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Knudsen Vapor Pressure Measurements on Pure Materials and Solutions Dispersed in Porous Media: Molded Nitroglycerin Tablets

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Abstract □ The gravimetric Knudsen method for vapor pressure measurement may be subject to serious systematic errors when the sample: (*a*) consists of the volatile component dispersed in an inert porous matrix and/or (*b*) contains a dissolved polymeric solute. Vaporization of water present as an impurity in the matrix may result in an appreciable "background" mass loss, and "nonequilibrium effects" may be present; *i.e.*, the vapor of interest may be unable to escape from the sample rapidly enough to maintain the equilibrium vapor pressure in the Knudsen cell. Methods for eliminating the interference due to background effects are described, and a theoretical analysis of nonequilibrium effects is presented. The essential validity of the theories for nonequilibrium effects and the effectiveness of the methods for circumventing background effects were verified by experimental studies with molded nitroglycerin tablets. With nitroglycerin tablets, accurate Knudsen vapor pressure data may be obtained using the modified procedures and data analysis presented in this report.

Keyphrases □ Vapor pressure—gravimetric measurement, pure materials and solutions dispersed in porous media, analysis of nonequilibrium and background effects □ Dispersions—solutions in porous media, gravimetric vapor pressure measurement, analysis of nonequilibrium and background effects □ Nitroglycerin—tablets, gravimetric vapor pressure measurement, analysis of nonequilibrium and background effects □ Dosage forms—nitroglycerin tablets, solutions dispersed in porous media, gravimetric vapor pressure measurement

The gravimetric Knudsen effusion technique is a convenient and accurate method for measuring vapor pressures of pure materials having low volatility (1–5). The rate of vapor loss through a small orifice is measured gravimetrically under conditions of free molecule flow (*i.e.*, large mean free path), and the vapor pressure is calculated directly from the proportionality between the rate of mass loss and vapor pressure. However, when the volatile material of interest is dispersed at trace levels in a porous nonvolatile matrix and/or contains a polymeric solute, several major problems may arise which are not discussed in the literature.

First, the amount of volatile water in the sample (*i.e.*, nitroglycerin tablet) may be of the same order of magnitude as the volatile material of interest (*i.e.*, nitroglycerin), and the measured rate of mass loss contains a "background" due to water evaporation.

Second, nonequilibrium effects may be present. That is, if the vapor of interest cannot leave the sample rapidly enough to maintain the equilibrium vapor pressure in the Knudsen cell, the measured vapor pressure will be lower than the equilibrium value.

Extension of the gravimetric Knudsen method of vapor pressure measurement to complex systems is described in this report. Specifically, a theoretical–experimental analysis of nonequilibrium effects is given, and the procedures required to circumvent errors due to nonequilibrium effects and background effects are described.

Although the theoretical results and most of the procedures are of general application, the discussion is presented in terms of molded nitroglycerin tablets as a specific example, and the experimental studies were limited to nitroglycerin tablets. The tablets were mostly α-lactose, containing 1–2% nitroglycerin (0.3–0.6 mg). "Stabilized" tablets also contained 1% povidone dissolved in the nitroglycerin.

EXPERIMENTAL

Materials—Reagent grade benzoic acid was recrystalled twice from warm water; reagent grade benzophenone was recrystallized once from water–ethanol. The crystals were dried overnight *in vacuo* (10 Torr) at 35°. The nitroglycerin samples were prepared and assayed as described elsewhere (6).

Apparatus—The Knudsen cells (*i.e.*, sample containers) used were similar to those described previously (2–4). The cell was basically an aluminum pot with a flanged screw-on lid, allowing a platinum foil cover to fit inside the lid. A small orifice was drilled in the foil, and a vaportight seal between the bottom of the pot and the platinum foil was achieved using a small "O" ring[1]. Three cells were used; they all had the same weight (1 g) and dimensions (height, 1 cm; diameter, 1 cm) and differed only in the orifice size.

The effusion rate was measured by suspending the cell from one arm of an electronic vacuum microbalance[2]. The noise level (due to building vibrations) was generally low enough to allow small mass changes to be measured with an accuracy of about ±0.5 μg. The original tubes on both the sample and tare sides of the balance were replaced by a combination sample tube–cold finger, which joined with the balance through an "O" ring joint. The cold finger was a 20-mm Pyrex tube, which joined the main sample tube about 10 cm above the Knudsen cell. The output of the balance was connected to a strip-chart recorder[3], thereby providing a curve of mass (m) *versus* time.

The pumping system was an oil diffusion pump backed by a rotary pump. During an experiment, the system was evacuated to less than 0.5 Torr with the rotary pump (within 1–2 min). The cold fingers were placed in liquid nitrogen, and the system was opened to the diffusion pump–rotary pump combination. The air pressure at the sample site was in the 10^{-5}-Torr range within 20 sec after the diffusion pump was placed in line. The ultimate air pressure was about 5×10^{-6} Torr. Temperature control was maintained within ±0.05° by a water thermostat.

Calibrations—With the vapor pressure, P (in Torr), and the effusion rate, R_0 (in micrograms per minute), the Knudsen equation may be written (4, 7):

$$10^4 P\,(\text{Torr}) = \frac{2.854}{10^3 A_0}\sqrt{\frac{T}{M}}R_0 \qquad \text{(Eq. 1)}$$

where A_0 is the "effective orifice area" in square centimeters and includes, in addition to the orifice area, several correction terms near unity (4, 7); T is the absolute temperature; and M is the molecular weight.

Measurements of R_0 for benzoic acid at 25° and the literature vapor pressure (4) were used to calibrate A_0 for Cells 1 and 2. The vapor pressure of nitroglycerin (10% trituration on lactose) was evaluated at 25° using Cells 1 and 2, and nitroglycerin at 25° was used to calibrate A_0 for Cell 3. The values of $10^3 A_0$ determined, in square centimeters, were 2.18 (Cell 1), 0.96 (Cell 2), and 27.4 (Cell 3). These data are in satisfactory agreement with the (less accurate) values determined by microscopic examination.

By using Cell 2 and the calibrated A_0 value, vapor pressures were measured for benzoic acid at 35° and for benzophenone at 25°. Agreement with the literature data (2, 4) was within 5%.

Origin of Background—The value of dm/dt computed (by numerical differentiation) directly from the recorder mass *versus* time curve contains significant contributions from several "background" effects, *i.e.*, mass loss other than effusion of nitroglycerin:

1. Presumably due to diffusion-limited loss of absorbed water, the balance system itself gives an apparent loss in mass with time, denoted "balance background."
2. The Knudsen cell loses mass, presumably adsorbed water, denoted "empty cell background."
3. In general, the samples of interest contain a small, although significant, quantity of volatile water[4], thereby producing a "water background."

Background effects were noted by other investigators (4). Background effects decrease in importance as time, t, increases, and the usual practice (4) is to wait until the background effects are small before calculating vapor pressure. However, for the samples studied, one cannot assume that vapor pressure is independent of time, and data as near time zero as possible must be obtained. Time zero is defined as the start of effusion, which to good approximation is when the diffusion pump is placed in line.

Table I—Experimental Test of the Placebo Background Approximation at 25°

Experiment	t, min	dm/dt, μg/min, Placebo at $t/2$	Δm (nitro)/t, μg/min: Gravimetric	Assay
One-Half Cut Commercial Tablets (1% Povidone)				
4-1	96	0.12	0.73	0.72
6-1	108	0.12	1.20	1.21
6-2	112	0.12	0.99	0.99
4-2	112	0.12	0.53	0.39
3-1	158	0.10	0.18	0.21
3-2	258	0.08	0.08_1	0.10_5
		Mean, gravimetric − assay =		$+0.01_5$
One-Half Crushed 0.4-mg Commercial Tablets (1% Povidone)				
4-2-A	92	0.22	0.66	0.75
4-2-B	97	0.22	0.49	0.64
4-2-C	98	0.22	0.46	0.57
		Mean, gravimetric − assay =		−0.12

Correction for Instrument Background—The sum of the balance background and the empty cell background, denoted "instrument background," is easily measured by performing the appropriate blank runs. All three cells gave nearly the same empty cell background, and another Knudsen cell was suspended from the tare arm of the balance to cancel most, if not all, of the empty cell background. Thus, the instrument background was determined for a given "configuration" (*e.g.*, Cell 2 tare arm, Cell 1 sample arm) by blank runs, and the total rate of mass loss for a given sample was corrected by subtraction of the blank.

Plots of instrument background *versus* time were roughly linear on a log–log plot and varied from about 1.0 μg/min at t = 2.5 min to about 0.07 μg/min at t = 90 min. Reproducibility at small t was rather poor, only about ±0.2 μg/min at t = 2.5 min; but for t > 10 min, reproducibility was good, about ±0.04 μg/min.

Correction for Water Background—*Placebo Method*—In this method, the water background for a given sample is assumed identical to that for a "placebo" sample, where the placebo contains no nitroglycerin but is identical in all other respects. In short, the presence of nitroglycerin is assumed to have no effect on the rate of water loss from a sample. Placebo water backgrounds were determined for a number of sample types where the water content was of the same order of magnitude, or less, than the nitroglycerin content. For the samples studied, the water background was independent of orifice area and directly proportional to the sample weight[5] (for a given type of sample).

As a check on the validity of the placebo background approximation, the loss in mass of nitroglycerin, Δm(nitro), in time t was determined gravimetrically (using the appropriate placebo background) and by chemical analysis. The procedure, illustrated for cut tablets, is as follows. A tablet is cut into four wedge-shaped pieces. Two pieces are assayed to obtain an "initial" nitroglycerin concentration. The remaining two pieces are placed in a Knudsen cell, and an effusion experiment is allowed to proceed for time t, after which the tablet pieces are assayed to obtain a "final" nitroglycerin concentration.

The loss of nitroglycerin is computed both from the mass *versus* time trace using the placebo background (gravimetric value) and from the assay results (Table I). The experiment number indicates the conditions of the experiment; *i.e.*, Experiment 4-1 refers to a 400-μg

[1] The first attempt was with a butyl rubber "O" ring, but it failed due to sorption of nitroglycerin in the rubber. Teflon (du Pont) "O" rings did not sorb significant quantities of nitroglycerin.

[2] Sartorius model 4102, Brinkmann Instruments, Westbury, NY 11590

[3] Omniscribe model 5121-5, Houston Instruments, Bellaire, TX 77401

[4] In the case of nitroglycerin tablets, the water of hydration in α-lactose is rather firmly bound and contributes little or nothing to the water background at temperatures near 25°.

[5] Some additional observations are: (*a*) plots of water background *versus* time are roughly linear on a log–log plot; (*b*) backgrounds are higher for samples containing povidone; (*c*) backgrounds are higher for crushed tablets than for tablets cut into four wedge-shaped pieces; (*d*) the background for tablets is independent of drying time for drying times between 0.5 and 2 hr and is also independent of sucrose level in the 0.1–0.5% range; and (*e*) the reproducibility of the water background is within ±20%.

tablet run in Cell 1, and 6-2 refers to a 600-μg tablet run in Cell 2. Comparison of the gravimetric and assay results for a given experiment with cut tablets shows that differences between the gravimetric and assay results are random in sign and generally small. Thus, at least as a first approximation, the placebo background approximation is valid for cut tablets. For the crushed tablets, the agreement is less satisfactory; it appears that the placebo background may be too high by about a factor of 2. Clearly, an alternative method for eliminating the water background would be useful.

Differential Method—As indicated earlier, the placebo background is independent of orifice size. By assuming that the water background for a sample is independent of orifice size, regardless of the accuracy of the placebo background approximation, the effects of volatile water may be canceled by the following differential experiment. Identical samples are placed in Cells 1 and 2. Cell 1 ($10^3 A_0 = 2.18$) is suspended from the sample arm of the balance, and Cell 2 ($10^3 A_0 = 0.96$) is suspended from the tare arm. During the effusion experiment, water evaporates from both samples *at the same rate*, thereby canceling, and nitroglycerin effuses from each cell at a rate proportional to the effective area of that cell's orifice. If the vapor pressure is independent of time t, the vapor pressure at any time is given by P_D:

$$10^4 P_D \text{ (Torr)} = \frac{2.854}{10^3 A_D}\sqrt{\frac{T}{M}} R_D \qquad \text{(Eq. 2)}$$

where P_D is the "differential vapor pressure," $A_D = A_0$ (Cell 1) $- A_0$ (Cell 2)[6], and R_D is the observed "net" effusion rate in the differential experiment.

In general, the vapor pressure decreases with time and P_D is equal to the vapor pressure only at $t = 0$. The physical interpretation of the variation of P_D with time will be given later. Empirically, observed P_D data are linear in time from the lowest time where data are taken[7] to a time corresponding to a 30–50% reduction in P_D. Similarly, data taken with either Cell 1 or 2 (using placebo backgrounds) are linear on a *P versus t* plot (one-component nitroglycerin phase) or on a ln *P versus t* plot (multicomponent nitroglycerin phase). Linearity begins at small times[7] and often extends over a fivefold reduction in P for multicomponent nitroglycerin systems.

Assuming that the linear plots remain valid in the small time regions where data are not obtained[8], data extrapolated to $t = 0$ yield the vapor pressure at $t = 0$. Therefore, a comparison of extrapolated differential results with the corresponding results obtained with Cells 1 and 2 (placebo background) is a test of the validity of the placebo background approximation. Several measurements were made on crushed 0.4-mg tablets containing povidone at 25° using Cell 1, Cell 2, and the differential technique.

Qualitatively, the results agree with those in Table I in that, for crushed tablets (1% povidone), the placebo background appears too high. However, the magnitude of the background error is much less, ~20%, rather than a factor of 2. The 20% figure is probably more accurate. Similar comparisons were made for a number of other additive–nitroglycerin–lactose systems. In all cases, good agreement was obtained between Cell 1, Cell 2, and differential measurements.

THEORETICAL

The equation relating mass loss from a Knudsen cell with equilibrium vapor pressure is derived assuming that all rate processes are sufficiently rapid to maintain the equilibrium vapor pressure within the Knudsen cell. While this "equilibrium" assumption is nearly always valid for homogeneous one-component systems, for the systems of interest to this research, there are two "mechanisms" by which the equilibrium assumption may be invalidated.

First, even if the maximum rate of evaporation of nitroglycerin is effectively infinite, as it would be if the nitroglycerin phase is pure nitroglycerin, the vapor cannot leave the sample at an infinite rate due to collisions with the tablet matrix. Thus, the vapor pressure maintained in steady state within the Knudsen cell, which is the vapor pressure measured in the experiment, is less than the equilibrium vapor pressure. This type of nonequilibrium effect is referred to as the "matrix effect."

The second type of nonequilibrium effect may arise when the nitroglycerin phase is a multicomponent system, as is the case in tablets containing stabilizing additives. Here, even if the matrix effect is negligibly small, a nonequilibrium effect can arise due to composition nonhomogeneities developing at the surface of the nitroglycerin phase as nitroglycerin is removed from the sample. If diffusion of nitroglycerin within the nitroglycerin phase is not sufficiently rapid to maintain approximate homogeneity, the vapor pressure measured in the Knudsen experiment corresponds to the composition at the surface layer, which is deficient in nitroglycerin, and not to the mean composition. Thus, this nonequilibrium effect, denoted the "diffusion effect," causes the measured vapor pressure to be lower than the equilibrium value.

The objective in this section is to develop mathematical models for the time dependence of the nonequilibrium effects discussed that are, upon parameterization, useful for a semiquantitative evaluation of nonequilibrium effects for a given set of experimental conditions.

Matrix Effect—The matrix effect will be approximated using a capillary pore model, defined by the following assumptions:

1. The tablet pore structure relevant to nonequilibrium effects is approximated as a network of cylindrical capillary tubes oriented normal to each surface. The capillaries are characterized by a "mean effective radius," a.

2. The number of capillary openings of area πa^2 per unit area of surface, denoted by $\hat{N}$, is taken to be a parameter characteristic of pore structure and, therefore, independent of gross sample geometry. Note that the total number of capillary tubes in the sample is then $\hat{N}A/2$, where A is the surface area. The factor of 1/2 arises since each tube intersects the surface at two points.

3. Nitroglycerin is assumed to exist in a phase that is (initially) homogeneously distributed on the interior surfaces of the capillary tubes. The fraction of capillary volume occupied by nitroglycerin is assumed small. For 0.6-mg tablets, about 95% of the total capillary volume is void.

4. The total area of capillary openings to the surface, $\hat{N}A\pi a^2$, is assumed large compared to the effective area of the Knudsen cell orifice, A_0.

One-Component Nitroglycerin Phase (Conventional Tablets)—Since, in this case, nitroglycerin is in the pure state, the vapor pressure in any volume element containing liquid nitroglycerin at distance or "depth" d from the surface is equal to the equilibrium vapor pressure P^0. Thus, all nitroglycerin is removed from a given volume element at depth d before any nitroglycerin is removed at depth $d + \delta d$. The concentration of *liquid* nitroglycerin is zero between the surface and depth d and is equal to the concentration at time zero at d. The vapor pressure outside the tablet, but within the Knudsen cell, is the apparent vapor pressure, P_a.

Consider a sample of undefined gross geometry but having volume V and surface area A and containing m^0 μg of nitroglycerin at time zero. At time t, evaporation has proceeded to depth d, removing $\Delta m(t)$ μg of nitroglycerin, where $\Delta m(t)/m^0 = \Delta V(t)/V$. Here, $\Delta V(t)$ is the volume of sample that has been "emptied" of liquid nitroglycerin. To first order in time, $\Delta V(t) = Ad$, and:

$$\frac{\Delta m(t)}{m^0} = \frac{Ad}{V} \qquad \text{(Eq. 3)}$$

Under conditions of free molecule flow (*i.e.*, large mean free path), conservation of mass requires that the flow through the Knudsen cell orifice, R_0, is equal to the net flow through the capillary openings, R_c. The flow rate, R_0, is given by the Knudsen relationship (8):

$$R_0 = \beta P_a \equiv \kappa A_0 P_a \qquad \text{(Eq. 4)}$$

where κ is a constant for the present purpose. Consistent with Assumption 4, R_c may be written (8):

$$R_c = \hat{N}A\pi a^3 \frac{8}{3}\kappa\left(\frac{P^0 - P_a}{d}\right) \qquad \text{(Eq. 5)}$$

The number of capillary openings per unit surface area, $\hat{N}$, may be related to the pore volume fraction, ϵ, by the following argument. In the volume element, δV, the total pore volume, V_p, is given by $V_p = \epsilon\delta V = \epsilon Ad$. However, the capillary model demands that the total pore volume is also given by $V_p = \hat{N}A\pi a^2 d$. Combination of the two ex-

[6] Although A_D may be evaluated from the calibrated orifice areas of Cells 1 and 2, it was determined by calibration with benzoic acid at 25° to avoid propagation of errors, yielding $10^3 A_D = 1.31 \pm 0.03$ cm^2.

[7] Because of background variability, reproducibility is poor at times where the background becomes comparable in magnitude to the effusion rate. Therefore, data are taken only for $t > 15$ min for Cell 2; for Cell 1 and differential measurements, data are taken for $t > 7$ min.

[8] Justification for this assumption as a good approximation will be given in the next section, where it is established that nonequilibrium effects for Cells 1 and 2 are negligible with crushed tablets.

pressions for pore volume yields:

$$\epsilon = \pi a^2 \hat{N} \qquad \text{(Eq. 6)}$$

By noting that, to first order in time, $\Delta m(t) = \beta P^0 t$, combination of Eqs. 3–6 yields the desired relationship between the observed vapor pressure, P_a, and the equilibrium vapor pressure, P^0:

$$\frac{P_a}{P^0} = 1 \sim \frac{\gamma \beta P^0}{m^0} t + 0(t^2, \ldots) \qquad \text{(Eq. 7)}$$

$$\beta = 10^4 \sqrt{\frac{M}{T}} \left(\frac{10^8 A_0}{2.854}\right) \qquad \text{(Eq. 8)}$$

where the nonequilibrium parameter, γ, is given by:

$$\gamma = \frac{3}{8}\left(\frac{A_0}{A}\right)\left(\frac{V}{A}\right)\frac{1}{\epsilon a} \qquad \text{(Eq. 9)}$$

The notation $0(t^2, \ldots)$ refers to higher order terms, which cannot be consistently evaluated using this simple capillary model. The result that all geometries behave alike to first order in time is a consequence of the model. The model essentially assumes that, at small times, flow from the sample surface is equal to flow from a slab of the same volume and area.

According to theory, the apparent vapor pressure, P_a, should decrease linearly with time, at least at small times, and the value of P_a extrapolated to $t = 0$ yields the equilibrium vapor pressure at time zero. Moreover, the magnitude of the nonequilibrium effect increases with the ratio A_0/A. To minimize nonequilibrium effects, effusion cells with small orifice areas, A_0, should be employed. Furthermore, a procedure found useful in this laboratory is to cut a given tablet into four equal wedge-shaped pieces, thus maximizing the area while still preserving the tablet character of the sample[9].

The "differential vapor pressure" analog for Eq. 7 may be developed by combination of Eqs. 2 and 7:

$$\frac{P_D}{P^0} = 1 - \left[1 - \frac{A_0(2)/A_0(1)}{[1 + A_0(2)/A_0(1)]^2}\right]\frac{\gamma_{12}\beta_{12}P^0}{m^0} t \qquad \text{(Eq. 10)}$$

$$\gamma_{12} = \frac{3}{8}\left[\frac{A_0(1) + A_0(2)}{A}\right]\frac{V}{A}\frac{1}{\epsilon a} \qquad \text{(Eq. 11)}$$

$$\beta_{12} = \frac{10^7}{2.854}\sqrt{\frac{M}{T}}\,[A_0(1) + A_0(2)] \qquad \text{(Eq. 12)}$$

where $A_0(1)$ and $A_0(2)$ are the effective orifice areas for Cells 1 and 2, respectively. The remaining symbols are as previously defined.

Multicomponent Nitroglycerin Phase (Tablets with Additives)—The diffusion effect is assumed negligible, and the same basic capillary model is used for both single- and multicomponent nitroglycerin phases. However, in the latter case, a significant variation of *equilibrium* vapor pressure with time may occur as the composition changes during a Knudsen experiment. For most additive–nitroglycerin systems studied, the nitroglycerin vapor pressure varied approximately linearly with concentration of nitroglycerin in the sample over a considerable concentration range. Thus, as a first approximation in general and as a rather good approximation[10] for the systems studied:

$$P = \frac{P^0}{c^0}\alpha_1 c + P^0(1 - \alpha_1) \qquad \text{(Eq. 13)}$$

Here, P is the equilibrium vapor pressure at concentration c, and P^0 is the equilibrium vapor pressure at time zero when $c = c^0$. For convenience, c is defined as micrograms of nitroglycerin per unit volume of capillary tubes, or $c = m/\epsilon V$, where ϵ is the pore volume fraction, V is the total volume of the sample, and m is the mass of nitroglycerin. The symbol α_1 denotes a unitless constant, reflecting the magnitude of the dependence of vapor pressure on concentration[10]. In the absence of nonequilibrium effects, use of Eq. 13 and the relationship $dm/dt = \beta P$ yields the equilibrium time dependence:

$$\ln P = \ln P^0 - \frac{\beta P^0 \alpha_1}{m^0} t \qquad \text{(Eq. 14)}$$

where P is the measured equilibrium vapor pressure at time t in the Knudsen experiment.

Nonequilibrium effects will now be estimated using the model defined by Assumptions 1–4 and Eq. 13. Consistent with the assumptions and the result for conventional tablets, at small times all geometries are assumed equivalent to a slab of thickness 2ι, with $\iota = V/A$; the calculations are based on such a slab model. This methodology is motivated largely by the difficulty in obtaining a solution to the problem for any geometry more complex than a slab.

Consider a small volume element of a given capillary tube. Consistent with Assumption 4, the flow past any plane normal to the tube axis is given by:

$$J = -\frac{8}{3} a\kappa \frac{\partial P}{\partial x} \qquad \text{(Eq. 15)}$$

where J is the vapor flux. Conservation of mass requires:

$$\frac{\partial c}{\partial t} = -\frac{\partial J}{\partial x} = \frac{8}{3} a\kappa \frac{\partial^2 P}{\partial x^2} \qquad \text{(Eq. 16)}$$

"Local equilibrium" is assumed in the following sense. At each point in (x, t) space, the vapor phase and the immediately adjacent liquid (or solid) nitroglycerin phase are in thermodynamic equilibrium. Thus, vaporization of nitroglycerin is assumed rapid. With the local equilibrium assumption, the vapor pressure $P(x, t)$ may be directly related to concentration $c(x, t)$ through Eq. 13, and the variable, P, in Eq. 16 may be eliminated to give:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} \qquad \text{(Eq. 17)}$$

$$D = \frac{8}{3} a\kappa \frac{P^0}{c^0}\alpha_1 \qquad \text{(Eq. 18)}$$

Equation 17 is of the same form as Fick's second law with a constant diffusion coefficient. However, in this case, D is not a diffusion coefficient but rather is a "conductance" coefficient for free molecule flow in a capillary tube.

Local equilibrium is likewise assumed at the tablet surface. At the surface, the vapor space adjacent to the liquid (or solid) nitroglycerin phase is the vapor space outside the tablet but within the Knudsen cell. Since the vapor pressure in this region is P_a, the vapor pressure measured in the Knudsen experiment, Eq. 13 implies that:

$$P_a = \frac{P^0}{c^0}\alpha_1 c(\iota, t) + P^0(1 - \alpha_1) \qquad \text{(Eq. 19)}$$

Therefore, if $c(x, t)$ is known from a solution of Eq. 17 subject to the appropriate boundary conditions, P_a may be calculated using Eq. 19.

The first boundary condition is:

$$c(x, 0) = c^0 \qquad \text{(Eq. 20)}$$

where c^0 is the concentration of nitroglycerin in the capillary tubes at $t = 0$. The second boundary condition may be determined by noting that the surface concentration, $c(\iota, t)$, must allow the evaporation rate from the tablet sample, R_c, to equal the rate of effusion through the Knudsen cell orifice, R_0. The total rate of nitroglycerin loss from a tablet containing $\hat{N}/2$ capillary tubes is twice the rate from one surface or:

$$R_c = \hat{N} A \pi a^2 D \left|\frac{\partial c(x, t)}{\partial x}\right| \qquad x = \iota \qquad \text{(Eq. 21)}$$

With R_0 given by Eq. 4 and R_c given by Eq. 21, the equality $R_0 = R_c$ yields:

$$D\left|\frac{\partial c}{\partial x}\right| = \frac{\alpha_1 \beta P^0 \iota}{m^0}(c - \hat{c}) \qquad x = \iota \qquad \text{(Eq. 22)}$$

$$\hat{c} = \left(\frac{\alpha_1 - 1}{\alpha_1}\right) c^0 \qquad \text{(Eq. 23)}$$

The differential equation, Eq. 17, subject to boundary conditions Eqs. 20 and 22 is readily solved using Fourier series. Evaluating $c(\iota, t)$ from the solution given by Crank (9) and using Eq. 19 yield the desired relationship:

$$P_a = P^0 \sum_{n=1} \frac{2\gamma}{\beta_n^2 + \gamma^2 + \gamma} \exp\left(-\beta_n^2 \frac{Dt}{\iota^2}\right) \qquad \text{(Eq. 24)}$$

where γ is the same nonequilibrium parameter defined by Eq. 9, and β_n's are the positive roots of:

$$\beta_n \tan \beta_n = \gamma \qquad \text{(Eq. 25)}$$

[9] The area for a single whole tablet is 0.56 cm^2; for a tablet cut into four equal wedge-shaped pieces (denoted cut tablet), $A = 0.96$ cm^2.

[10] It is readily demonstrated that Eq. 13 should be valid at small times. Assuming $(m^0 - m)/m^0$ is small and adopting a simple model for the polymer additive–nitroglycerin interaction (G. N. Lewis and M. Randall, in "Thermodynamics," revised by K. S. Pitzer and L. Brewer, McGraw-Hill, New York, N.Y., 1961, Eqs. 21–36), one may demonstrate that α_1 is $\alpha_1 = \Phi_2^2[1 - 2(W_\iota/RT)\Phi_1]$, where Φ_2 and Φ_1 are the volume fractions of additive and nitroglycerin, respectively, at time zero; and W_ι is an energy parameter reflecting the interaction between additive and nitroglycerin. When $(m^0 - m)/m^0$ is of order of magnitude of unity, Eq. 13 has no fundamental basis.

Combining Eqs. 9 and 18 and making the substitutions, $\beta = \kappa A_0$ and $c = m/\epsilon V$, give:

$$\frac{D}{\iota^2} = \frac{1}{\gamma}\frac{\alpha_1 \beta P^0}{m^0} \qquad \text{(Eq. 26)}$$

The evaluation of γ from data on conventional tablets, using Eq. 7, indicates that γ is small for the usual nitroglycerin experimental conditions. Furthermore, scatter in background data at small t limits reliable data to $t > 7$ min. Therefore, the form of Eq. 24 for small γ and $t > 7$ min is of particular importance. For $\gamma \sim 1$ or less, solution of Eq. 25 yields:

$$\beta_1^2 \simeq \frac{\gamma}{1 + \gamma/3} \qquad \text{(Eq. 27)}$$

$$\beta_n^2 \simeq (n-1)^2\pi^2 + 2\gamma \qquad n \geq 2 \qquad \text{(Eq. 28)}$$

When γ is nonzero but small (*i.e.*, $\gamma \ll \pi^2$), the terms corresponding to $n \geq 2$ are negligible except at very small times. Specifically, consider a tablet sample, having a mean pore radius, a, of 4 μm (6), which is cut into four wedge-shaped pieces. Here, numerical calculations show that at times greater than 7 min, the $n \geq 2$ terms are less than 3% of the $n = 1$ term. Combination of Eqs. 24–28 yields:

$$\ln P_a = \ln P_a{}^0 - \frac{\alpha_1 \beta P_a{}^0}{m^0} t \qquad \gamma \lesssim 1 \qquad t > \tau \qquad \text{(Eq. 29)}$$

$$P_a{}^0 = \frac{P^0}{1 + \gamma/3} \qquad \text{(Eq. 30)}$$

where $\tau \sim 5$–10 min for cut nitroglycerin tablets. Thus, when nonequilibrium effects are small to moderate in magnitude, the observed vapor pressure, P_a, decreases sharply at very small times to a value slightly less than the equilibrium vapor pressure and thereafter follows a simple exponential decrease with time. Numerical calculations show that Eqs. 29 and 30 are fair approximations even when $\gamma \sim 5$.

For γ_{12} small and $A_0(2)/A_0(1) < 0.5$, the differential vapor pressure analog for Eqs. 29 and 30 may be written:

$$P_D = P_D{}^0 - \frac{\alpha_1 \beta_{12} (P_D{}^0)^2}{m^0} t \qquad \text{(Eq. 31)}$$

$$P_D{}^0 = \frac{P^0}{1 + \gamma_{12}/3} \qquad \text{(Eq. 32)}$$

where pressure is in Torr. All symbols are as previously defined.

In summary, except at very small times, linearity (*i.e.*, $\ln P_a$ *versus* t or P_D *versus* t) is predicted. Extrapolation of vapor pressure data to $t = 0$ does *not* yield directly the equilibrium vapor pressure. However, with a small orifice area and $a \sim 4$ μm, the matrix effect is small. For example, for a sample of one cut nitroglycerin tablet, the matrix effect causes the extrapolated vapor pressure to be lower than the equilibrium vapor pressure by 9% for Cell 1 and 4% for Cell 2.

Critique of Capillary Model—The model assumes that nitroglycerin exists *only* on the interior surface of the capillary tubes and thereby ignores the presence of nitroglycerin on any surface that is not part of a capillary tube. It may be more reasonable to assume that nitroglycerin is uniformly distributed over the *entire* sample surface. The theoretical analysis for *conventional tablets* may be carried out with this modification of the basic model. The results may be summarized as follows. The amount of nitroglycerin outside the capillary tubes, *ms*, is given by:

$$\frac{ms}{m^0} = \frac{1}{1 + 2\epsilon\iota/a} \qquad \text{(Eq. 33)}$$

where the other symbols are as previously defined. The measured vapor pressure, P_a, is constant and equal to P^0 until *ms* μg of nitroglycerin are removed from the surface. Then Eq. 7 applies if t is replaced by $t - t_0$, where:

$$t_0 = \frac{ms/m^0}{\beta P^0/m^0} \qquad \text{(Eq. 34)}$$

In this research, all experimental (P_a, t) data pairs correspond to $t > t_0$. From these considerations, it then follows that the $t = 0$ intercept of a plot of P_a *versus* t will be *higher* than P^0 by the amount δP (surface error), where:

$$\delta P \text{ (surface error)} = +P^0 \frac{3}{16}\frac{1}{\epsilon^2}\frac{A_0}{A} \qquad \text{(Eq. 35)}$$

With $A_0 \sim 2 \times 10^{-3}$ cm^2, the "surface error" is on the order of 0.5% for nitroglycerin tablets, which is negligible. Equation 35 applies only to a one-component nitroglycerin phase. For the multicomponent case, the surface error will be of the same sign but smaller in magnitude.

The error introduced by Assumption 4 may be evaluated by considering each capillary opening as an orifice and thereby offering "resistance" to flow. The resistance to free molecule flow offered by a tube of length L and radius a may, with good approximation, be taken as proportional to the sum (8):

$$\frac{1}{\pi a^2} + \frac{1}{\pi a^2}\frac{3}{8}\frac{L}{a}$$

The first term is due to the end of the tube acting as an orifice (8) and may be termed an "end effect." Assumption 4 is equivalent to neglecting end effects, thereby assuming that when nonequilibrium effects are significant, the resistance to flow is due mainly to the second term, *i.e.*, $L \gg a$.

End effects may be included in the basic model, and the calculations may be performed without the restrictions imposed by Assumption 4. The vapor pressure extrapolated to $t = 0$ is found to be in error by the amount δP (end effect):

$$\delta P \text{ (end effect)} = -P^0 \frac{A_0}{A\epsilon} \qquad \text{(Eq. 36)}$$

In general, the end effect error is small compared to the calculated nonequilibrium effect and, in part, cancels with the error introduced by assuming all nitroglycerin is within the capillary tubes. Comparison of Eqs. 35 and 36 reveals that the cancellation is nearly complete with conventional tablets.

The model ignores capillary condensation of nitroglycerin. It may be more realistic to postulate that a portion of the nitroglycerin is condensed in small short capillaries (or cracks) which empty into either the larger capillaries or the sample surface. Consider the special case of a one-component nitroglycerin phase. If the amount condensed is less than the total amount present, the equilibrium vapor pressure is constant until enough nitroglycerin is evaporated to reach the point where all remaining nitroglycerin is in a "capillary" state.

For this time period, the only factor causing a decrease in vapor pressure with time is the nonequilibrium effect, which should be well approximated by the model. The only correction is due to the amount of nitroglycerin remaining between depth d and the surface. This correction was estimated for nitroglycerin tablets and found to be negligible to first order in time. However, if *all* the nitroglycerin is condensed, the *equilibrium* vapor pressure varies with time from time zero. Assuming a Fruendlich-type isotherm:

$$\frac{m}{\bar{m}} = \left(\frac{P}{P^0}\right)^n \qquad \text{(Eq. 37)}$$

where $\bar{m}$ is the amount of "capillary" nitroglycerin at $t = 0$ and $P = P^0$:

$$\frac{P}{P^0} = 1 - \frac{\beta P^0}{n\bar{m}} t + 0(t^2, \ldots) \qquad \text{(Eq. 38)}$$

The data for nitroglycerin tablets (6) suggest that $n \sim 8$ and $\bar{m} \sim 300$ μg. Thus, comparison of Eq. 38 with Eq. 7 shows that, when γ is small, the variation of equilibrium vapor pressure with time is comparable in magnitude to the calculated nonequilibrium effect. Under these conditions, the matrix effect model is probably a poor approximation. However, when γ is small, nonequilibrium effects are small and even a crude approximation suffices.

In summary, while these model deficiencies may be significant for some types of porous systems, these deficiencies do not introduce serious error for molded nitroglycerin tablets. The poorest approximation made in the theoretical analysis is the assumption that a porous body with flow in three dimensions is equivalent to a capillary impregnated slab of equivalent volume and area with flow in one dimension. While this is a plausible model for small distances from the sample surface, the calculated nonequilibrium effect may be seriously in error at times when flow from the "core" of the sample becomes important.

Thus, for conventional tablets, deviations from the theoretical result (Eq. 7) may be expected when $\beta P^0 t/m^0$ is greater than about 0.5. For tablets with additives, concentration profiles calculated from the slab theory (9) show that flow from the core of the sample becomes significant at about the same time that $\ln P_a$ becomes linear in time. In short, the $t = 0$ intercept in Eq. 29 is probably a good approximation, but the real dependence of the slope on γ may not correspond well with Eqs. 29 and 30. However, since the calculated effect of γ on the slope is quite small for moderate γ, it does not appear likely that a better model would result in a slope dramatically different.

Diffusion Effect—The diffusion effect is assumed to be the only *significant nonequilibrium effect.* The *nitroglycerin–additive phase* is approximated as a "slab" of constant thickness ι and area A_s. Area A_s refers to the total area of the nitroglycerin–additive phase exposed to the vapor phase. At the slab surface ($x = 0$), evaporation of nitroglycerin occurs, resulting in a lower nitroglycerin concentration, C, where C is concentration in *micrograms of nitroglycerin per cubic centimeter of nitroglycerin–additive phase.*

Evaporation at the surface is assumed to be sufficiently rapid to maintain an equilibrium between nitroglycerin *at the surface* and nitroglycerin in the vapor phase. However, in general, the surface concentration, C_s, is less than the mean concentration due to a finite *diffusion rate of nitroglycerin in the nitroglycerin–additive phase.* A relationship between concentration and vapor pressure equivalent to Eq. 13 is assumed. Thus, the measured vapor pressure, P_a, is related to the surface concentration, C_s, by:

$$P_a = \frac{P^0}{C^0}\alpha_1 C_s + P^0(1 - \alpha_1) \qquad \text{(Eq. 39)}$$

To evaluate C_s as a function of time, Fickian diffusion with a concentration-dependent diffusion coefficient is assumed:

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right) \qquad \text{(Eq. 40)}$$

The zero-time boundary condition is:

$$C(x, 0) = C^0 \qquad \text{(Eq. 41)}$$

where C^0 is the initial concentration. The second boundary condition follows from the requirement that the rate of evaporation from the sample, $A_s\,(D\partial C/\partial x)$, $x = 0$, is equal to the rate of effusion from the Knudsen cell, βP_a. By using Eq. 39 to relate P_a to C_s:

$$D\frac{\partial C}{\partial x} = \frac{\alpha_1 \beta P^0 \iota}{m^0}[C_s - \hat{C}] \qquad x = 0 \qquad \text{(Eq. 42)}$$

$$\hat{C} = \left(\frac{\alpha_1 - 1}{\alpha_1}\right) C_0 \qquad \text{(Eq. 43)}$$

For the special case of a constant diffusion coefficient, Eqs. 40–43 are exactly the same in form as the corresponding equations used to evaluate the matrix effect for tablets with additives. Thus, for constant D, the solution of Eqs. 40–43 is given by Eqs. 24–26, provided γ in Eqs. 24–26 is replaced by γ_D where:

$$\gamma_D = \frac{\alpha_1 \beta P^0}{m^0}\frac{\iota^2}{D} \qquad \text{(Eq. 44)}$$

The assumption of a constant diffusion coefficient is realistic if the additive is a liquid that does not interact strongly with nitroglycerin. For this case, $D \sim 10^{-5}$ cm^2/sec. For the usual nitroglycerin experiments (6), $\alpha_1\beta P^0/m^0 \sim 10^{-4}$ sec^{-1} and $\iota \ll 10^{-1}$ cm. Thus, with constant D, $\gamma_D \ll 0.1$, and the diffusion effect is negligible.

If the additive is an amorphous solid "miscible" with nitroglycerin over a wide composition range (*i.e., such as povidone*), the assumption of constant D is a poor approximation for high levels of additive. As a first approximation, D is assumed to vary with concentration exponentially during a Knudsen experiment:

$$D = D_0 \exp(kC/C_0) \qquad \text{(Eq. 45)}$$

where D_0 and k are constants. The constant D_0 is, in effect, the tracer diffusion coefficient of nitroglycerin in the pure additive. While the exponential form is often used to relate D to concentration (9) and is a plausible relationship (10, 11), there is no firm evidence to support this choice of function for systems of interest to this research. Therefore, results based on Eq. 45 must be regarded as semiquantitative, with perhaps only an order of magnitude accuracy in predicting nonequilibrium effects for a given real system.

With D given by Eq. 45, the differential equation cannot be solved analytically; the solution must be obtained numerically. To facilitate numerical calculations, the following dimensionless variables are introduced:

$$X = \frac{x}{\iota} \qquad \text{(Eq. 46)}$$

$$T = \frac{D_0 t}{\iota^2}\exp\left[\frac{k(\alpha_1 - 1)}{\alpha_1}\right] \qquad \text{(Eq. 47)}$$

$$Y = \alpha_1\left(\frac{C}{C^0}\right) - (\alpha_1 - 1) \qquad \text{(Eq. 48)}$$

In terms of X, Y, and T, the differential equation and boundary conditions become:

$$\frac{\partial Y}{\partial T} = \frac{\partial}{\partial X}\left(e^{kY}\frac{\partial Y}{\partial X}\right) \qquad \text{(Eq. 49)}$$

$$Y(X, 0) = 1 \qquad \text{(Eq. 50)}$$

$$e^{kY}\left(\frac{\partial Y}{\partial X}\right) = e^{k\bar{\gamma}Y} \qquad X = 0 \qquad \text{(Eq. 51)}$$

$$Y(0, T) = P_a/P^0 \qquad \text{(Eq. 52)}$$

$$\hat{k} = \frac{1}{\alpha_1}\ln\left(\frac{D^0}{D_0}\right) \qquad \text{(Eq. 53)}$$

$$D^0 = D(t = 0) \qquad D_0 = D(t \to \infty) \qquad \text{(Eq. 54)}$$

$$\bar{\gamma} = \left(\frac{\alpha_1 \beta P^0}{m^0}\right)\frac{\iota^2}{D^0} \qquad \text{(Eq. 55)}$$

Using standard finite difference methods (9), solutions of Eqs. 49–51, were obtained with a computer. Specifically, values of P_a/P^0 were calculated as a function of $(\alpha_1\beta P^0/m^0)t$ for $\bar{\gamma}$ and $\hat{k}$ in the range $0.05 \le \bar{\gamma} \le 10$; $0 \le \hat{k} \le 8$. Agreement between the numerical solutions and the analytical results, Eq. 24, for $\hat{k} = 0$ is within 2% in P_a/P^0.

A selection of the results obtained are shown in Figs. 1 and 2. The equilibrium case, $\bar{\gamma} = 0$, is shown in Fig. 2 as a dashed line. Within the resolution of the graphs, the $\hat{k} = 0$ curves represent the equilibrium case in Fig. 1. The magnitude of the nonequilibrium effect depends strongly on both $\hat{k}$ and $\bar{\gamma}$; even for small (but nonzero) $\bar{\gamma}$, the nonequilibrium effect can be large.

When $\bar{\gamma}$ is small and $\hat{k}$ is large, nonequilibrium effects are small at small t, and the slope of ln P_a *versus* t *increases* as t increases from zero. However, when $\bar{\gamma}$ is large and $\hat{k}$ is small, nonequilibrium effects are large even at very small (but nonzero) times, and the ln P_a *versus* t slope *decreases* as t increases from zero.

Now consider the estimation of $\bar{\gamma}$ and $\hat{k}$ for a typical experiment. As a concrete example, consider the case of a 0.4-mg nitroglycerin tablet containing 0.36 mg of povidone where the Knudsen experiment is performed at 25° using Cell 1. For a sample of this composition, the povidone–nitroglycerin phase is a very viscous gel-like system. As a *rough* guess, the diffusion coefficient of nitroglycerin in this system, D^0, is estimated at $\sim 10^{-7}$ cm^2/sec. The diffusion coefficient of nitroglycerin in low density polyethylene was determined (in this research) to be $\sim 10^{-12}$ cm^2/sec, a value rather typical for large molecules diffusing in amorphous polymers (10–12). Thus, D_0 is estimated as $D_0 \sim 10^{-12}$ cm^2/sec. From Eq. 53 and these estimates of D_0 and D^0, $k \sim 11$. Experimentally, $\alpha_1 \sim 2$, so $\hat{k} \sim 5.5$. Of course, this estimate is very crude and may well be in error by as much as 50%.

Now consider the estimation of $\bar{\gamma}$. For a tablet, scanning electron microscope studies (6) suggest that much of the nitroglycerin–povidone phase is coated on the lactose surface. To evaluate ι, where $\iota = V/A_s$, the surface area must be estimated. The surface area determined by nitrogen adsorption (6) is probably too high for this purpose since much of the surface roughness is "lost" when the crystals are coated with a semiliquid phase. As a better approximation, the surface area is evaluated from the particle-size distribution curve for a sample of the lactose powder used in tablet preparation. The mean particle diameter is 60 μm, and the calculated surface area per tablet (35.6 mg) is 32 cm^2. By assuming that volumes are additive, $\iota \sim 2 \times 10^{-5}$ cm. For this example, $\beta P^0 = 0.033$ μg/sec. Thus, from Eq. 55 and the above estimates, $\bar{\gamma} \sim 10^{-6}$. Even if this estimate is in error by one or two orders of magnitude, the trends shown in Figs. 1 and 2 suggest that with $\hat{k} \sim 6$, the diffusion effect is not even close to being significant *for nitroglycerin tablet samples.*

The theory developed for the diffusion effect is only a rough approximation. The assumed relationship between diffusion coefficient and concentration is probably a reasonable approximation but is not likely to be quantitative. Moreover, the model assumes that the nitroglycerin phase is characterized by a constant thickness. While this is a good approximation for small times, the nonequilibrium effect will probably be overestimated at large times (*i.e.*, when $\Delta m/m^0$ approaches unity). In short, as nitroglycerin is removed from the sample, the effective thickness of the nitroglycerin phase is reduced, thereby decreasing the magnitude of the nonequilibrium effect.

RESULTS

Matrix Effect—*One-Component Nitroglycerin Phase*—As a test of the theory (Eq. 7), several effusion experiments were carried out

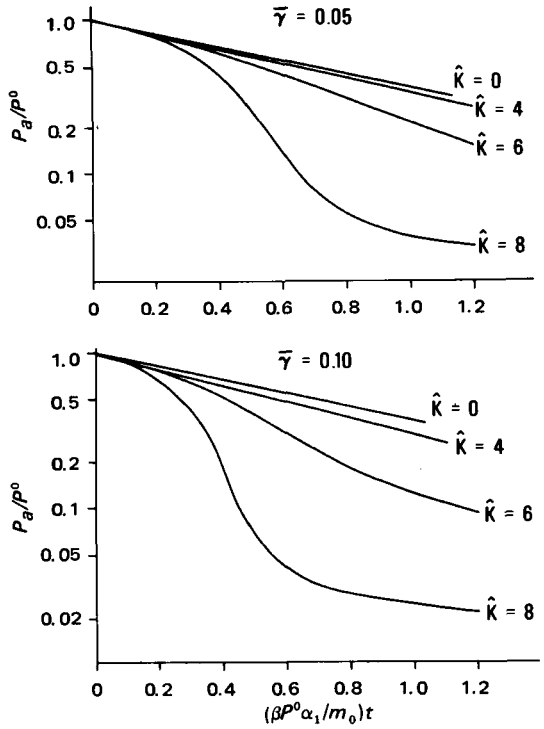

Figure 1—*Numerical solutions of Eqs. 49–51 for selected values of* $\bar{\gamma}$ *and* $\hat{k}$.

at 25° using well aged (6) 0.6-mg conventional commercial tablets (Lot A) from the same bottle. Being well aged, all tablets were assumed to have the same equilibrium vapor pressure at time zero. However, due to intertablet variations, the pore radii evaluated from the data using Eqs. 7–9 may not be identical.

As an example of the observed time dependence of P_a, a portion of the data obtained is illustrated in Fig. 3. As required by theory, P_a *versus* t is linear; in spite of a large variation in slope, all data ex-

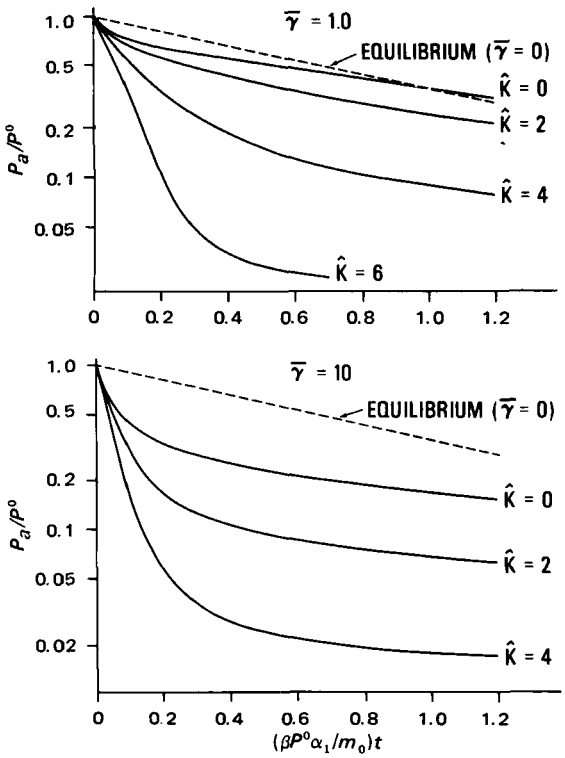

Figure 2—*Numerical solutions of Eqs. 49–51 for selected values of* $\bar{\gamma}$ *and* $\hat{k}$.

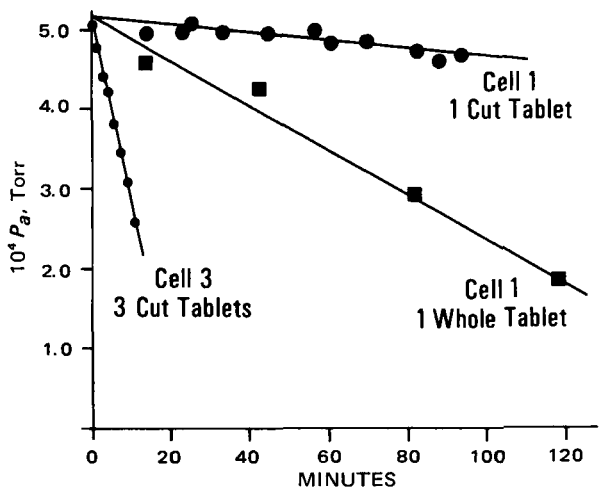

Figure 3—*Observed time dependence of apparent vapor pressure for nitroglycerin in conventional tablets at 25°.*

trapolate to a common value at $t = 0$. For each experiment performed with Lot A, the intercept and slope of the P_a *versus* t curve were evaluated by least-squares analysis; the corresponding value of the pore radius, a, was evaluated using Eqs. 7–9 (Table II). Within the precision of the data, the intercept does not depend on the magnitude of the nonequilibrium effect. While the pore radii calculated from Cell 1 data are in agreement within the precision of the data, the mean pore radius evaluated from the Cell 3 data (large nonequilibrium effect) appears significantly low relative to the other data.

A similar, although less extensive, analysis was carried out with a laboratory lot (0.5 mg) of aged conventional tablets. Three experiments with single tablets in Cell 1 at 25° yielded a mean pore radius of 2.9 ± 0.5 μm. Thus, it is not obvious whether the trend in a values shown in Table II represents a general defect in the theory or a phenomenon peculiar to Lot A. In any case, the data support the following conclusions:

1. The time dependence given by Eq. 7 is a good approximation.
2. The $t = 0$ intercept of Eq. 7 does represent the equilibrium vapor pressure.
3. The slope of P_a *versus* t is semiquantitatively represented by Eqs. 7–9 with $a \sim 4$ μm. Other experimental measures of the pore radius for molded tablets (6) give $a \sim 2$–5 μm.

Multicomponent Nitroglycerin Phase—Numerous data accumulated with Cells 1 and 2 support the theoretical predictions of Eq. 29. Specifically, plots of ln P_a *versus* t are linear. The extrapolated vapor pressures, $P_a{}^0$, obtained with Cell 1 ($A_0 = 2.18 \times 10^{-3}$ cm^2) are, on the average, slightly lower than those found with Cell 2 ($A_0 = 0.96 \times 10^{-3}$ cm^2) on the same sample. However, the uncertainty of the $P_a{}^0$ data is of the same magnitude as the nonequilibrium effect, so a more sensitive test of the theory is required. To this end, a number of experiments with Cell 3 ($A_0 = 27.4 \times 10^{-3}$ cm^2), designed to magnify the nonequilibrium effect, were performed on a single lot of 0.6-mg "stabilized" commercial tablets containing 1% povidone (Fig. 4 and Table III).

Because of the large effusion rate with Cell 3, background uncertainties are not a problem; measurements are possible at very small t. Thus, the data in Fig. 4 reveal not only the linear ln P_a *versus* t plot predicted for $t \gtrsim 7$ min but also show the sharp drop in P_a at very small times required by theory. Also, as predicted from theory, the (linear) intercept at $t = 0$ is smaller for the case of two tablets. Therefore, the theoretical results have at least qualitative validity.

As a quantitative check of the theory, the pore size parameter, a, was evaluated from the Cell 3 data by the following iterative procedure. To obtain a first approximation for P^0, differential data ($P_D{}^0$) are corrected for the small nonequilibrium effect using $a = 4$ μm. Next, this value of P^0 is used to obtain a first approximation for a from the Cell 3 data and Eq. 24. By using the value of a obtained, the calculations are repeated. Since the value of P^0 calculated from $P_D{}^0$ is not particularly sensitive to the choice of a, the iteration converges after several cycles (Table III).

The values of a obtained are of the correct order of magnitude and are, *as a first approximation*, independent of γ. In particular, the

Table II—Effective Pore Radius, a, Calculated from Vapor Pressures for Conventional Tablets at 25°[a]

Cell Used/ Sample	Number of Experiments	Mean $10^4 P^0$	Mean Slope $10^4 P$ *versus* t, min	Mean γ	Mean $a_{\mu m}$
Cell 1/one cut tablet	3	$5.3_7 \pm 0.1_8$[b]	−0.005	0.1_7	$7._2 \pm 1._2$[b]
Cell 1/one whole tablet	3	$5.3_6 \pm 0.1_0$	-0.02_1	0.6_4	5.5 ± 1.0
Cell 3/three cut tablets	2	$5.1_7 \pm 0.0_4$	-0.22_7	1.8_1	2.6 ± 0.01
Mean: all experiments		5.3_0			5

[a] All tablets were 0.6-mg commercial tablets, Lot A; units of pressure are Torr. The vapor pressure of pure nitroglycerin (bulk liquid) at 25° is 5.5×10^{-4} Torr (6). [b] The "uncertainty" given is the standard deviation of the mean and is significant only as a measure of the precision obtained.

agreement between the three-tablet sample in Table III (3.0 μm) is in excellent agreement with the Cell 3 result in Table II (2.6 μm). However, several features of the data suggest that the correspondence between theory and experiment is only semiquantitative.

Consistent with the trend shown in Table II, the data in Table III suggest that values of the a parameter determined from data at large γ are less than a values determined at small γ. Moreover, the slopes of the linear ln P_a *versus* t region are larger than predicted from theory. The theoretical slopes, as calculated from Eqs. 24–26 for the values of γ in Table III, are −0.020 for both three- and two-tablet samples, about 40% lower than the observed slopes.

Although the lack of quantitative agreement between theory and experiment may reflect defects in the theory, experimental error may also be a factor. Small systematic errors in background corrections have a significant effect on a values determined from data where γ is small. Furthermore, measurements with Cell 3 may be subject to small, but detectable, errors arising from the cooling effect of rapidly vaporizing nitroglycerin. The cooling effect would reduce the measured value of the a parameter.

Diffusion Effect—Nearly all experiments in this laboratory have been with samples where $\bar{\gamma}$ (Eq. 55) is expected to be very small, due to either small ι (as in the case of tablets) or large D^0 (as with liquid additives or small amounts of solid additive). For these sample classes, the diffusion effect should be negligible, and the data support this prediction. However, clear indications of a significant diffusion effect were observed for "dry mix" povidone–nitroglycerin samples at povidone–nitroglycerin weight ratios of 1.0 and higher.

Dry mix samples were prepared by dry blending appropriate quantities of povidone and a 10% nitroglycerin trituration on β-lactose. For example, one sample, denoted Dry Mix 3, consisted of aggregates of lactose crystals fused together by a "glue" of povidone–nitroglycerin. Microscopic examination indicated $\iota \sim 10^{-2}$ cm. Following the estimation procedure outlined in the theory section for m^0 = 900 μg (the value corresponding to the experiments), $\bar{\gamma}$ = 0.3 and 4 for measurements with Cells 1 and 3, respectively, at 25°. The parameter $\hat{k}$ is estimated at $\hat{k} \sim 5$. As indicated in the *Theoretical* section, the estimation procedure is very crude. It is clear, however, that a significant nonequilibrium effect is expected, particularly with Cell 3.

Table III—Effective Pore Radius from Vapor Pressure Data on Tablets with Povidone as Calculated from Eqs. 24–26[a]

Experiment	Number of Tablets in Sample	$10^4 P_a{}^0$	Slope[b], Linear ln P_a *versus* t, min	γ[c]	$a_{\mu m}$
1	3	2.9	−0.032	1.7_4	2.7
2	3	3.1	−0.036	1.4_8	3.2
3	2	1.9	−0.039	3.7	1.9
4	2	2.1	−0.035	3.2	2.2

[a] All tablets were from the same lot of commercial 0.6-mg tablets and were cut into four wedge-shaped pieces. All experiments were at 25° with Cell 3. [b] When using α_1 = 1.5, as evaluated from differential data (Cells 1 and 2), the theoretical slopes are −0.021 for three tablets and −0.019 for two tablets. [c] The value of γ is calculated by an iterative procedure using the experimental value (for one cut tablet), $10^4 P_D{}^0 = 4.06$; see text for more detail.

The data obtained with Dry Mix 3 are shown in Fig. 5 as solid symbols. The open symbols correspond to Cell 3 data for one crushed 0.4-mg commercial tablet with povidone. Each crushed tablet point is the mean of two experiments, and vertical lines reflect the uncertainty in the data. The equilibrium curve (solid line) was calculated from Eq. 14. The broken lines are theoretical curves for the indicated values of $\hat{k}$ and $\bar{\gamma}$. Figure 5 is not intended as a quantitative check of theory. Neither the theory nor the data are of sufficient accuracy to warrant such a comparison. However, a very significant nonequilibrium effect does exist with the Dry Mix 3 data. Moreover, the theoretical curves are a reasonable, although far from exact, representation of the data. In particular, at the point where both Cell 3 and Cell 1 data are available, the experimental ratio of Cell 1–Cell 3 P_a data is 3. The theoretical ratio at this point is 4.

Although there appears to be a small nonequilibrium effect for the crushed tablet data, the effect is much smaller than the corresponding effect with Dry Mix 3. This result is due, for the most part, to the smaller ι value for tablets. In fact, the nonequilibrium effect shown for crushed tablets is probably not due to the diffusion effect. Even crushed conventional tablets (one-component nitroglycerin phase) show a small nonequilibrium effect. These nonequilibrium effects are probably due to the powder bed behaving as a matrix. A good fit to the crushed tablet data in Fig. 5 can be obtained with the matrix effect theory using γ = 1.3. For measurements with Cell 1 or 2 on crushed nitroglycerin tablets, the "powder matrix" effect is small (less than ~3%) and may be ignored.

SUMMARY AND CONCLUSIONS

Theoretical and experimental evidence demonstrate that the Knudsen vapor pressure method may yield erroneous results when the sample consists of a small quantity of volatile material dispersed in an inert porous matrix or when the volatile component contains a dissolved polymer. However, with proper experimental design and suitable data analysis, reliable vapor pressure data may be obtained for the special case of molded nitroglycerin tablets and, presumably, for other porous systems as well. Errors due to background effects may

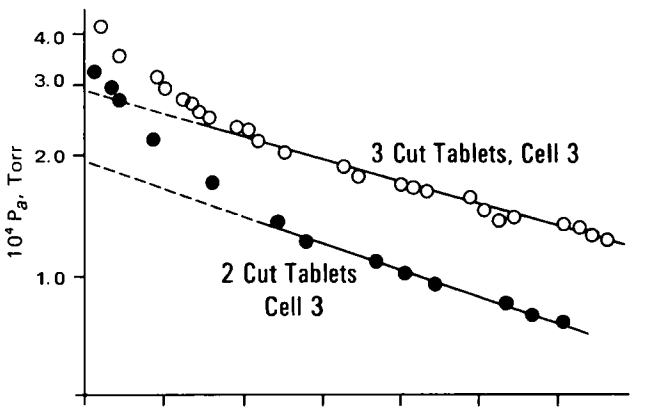

Figure 4—*Observed time dependence of apparent vapor pressure for nitroglycerin in tablets with povidone at 25°.*

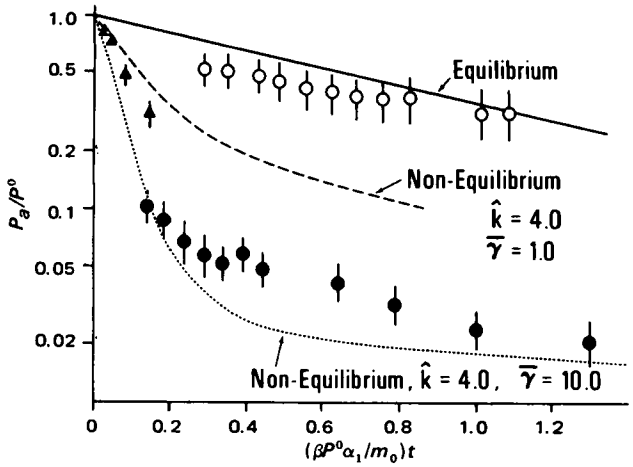

Figure 5—*Experimental evidence for the diffusion effect in povidone–nitroglycerin systems at 25°. Dry Mix 3 is 8.7% nitroglycerin, 9.0% povidone, 0.6% water, and 81.7% β-lactose. The crushed tablet contains 1.1% nitroglycerin and 1.0% povidone. Key: ○, one crushed tablet (0.4 mg), Cell 3; ▲, 10 mg of Dry Mix 3, Cell 1; and ●, 10 mg of Dry Mix 3, Cell 3.*

be minimized by performing blank placebo runs or by the differential technique.

While the numerical data in this report refer only to molded nitroglycerin tablets, the general procedures are probably valid for any porous system where the amount of highly volatile impurity, such as water, is of the same order of magnitude, or less, than the amount of the material under investigation. Nonequilibrium effects are minimized by using Knudsen cells with small orifice areas and (with tablet samples) by cutting the tablet to increase the exterior surface area while maintaining the tablet character of the sample.

When the volatile component is present in the pure state (not a solution), apparent vapor pressures decrease linearly with time due to the matrix effect, and the extrapolated ($t = 0$) value is the equilibrium vapor pressure of the sample (*cf.*, Eqs. 7 and 10). However, if the volatile component is present in a solution phase, the matrix effect cannot be removed by extrapolation; even data extrapolated according to the appropriate equation (*cf.*, Eqs. 29 and 31) are subject to a residual nonequilibrium effect which, if significant, necessitates a correction to the data. Provided a Knudsen cell with a small orifice ($\sim 10^{-3}$ cm^2) is used, the correction is small for molded nitroglycerin tablets.

The diffusion effect may result in the measured vapor pressure being significantly lower than the equilibrium value when the volatile component (solvent) is in solution form. Although negligible for the special case of nitroglycerin tablets, this type of nonequilibrium effect may be sizable when the solute is a highly soluble polymer and the thickness of the solution phase approaches 10^{-2} cm in order of magnitude.

Increasing the Knudsen cell orifice area *decreases* errors arising from background variability but *increases* the magnitude of nonequilibrium effects. The optimum orifice area and the corresponding accuracy of the vapor pressure data depend on the nature of the sample. For cut nitroglycerin tablets containing povidone, the observed precision at 25° was $\sim \pm 0.1$ in $10^4 P$ (Torr) for Cell 1 and differential measurements and $\sim \pm 0.2$ for measurements with Cell 2. Provided the data are corrected for the small matrix effect (using 4 μm for the pore size parameter, a), systematic errors in $10^4 P$ (Torr) from all sources are probably less than $\sim \pm 0.2$.

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