stirring bar;* D, *ground-glass end;* E, *Teflon washer;* F, *silver membrane;* G, *250-ml. conical flask, adapted as shown.*

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[1] Versapor filter, Gelman Industries, Ann Arbor, Mich.
[2] Flotronics Membrane, Selas Flotronics, Spring House, Pa.

effects, despite there being what appears to be a silver oxide film on the filters. Due to its thinness (2 mils), most diffusion coefficients can be determined in about 2 hr. once a cell is calibrated.

The other change is in the cell itself. Desai and workers (3) used a cell of unit construction. The cell used here is similar to that described by Singh (4) and is formed from two 250-ml. conical flasks that have been previously modified to contain side-arm attachments with ground-glass ends, as in Fig. 1. Between these ground-glass ends are placed two Teflon washers, one of which effectively has a rim around its perimeter (see cut in Fig. 1). The 37-mm. diameter silver filter of 1.2 μ pore size is placed between the two Teflon washers. The flasks are then clamped together using a triangular clamp fastened by nuts and bolts. To insure complete wetting of the entire membrane, Flask I is initially filled with a 0.05% polysorbate 80 solution and allowed to flow into Flask II. The cell is then allowed to bathe overnight in the surfactant solution. Then the cell is emptied, filled with enough distilled water to completely cover the membrane, and stirred for 2–3 days. The cell is then emptied and rinsed before use. This procedure is only necessary the first time a cell is constructed. Thereafter, the cell is kept filled with water when not in use. The cell is never dismantled. If the cell is taken apart, new calibrations are required.

Theoretical Considerations—The thickness of the silver membrane is approximately only 50 μ. Since the membranes are purported to have a tortuosity of near unity, and a high porosity, it becomes evident that mass transfer resistance through the aqueous films on either side of the membrane may contribute significantly to the cell constant. Thus it is necessary to explore the question of whether or not mass transport in the aqueous films is essentially molecular diffusion. If, for example, mass transfer mechanisms other than molecular diffusion is important (5), one may expect a nonlinear dependence upon the diffusion coefficient.

To determine this dependency, cell constants can be calculated using several substances of known diffusion coefficients. These diffusion coefficients encompass as large a difference between them as is practically feasible, and in the range of the diffusion coefficients to be measured.

EXPERIMENTAL

For the rate determinations, the flasks are filled and stoppered in a similar manner as previously described (3). The solution containing the drug is put into Flask II, along with a 5-cm. (2-in.) Teflon-coated magnetic stirring bar. The "Y" tube (see Fig. 1) is filled to overflowing by injecting the drug solution through the hole of one stopcock, and then closing both stopcocks. Distilled water (250 ml.) is then added to Flask I, along with an identical stirring bar to the one in Flask II. The entire cell is then immersed in a constant-temperature water bath, under which are placed the synchronous motors. After enough time to allow for steady-state diffusion and temperature equilibration, 10-ml. samples are withdrawn from Flask I, and are replaced by 10 ml. of distilled water. The concentration of drug appearing in Flask I is corrected for the volume replacement factor.

The calculation of the cell constant is given as:

$$L = \frac{G_{(\text{known})}}{D_{(\text{known})}\,(C_2 - C_1)} \qquad \text{(Eq. 1)}$$

where L is the cell constant, G is the rate of transport from Flask II to Flask I of a substance whose diffusion coefficient is known, D is the diffusion coefficient of that substance, C_1 and C_2 are the concentrations in Flasks I and II, respectively. C_1 is zero if no drug is put into Flask I. Once the cell constant, L, has been determined, Eq. 1 is rewritten to:

$$D_{(\text{unknown})} = \frac{G_{(\text{unknown})}}{L_{(\text{cell})}\,(C_2 - C_1)} \qquad \text{(Eq. 2)}$$

The rate, G, is determined as discussed earlier, leaving only the diffusion coefficient, D, to be calculated.

The cell constants were determined at 25 and 30° using KCl solutions and sucrose solutions. Sucrose has diffusion coefficients approximately one-fourth that of potassium chloride. The integral diffusion coefficient for 0.10 M KCl is 1.873×10^{-5} cm.^{2} sec.$^{-1}$ (6) at 25° and 2.093×10^{-5} cm.^{2} sec.$^{-1}$ (7) at 30°. The diffusion coefficients of sucrose, 1% and 0.1% both at 25° are reported as 5.148×10^{-6} cm.^{2} sec.$^{-1}$ and 5.213×10^{-6} cm.^{2} sec.$^{-1}$, respectively (8).

The precision of the cells was then tested by quadruplicate determinations of the diffusion coefficient of benzoic acid, 0.01 M at 30°. Benzoic acid was also used to determine the effect of stirring on the cell constant, by recalibrating the cell using 150 r.p.m. synchronous motors.

DISCUSSION

The calibrations performed in this laboratory indicate that these cells are an improvement over the ones previously employed. The cell constants calculated using Eq. 1, for each trial of two cells using potassium chloride and sucrose are reported in Table I, along with their standard deviations. One

Table I—Cell Constant Determinations Under Varying Conditions

	Cell Constant, cm.	
	Cell B	Cell C
Potassium chloride, 0.1 M, 25°	84.17	87.17
Potassium chloride, 0.1 M, 30°	84.92	87.92
Sucrose, 1.0%, 25°	84.50	89.72
Sucrose, 0.1%, 25°	84.31	87.31
Mean	84.49	88.03
SD	0.275 (±.33%)	1.018 (±1.16%)

cell (B) has a cell constant of 84.49 cm. and the other a cell constant of 88.03 cm. In order to determine whether this standard deviation is due to the changing conditions or to the technique itself, the diffusion coefficient of benzoic acid, 0.01 M was repeatedly determined at 30°. The results are reported in Table II. The diffusion coefficient found (1.113×10^{-5} cm.^{2} sec.$^{-1}$) is in excellent agreement with the reported value of 1.11×10^{-5} cm.^{2} sec.$^{-1}$ (9). Typical data for the benzoic acid rates are shown in Fig. 2.

After noting that the determinations made using benzoic acid showed a slightly larger standard deviation than obtained by the potassium chloride and sucrose calibrations, it was assumed that the small differences found with potassium chloride and sucrose were not due to the changing conditions. This shows that small temperature changes do not affect the cell constant, nor does a 2% change in viscosity. If, however, it is assumed that the standard deviation (from the benzoic acid trials) is attributable to the exponential dependency of the diffusion coefficient, it can be shown that at 300 r.p.m. the maximum dependency is $D^{(1.00 \pm 0.08)}$. For the purposes found to date in the pharmaceutical literature, this leads to only small errors in the determined diffusion coefficient.

If the cell constant is recalculated using 150 r.p.m. rather than 300 r.p.m., a large reduction in cell constant is obtained. The cell constants at 150 r.p.m. for cells B and C were 68.53 and 74.25 cm., respectively. The reproducibility of each cell was excellent. This result indicates the necessity for constant speed stirring. The lower the rates of stirring, the greater the magnification of the differences between the cells. When four more cells were calibrated at 300 r.p.m., the cell constants ranged from 83.33 to 102.22 cm., with each individual cell showing about the same standard deviations as reported for cells B and C. This indicates the necessity of calibrating each cell individually, and using the individual cell constants for calculating the diffusion coefficients obtained from the rate experiments.

TABLE II—REPEATED DETERMINATIONS OF DIFFUSION COEFFICIENT OF BENZOIC ACID, 0.01 M, AT 30.0°

Trial	G (mg./sec.) ($\times 10^3$)	Concn. (mg./ml.)	D ($\times 10^5$)
	Cell B (L = 84.49 cm.)		
1	1.122	1.2212	1.087
2	1.151	1.1813	1.153
3	1.185	1.2188	1.151
4	1.133	1.1813	1.135
	Cell C (L = 88.03 cm.)		
1	1.169	1.2212	1.087
2	1.139	1.1813	1.095
3	1.200	1.2188	1.118
4	1.118	1.1813	1.075
Mean	1.113		
SD	0.029	(± 2.6%)	

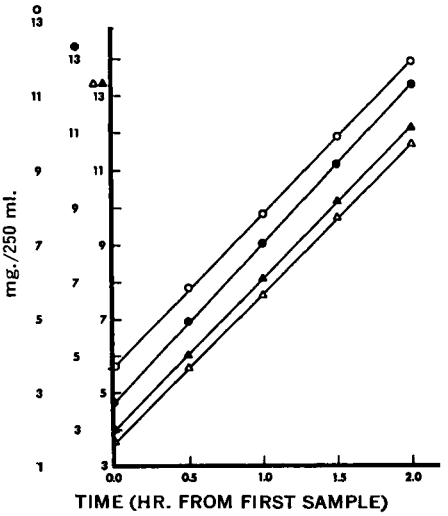

Fig. 2—Typical data from rate experiments. Slope of line is G of Eq. 1. Key: △, ▲, ○, ● are four different rate experiments from cell B.

SUMMARY

An improved method for determining diffusion coefficients is proposed, encompassing the use of a new silver membrane. The advantages are the speed at which diffusion coefficients can be determined, and the good precision of the data. It was also shown that, despite a stirring-rate dependent barrier being present, the diffusion coefficients obtained agree well with the literature and that diffusion through this barrier appears to follow molecular diffusion. It was also shown that small changes in temperature and/or viscosity do not affect the cell constant. These cells offer better precision than the previously reported cells using sintered-glass disks. They combine the physical stability of sintered-glass disks with the advantages of thin membrane filters.

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Keyphrases

Diffusion coefficients—determination
Silver membrane filter—diffusion coefficients
Diagram—diffusion cell