Vapor Pressure of Nitroglycerin in Sublingual Molded Tablets: Implications for Stability

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Abstract □ To understand nitroglycerin intertablet migration, vapor pressures of nitroglycerin in tablets were measured using a modified gravimetric Knudsen effusion technique. To supplement the vapor pressure data, adsorption isotherms at 296°K were determined, and tablets were studied by scanning electron microscopy. For conventional tablets (*i.e.*, tablets without stabilizing additives such as polyethylene glycol 400), the nitroglycerin vapor pressure in a tablet is within about 10% of that for pure liquid nitroglycerin, provided the potency is greater than 0.3 mg. Significant capillary condensation in tablets at relative vapor pressures close to unity is demonstrated. Stabilizing additives lower the vapor pressure of nitroglycerin, the magnitude of the effect depending on both the nature of the additive and the additive–nitroglycerin weight ratio. The mechanism of intertablet migration involves capillary condensation. Vapor pressure reduction of about 15%, achieved through the use of an additive, appears sufficient to prevent significant intertablet migration.

Keyphrases □ Nitroglycerin—vapor pressure in sublingual molded tablets, intertablet migration, effect of additives □ Vapor pressure—nitroglycerin, sublingual molded tablets, effect of additives □ Stability—nitroglycerin sublingual molded tablets, vapor pressure, intertablet migration, effect of additives □ Tablets, sublingual molded—nitroglycerin, vapor pressure, intertablet migration, effect of additives □ Dosage forms—nitroglycerin tablets, vapor pressure, intertablet migration, effect of additives

Several recent studies concerned the stability of molded sublingual nitroglycerin tablets (1–7). Although nitroglycerin undergoes thermal decomposition at elevated temperature (8) and may undergo basic hydrolysis (9), chemical decomposition does not appear to be a serious problem for nitroglycerin tablets (2). The major problem is physical instability. Nitroglycerin volatilizes and readily dissolves in, or adsorbs on, many types of packaging materials (2, 5). Moreover, a "migration effect" was demonstrated recently (2). That is, when nitroglycerin tablets are in a container for several months, nitroglycerin undergoes *permanent intertablet transfer* among a set of nominally equivalent tablets, resulting in decreased content uniformity. The mean potency, however, remains essentially constant.

The migration effect may be nearly eliminated by incorporating a stabilizing additive in the tablet (1). Povidone, polyethylene glycol 400, and polyethylene glycol 4000 have been used commercially[1]. However, both the mechanism responsible for the migration effect and the role of the "stabilizing" additive remain obscure. Nitroglycerin migration probably proceeds *via* the vapor phase (1, 2). If spontaneous transfer of nitroglycerin between two tablets does occur, thermodynamics require that gradients in the nitroglycerin chemical potential exist that do not time average to zero. The cause of the chemical potential gradients (*i.e.*, the driving force) has not been identified.

Fusari (1) suggested that the role of the stabilizing additive is to lower the vapor pressure of nitroglycerin to a point where vaporization is too slow to result in significant nitroglycerin migration. Vapor pressure data are available for liquid nitroglycerin (10–12). No data are available for nitroglycerin in tablets, and the effect of povidone or polyethylene glycol 400 on the vapor pressure of nitroglycerin has not been investigated.

To understand the migration effect and the role of stabilizing additives, vapor pressures of nitroglycerin were measured as a function of: (*a*) nitroglycerin environment (*i.e.*, nitroglycerin in molded sublingual tablets compared to nitroglycerin coated on lactose powder), (*b*) temperature, and (*c*) the nature of the stabilizing additive at selected additive–nitroglycerin ratios. To supplement the vapor pressure data, nitroglycerin adsorption isotherms at 23° were measured for placebo tablets and lactose powder, and scanning electron microscopy studies were carried out with molded tablets.

EXPERIMENTAL

Materials—Commercial tablets[2] were used as received.

Laboratory nitroglycerin samples were all prepared from the same lot of 10% nitroglycerin trituration on β-lactose. Contamination of the nitroglycerin by mono- and dinitrate esters of glycerin, as estimated by TLC, was less than 1%. Acid contamination, as nitric acid, was ~0.02% (w/w nitroglycerin), and the water content (Karl Fischer) of the trituration was ~0.23% (w/w 10% trituration). The solubility of water in nitroglycerin at 25° is only ~0.3% (w/w) (13), so most of the water is external to the nitroglycerin.

Povidone NF, polyethylene glycol USP, and bis(2-ethylhexyl) phthalate[3] samples were used as received except for vacuum drying to remove volatiles. The water used was deionized.

Preparation of Nitroglycerin Samples and Assay—Blending was done with a glass mortar and pestle, and laboratory lots of molded tablets were prepared by the usual procedure (1). The molded tablets were dried in a forced-air oven at 43°, normally for 2 hr. The α-lactose (−120 mesh) used as the diluent had the same specifications as the diluent used in the manufacture of commercial tablets[4]. Samples denoted "powder" were prepared using essentially the same procedure. Samples denoted "dry mix" were nitroglycerin–povidone samples prepared by dry blending appropriate quantities of povidone and the 10% nitroglycerin trituration on β-lactose.

The bis(2-ethylhexyl) phthalate–nitroglycerin samples were prepared by blending appropriate quantities of bis(2-ethylhexyl) phthalate and the 10% nitroglycerin trituration. At lower levels of bis(2-ethylhexyl) phthalate, acetone was added to form a slurry to achieve better mixing. All samples were forced-air dried at 43° for 2 hr.

Unless indicated otherwise, vapor pressure measurements were made only on "aged" samples, *i.e.*, tablets more than 4 months old and powder or dry mix samples more than 2 weeks old.

Nitroglycerin was assayed by a modified Bell (7) procedure.

Vapor Pressure Measurements—Vapor pressures were deter-

[1] Since December 1972, Lilly sublingual nitroglycerin tablets have contained povidone, present as 1% of the total tablet weight. Initially, Nitrostat, the Parke-Davis brand of stabilized nitroglycerin tablets, contained polyethylene glycol 400 at a level of 85% (w/w) of the nitroglycerin content (1). Recently, polyethylene glycol 4000 has replaced polyethylene glycol 400.

[2] All commercial tablets were Lilly molded sublingual nitroglycerin tablets except when noted otherwise.

[3] Bendix Corp.; purified bis(2-ethylhexyl) phthalate was used to prepare solutions of selected nitroglycerin vapor pressures for adsorption studies.

[4] Lilly.

mined by the modified Knudsen effusion method (14). Background and effusion rate data were obtained from the appropriate mass *versus* time curve by numerical differentiation. To minimize nonequilibrium effects (14), all vapor pressure data were determined with Cell 1 (orifice area 2.18×10^{-3} cm^2), Cell 2 (area 0.96×10^{-3} cm^2), or the differential method (14), and most of the tablet data were taken on tablets cut with a razor blade into four equal wedge-shaped pieces (14). The data for tablets with additives were corrected for the small nonequilibrium effect using 4 μm for the pore size parameter, a (14).

As a guard against unexpected nonequilibrium effects, one or both of the following procedures were followed:

1. Replicate measurements were made on each sample using both Cells 1 and 2.
2. For measurements with the differential method, the amount of sample was varied by at least a factor of 2.

Within the expected uncertainty of the data, equilibrium vapor pressures were independent of measurement conditions.

When nonequilibrium effects are negligible, vapor pressure data for additive–nitroglycerin systems may be obtained over a considerable composition range from a single effusion experiment. The loss of nitroglycerin, $\Delta m(t)$, at time t is given by:

$$\Delta m(t) = m^0 - m(t) = \beta \int_0^t P(t)\, dt \qquad \text{(Eq. 1)}$$

where $m(t)$ and m^0 are the masses of nitroglycerin at time t and time zero, respectively; and β is a constant for a given Knudsen cell as defined elsewhere (14). Thus, at any time t, both the vapor pressure and the corresponding composition may be calculated from the effusion experiment. Vapor pressures determined through the use of Eq. 1 are denoted "real time" data.

To eliminate systematic calibration errors, data are reported in the form $P/P^\cdot$, where $P^\cdot$ is the vapor pressure of pure nitroglycerin measured with the same procedure as is used to measure vapor pressure P. The $P/P^\cdot$ data are estimated to be accurate within ± 0.05 in general and within ± 0.02 for the nitroglycerin–bis(2-ethylhexyl) phthalate systems.

Adsorption Isotherms—Nitroglycerin adsorption isotherms for placebo tablets and lactose powder at $23 \pm 2°$ were determined by the following procedure. The placebo tablets, lactose powder, and a given bis(2-ethylhexyl) phthalate–nitroglycerin system of known vapor pressure were all placed in separate cups inside a small chamber[5]. A moderate vacuum (10 Torr) was applied, and the system was sealed. After an equilibration time of 1 month, the placebo tablets and powder were assayed for nitroglycerin.

Preliminary experiments with the 10% nitroglycerin trituration on lactose showed that about 50% of the nitroglycerin transfer to placebo tablets observed after 1 month had occurred within 1 week. Theoretical considerations[6] suggest that equilibrium is reached within about 2 weeks and, at least within the precision of the data, the data obtained at 1 month are assumed to be equilibrium data.

Since bis(2-ethylhexyl) phthalate has a very low vapor pressure, about 10^{-7} Torr (15), essentially no transfer of bis(2-ethylhexyl) phthalate occurs. The quantity of nitroglycerin in the nitroglycerin source was large compared to the amount transferred, and Knudsen vapor pressure measurements before and after the adsorption experiments verified that no significant changes in vapor pressure occurred during the experiment.

Scanning Electron Microscopy—The studies were carried out with a scanning electron microscope equipped with a hot–cold stage[7]. To prevent volatilization during coating and scanning electron microscopic examination, the tablet sample was maintained at low temperatures using procedures similar (but not identical) to those described by Echlin and Moreton (16). A cut tablet was mounted on a specimen stub. A holder[7] (which encloses the sample) was placed on the specimen stub, and the sample was quenched in liquid nitrogen. Nitroglycerin coated on lactose readily supercools[8] so the physical state of nitroglycerin at this point was either a supercooled liquid or a glass, probably the latter.

In preparation for coating, the sample was transferred *via* the holder to a precooled (liquid nitrogen temperature) cold table in a vacuum evaporator. The sample stub was ejected from the holder onto the cold table, and the vacuum chamber was quickly closed and evacuated. After coating with gold and carbon, the vacuum chamber was vented with dry air, the chamber was opened, and the precooled stub holder was immediately placed on the specimen stub. The sample was transferred *via* the holder to the cold stage ($-150°$) of the scanning electron microscope, and the cold stage chamber was immediately evacuated.

Because of the brief exposures of the sample to the atmosphere during the transfer procedures, this technique carries the risk of frost contamination. However, blank experiments carried out with tablets devoid of nitroglycerin (*i.e.*, removed in high vacuum at ambient temperature) showed that frost contamination was slight. The frost that did form was removed by sublimation within 5–10 min at $-100°$ under the high vacuum conditions of the scanning electron microscopic experiment. For samples containing nitroglycerin, frost contamination was not detectable; pictures obtained at $-150°$ were identical, within the resolution obtained, to those of the same area at $-100°$

RESULTS AND DISCUSSION

Physical Characteristics of Molded Tablets (Table I)—The porosity, ϵ, or pore volume fraction is somewhat specific for a given tablet but normally is within the range indicated. Hexagonal closest packing of uniform spheres would give $\epsilon = 0.26$ (18). Since the pore radius data are based upon rather different methods of measurement, only a very rough correspondence may be expected. The pore radii data appear consistent with mercury porosimetry measurements on lactose tablets prepared by direct compression of crystalline lactose (19). The specific surface area [Brunauer, Emmett, and Teller (BET)] is 0.57 m^2/g, a value consistent with a crystalline material having a significant fraction of particles in the micrometer range.

Since the tablets contain 90% α-lactose (monohydrate), the total water content is about 5%. The term "free water," as used in Table I, refers to water in excess of that needed for a monohydrate. The quantity of free water is comparable in magnitude to the nitroglycerin content. However, the solubility of water in the nitroglycerin–povidone phase is small[9], so most of the water is external to this phase and probably forms a film of aqueous lactose on the crystalline surface.

To determine if the distribution of nitroglycerin is uniform in a given tablet, about 0.5 mm of a tablet's surface was removed with a razor blade. This "surface" portion and the remaining "core" portion were assayed for nitroglycerin. For aged 0.6-mg tablets, the surface concentration of nitroglycerin (w/w) was about 25% higher than the corresponding core concentration. *No difference* between conventional and stabilized (1% povidone) tablets was detected. Thus, in

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[5] The chamber was fashioned from inner and outer standard taper vented ground-glass joints (24/40). The total assembly was essentially a tube 15 cm long and 2 cm in diameter. The joints were *lightly* greased with high vacuum silicone grease.

[6] As demonstrated later, when significant quantities of nitroglycerin are adsorbed, most of it is condensed in the smaller tablet pores or "capillaries." Thus, equilibrium is reached when all pores small enough to condense nitroglycerin at vapor pressure P^0 are filled. If it is assumed that the rate of this process is controlled by the rate of gas phase diffusion from the nitroglycerin–bis(2-ethylhexyl) phthalate system to the sample, the rate of mass transfer is independent of time until equilibrium is reached (*i.e.*, the pores are filled). Furthermore, when assuming a Gaussian pore-size distribution with a mean pore size of ~ 4 μm, a first approximation for the equilibration time, τ, may be written:

$$\tau = B \frac{P_T}{P^\cdot} \left(\frac{P^\cdot}{P^0}\right)^2 \frac{1}{\ln (P^\cdot/P^0)}$$

when $(P^\cdot/P^0) - 1 > 0.02$. Here, B is a constant, P_T is the total pressure (~ 10 Torr for these experiments), $P^\cdot$ is the vapor pressure of pure liquid state nitroglycerin, and P^0 is the vapor pressure of nitroglycerin in the bis(2-ethylhexyl) phthalate–nitroglycerin phase. Over the range of $P^\cdot/P^0$ values where capillary condensation occurs, τ calculated from this equation increases as P^0 increases. Although the equation for τ is not defined for $P^0 = P^\cdot$, it is reasonable to assume that, for $0.98P^\cdot \leq P^0 \leq P^\cdot$, τ either remains constant or increases as P^0 increases. The latter is most likely.

Due to a finite nitroglycerin source, impurities, and multilayer condensation on all surfaces within the chamber, the nitroglycerin vapor pressure in the chamber at equilibrium will be slightly less than $P^\cdot$, even when no bis(2-ethylhexyl) phthalate is present. Thus, the equilibration time will always be finite. In particular, for the case of a 10% trituration of nitroglycerin on lactose as the nitroglycerin source, the observed rate is consistent with P^0 being 1 or 2% lower than the vapor pressure of pure liquid nitroglycerin and $\tau \sim 2$ weeks. When the nitroglycerin source is a bis(2-ethylhexyl) phthalate–nitroglycerin solution, $P^\cdot/P^0$ is greater and less time is required to reach equilibrium.

[7] ETEC Inc., Hayward, Calif.

[8] Differential thermal analysis studies did not show any evidence for a first-order phase transition near the melting point on samples of 10% nitroglycerin–90% α-lactose that were quenched in liquid nitrogen.

[9] That is, while the povidone–nitroglycerin system is a single phase, addition of water at about a 1:1 volume ratio produces a two-phase system of roughly the same volume ratio as before mixing.

Table I—Physical Characteristics of Molded Nitroglycerin Tablets

Property	Value
Weight	35 mg
Volume	0.032 cm^3
Pore volume fraction[a], ϵ	0.2–0.3
Effective pore radius; Poiseuille's law gas flow[b]	2 μm
Maximum pore radius; ASTM Test E128-61[c]	5 μm
Effective pore radius; nonequilibrium vapor pressure effects[d]	4 μm
Free water (*i.e.*, nonhydrate water)[e]; tablet with 1% povidone	0.18 mg
Surface area; BET nitrogen adsorption	200 cm^2

[a] Evaluated from the tablet weight and volume and the density of α-lactose. Measurements of the volume of ethanol "absorbed" by tablets gave essentially the same results. [b] Evaluated from experimental data for the volume of nitrogen flow at various pressures (17). A capillary model was used for the tablet pores, and Poiseuille's law was employed to develop the equation used to evaluate the pore radius from the experimental data. The value obtained may be slightly low due to turbulent flow. [c] This test is the standard ASTM test for the maximum pore size of porous filters. The porous body (*i.e.*, tablet) is immersed in a liquid (ethanol), and air pressure is applied until the first bubble of air passes through the porous body. The effective maximum pore radius is then calculated from the surface tension of the liquid and the applied pressure. The tablet was sealed with wax in a holder to eliminate leakage around the tablet sides. Numerous pores near the maximum pore size were observed. [d] From Ref. 14. [e] Determined from loss on drying placebo tablets under high vacuum. Karl Fischer water assays gave essentially the same results.

agreement with earlier speculation (2), some flow of nitroglycerin toward the surface appears to occur during the drying process, presumably due to capillary action.

Scanning Electron Microscopy—Scanning electron microscopy was undertaken to gain information concerning the physical state of nitroglycerin in a tablet. Fresh (*i.e.*, 1 month old) 0.3-mg tablets were used. The areas investigated were freshly cut surfaces located near one of the original tablet surfaces.

Representative scanning electron microscopy results are given in Fig. 1. Figure 1A is a photograph of a conventional tablet (no stabilizing additive) which was taken at −150°. A photograph of the area covered by the top portion of Fig. 1A was taken at −100° and, within the resolution obtained, the photographs were identical. Several areas were scanned at −100° over about 30 min, and all had the same general appearance.

Figure 1B is an example of the surface structure observed for a conventional tablet that had been subjected to high vacuum at ambient temperature prior to the scanning electron microscopic experiment. This procedure removed all nitroglycerin, so the surface structure in Fig. 1B is due to lactose and the small amounts of sucrose (0.1%) and impurities present. Thus, the difference between Figs. 1A and 1B is due to nitroglycerin. Figures 1C and 1D are representative photographs of a tablet containing povidone at temperatures of −100 and −10°, respectively.

To determine the temperature dependence of the surface structure, the temperature of a sample was increased from −100 to +35°, and the surface was monitored on the scanning electron microscope screen. The lactose surface (Fig. 1B) showed no changes in the temperature range investigated. The tablet containing nitroglycerin without povidone (Fig. 1A) yielded several dramatic effects. At a temperature around −80°, the sphere-like structure seen in Fig. 1A started to disappear; within about 1 min, the sample surface was essentially the same as that observed for a sample devoid of nitroglycerin (Fig. 1B).

At this point, several small patches of liquid-like material were observed on the surface. These patches grew in size, diminished in size, and finally disappeared, all within 10–20 sec. These phenomena ceased within 1–2 min; but before a photograph could be made, resolution was lost due to excessive surface charging. Evidently, the dynamic phenomena observed had badly eroded the conductive coating. All of the sample changes referred to occurred within about 5 min at temperatures between −80 and −50°.

With the tablet containing povidone, changes were not obvious until around −10°, where the vacuum gauge indicated a significant loss of volatiles from the sample and some of the surface features appeared to shrink. The changes ceased after 5–10 min; no further changes were obvious up to +35°, where the experiment was terminated. Figure 1D is representative of the "stable" surface structure from −10 to +35°.

The lactose surface is characterized by three main features, which are all illustrated in Fig. 1B:

1. Numerous examples of sharp angles characteristic of a crystalline sample are observed, and some of the larger crystals contain cracks. These features are particularly evident in the lower left quadrant of Fig. 1B.
2. A large number of fines are distributed on the surface.
3. A minor fraction of the surface has the appearance of an amorphous solid containing numerous craters. A few of these craters are visible in the center area of Fig. 1B. The straight horizontal lines, particularly evident in the top half of Fig. 1B, are charging artifacts due to the sample.

As a first approximation, nitroglycerin is absent from Fig. 1D, and the difference between Figs. 1B and 1D represents the contribution of povidone to the surface structure. Except for several crystal faces in the center of Fig. 1D, povidone obscures the crystalline character of the lactose and appears to be present in two forms: (*a*) a coating on the lactose fines and surface irregularities, as is evident in the upper and lower left quadrants of Fig. 1D; and (*b*) a nonuniform "spider web" form covering some of the crystalline surface. This form is particularly evident in the center of Fig. 1D. Presumably, the areas covered by povidone in Fig. 1D also contained nitroglycerin in the original tablet.

For tablets containing nitroglycerin (Figs. 1A and 1C), the tablet surface appears as an aggregate of sphere-like particles ranging in diameter from the limit of resolution, about 0.1 μm, up to about 3 μm. In particular, there was an obvious lack of sharp angles which are characteristic of a crystalline sample. Both stabilized (Fig. 1C) and conventional (Fig. 1A) tablets have the same general appearance when allowance is made for the difference in magnification. The main difference is that the sphere-like particles are less well defined in the case of the tablet with povidone, an observation consistent with a larger volume of liquid phase. Povidone and nitroglycerin are mutually soluble at 25° and form a viscous, gel-like liquid at a 1:1 weight ratio. Thus, a larger volume of liquid phase for a tablet containing povidone is expected. The temperature dependence of the sphere-like structure is undoubtedly due to evaporation of nitroglycerin under high vacuum. The interpretation of the observations regarding appearance and disappearance of liquid-like material is less obvious. Perhaps supercooled liquid nitroglycerin was being forced out of small pores by thermal expansion, forming pools of liquid which then evaporated.

In view of the aggregate nature of the structure, the sphere-like particles are most likely *not* completely liquid; that is, a system of liquid droplets would be mechanically stable only if the droplets were not in contact. Moreover, most of the sphere-like particles are not *perfect* spheres. Thus, the sphere-like structure probably represents nitroglycerin (Fig. 1A) or nitroglycerin–povidone (Fig. 1C) coated on the fines and surface irregularities characteristic of the lactose surface. The coating is sufficiently thick and uniform to obscure the "sharp angles" characteristic of a crystalline surface but, at least in some areas, sufficiently thin to allow surface irregularities on the order of 0.2 μm to be observed, suggesting that at least the larger sphere-like objects are mostly lactose.

If it is assumed that the Kelvin equation (20) may be applied to the sphere-like state for nitroglycerin, the vapor pressure for this state would be slightly greater than for bulk phase nitroglycerin (due to the convex liquid–vapor interface). However, the vapor pressure elevation would be quite small, about 1%, for spheres 1 μm in diameter[10].

Adsorption Isotherms—To investigate the surface properties of a molded tablet, in particular the pore structure, adsorption isotherms for nitroglycerin were determined. The multilayer condensation curve is approximated by the adsorption isotherm for the lactose powder used in tablet preparation, and the difference between the tablet and powder isotherms represents "capillary" condensation in the tablet. The tablet sample in most cases was five tablets. Two independent experiments were performed at 23°, using different batches of nom-

[10] Based on the Kelvin equation and the data for nitroglycerin (21) at 25°, $\bar{V}$ = 143 cm^3/mole, surface tension = 50 dynes/cm^2, and density = 1.59 g/cm^3.

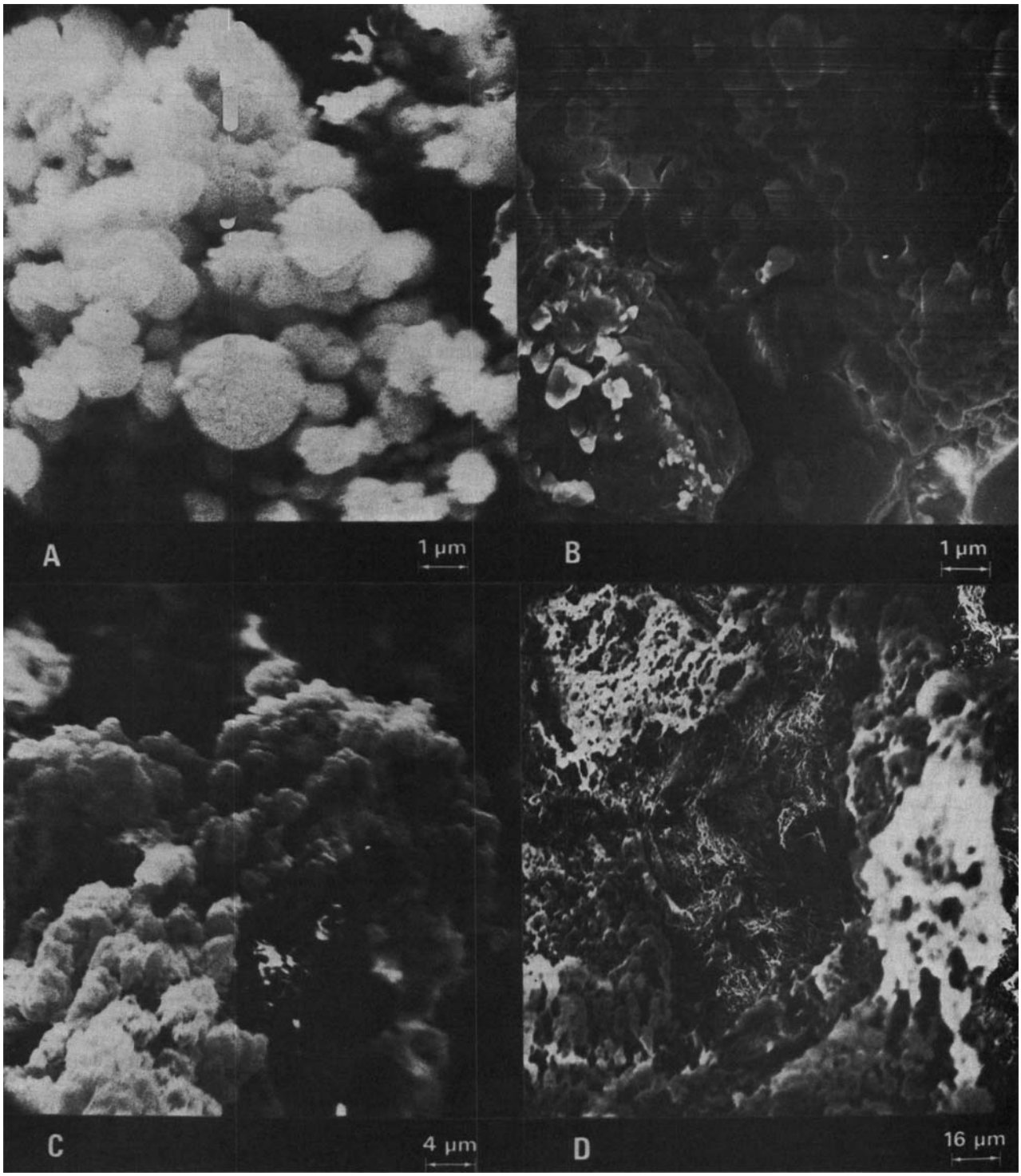

Figure 1—*Scanning electron micrographs of molded sublingual nitroglycerin tablets. Key: A, 0.3-mg conventional tablet, from −150 to −100° (both temperatures gave identical results); B, 0.3-mg conventional tablet with nitroglycerin removed prior to experiment, −100°; C, 0.3-mg stabilized tablet (1% povidone), −100°; and D, 0.3-mg stabilized tablet (1% povidone), −10°.*

inally equivalent "laboratory" placebo tablets without stabilizing additives. The estimated uncertainty is ±10% for the tablet data and ±20% for the powder data.

A given relative vapor pressure of nitroglycerin was maintained through the use of bis(2-ethylhexyl) phthalate–nitroglycerin solutions. Vapor pressure data for these solutions are given in Table II. The adsorption data are shown in Fig. 2, where nitroglycerin adsorbed, in micrograms per 35.6-mg sample, is plotted as a function of relative pressure, $P/P^{\cdot}$, where $P^{\cdot}$ is the vapor pressure of pure "bulk phase" nitroglycerin. The uncertainty in $P/P^{\cdot}$ is ±0.02 at all pressure values. The insert in the upper left quadrant of Fig. 2 gives the low pressure data on an expanded scale.

At relative pressures of 0.6 and lower, the multilayer (*i.e.*, powder) data and the tablet data are in agreement within experimental error. Thus, capillary condensation of nitroglycerin is undetectable (less than ~2 μg) below $P/P^{\cdot} = 0.6$. However, tablets show much greater adsorption at higher pressures. At relative pressures of 0.9 and higher, large quantities of nitroglycerin (~200 μg) are condensed in the pore structure of the tablet.

In general, the tablets were assayed as composite samples and no

Table II—Vapor Pressures of Nitroglycerin in Nitroglycerin–Bis(2-ethylhexyl) Phthalate Solutions at 25.0°

Nominal Mole Fraction Bis(2-ethylhexyl) Phthalate[a]	Measured Weight Ratio: Bis(2-ethylhexyl) Phthalate–Nitroglycerin[b]	P/P°[c] (±0.02)
0.0	0.00	1.0
0.3	0.82	0.97_5
0.4	1.26	0.91
0.5	1.91	0.79
0.55	2.33	0.70
0.60	2.86	0.60
0.65	3.5	0.50
0.70	4.4	0.39
0.75	5.7	0.29
0.80	7.6	0.22
0.90	17	0.11

[a] Mole fraction of bis(2-ethylhexyl) phthalate before drying at 43° in forced air for 2 hr. [b] Determined by nitroglycerin assay on dried samples. [c] P° ≡ vapor pressure of pure nitroglycerin.

information concerning variability of adsorption between tablets was obtained. However, for one group of six tablets at equilibrium (in the same experiment) with $P/P^{\circ} = 1.00 \pm 0.02$, single-tablet assays were performed. The results, in micrograms of nitroglycerin per 35.6-mg tablet sample, are 413, 338, 329, 326, 286, and 260. The standard deviation for these six assay results is ±15%. Thus, nitroglycerin adsorption is quite variable, indicating that the volume of *small* pores varies considerably among nominally equivalent tablets. It is interesting, and probably significant, that the standard deviation of 15% is of the same magnitude as the average standard deviation (12%) for assays on single, aged, conventional 0.3-mg tablets (2).

Nitrogen adsorption–desorption isotherms at 79°K were also determined for molded tablet samples (free of nitroglycerin). The nitrogen isotherms are in qualitative agreement with the nitroglycerin isotherms; that is, condensation of nitrogen in tablet pores is indicated by the data at high relative pressures.

Vapor Pressure Measurements—*Liquid Phase Nitroglycerin*—Since the thickness of the nitroglycerin coating on lactose at a 10% level corresponds to a multilayer thickness of several thousand molecules, the physical state of nitroglycerin in a 10% trituration on lactose is essentially that of bulk phase nitroglycerin, and vapor pressure data for such a sample refer to pure liquid nitroglycerin. Consistent with this conclusion, vapor pressures for samples of the 10% trituration were independent of the amount of nitroglycerin remaining in the sample until essentially all nitroglycerin was removed. At 25°, the vapor pressure of liquid nitroglycerin is, in units of 10^4 P (Torr), 5.4_9 (Cell 1), 5.3_8 (Cell 2), and 5.6_0 [differential method (14)]. The mean of these data, 5.5×10^{-4} Torr, is in excellent agreement with the mean of the best literature data (10–12), 5.0×10^{-4} Torr. At 37°, $P = 22.0 \times 10^{-4}$ Torr.

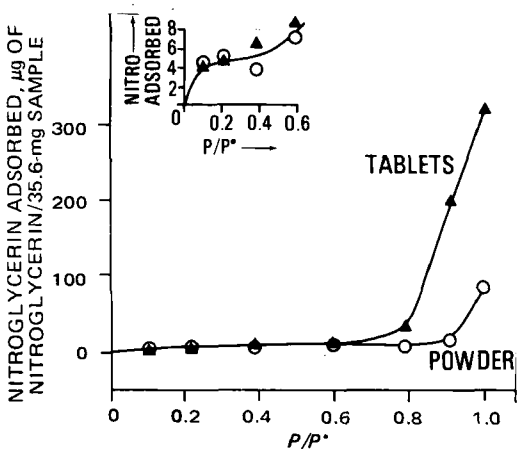

Figure 2—*Nitroglycerin adsorption isotherm at 23° for conventional molded sublingual tablets and α-lactose powder.*

Table III—Vapor Pressure Data for Conventional 0.3-mg Sublingual Tablets: Comparison of Aged and Fresh Tablets at 25°[a]

Tablet	$\sigma(10^4 P)$[b]	P/P°	−Slope[c]
	Aged Tablets		
1	±0.10	0.83	0.000
2	±0.17	0.89	0.000
3	±0.09	0.90	0.000
4	±0.05	0.91	$0.001_7 \pm 0.000_9$
Mean 1–4	0.10	0.88	
SD in $P/P^{\circ} = \pm 0.035$			
	Fresh Tablets		
5	±0.13	1.00	0.014 ± 0.003
6	±0.09	0.90	0.003 ± 0.002
7	±0.13	0.92	0.004 ± 0.002
8	±0.18	1.09	0.027 ± 0.004
Mean 5–8	±0.13	0.98	0.012
SD in $P/P^{\circ} = \pm 0.08_4$			

[a] Aged tablets are Lot C: mean potency is 262 μg, standard deviation for assay of 30 tablets is 19%, and age is 2 years. Fresh tablets are Lot D: mean potency is 316 μg, standard deviation is 9%, and age is 1 month. All measurements were with Cell 2 on tablets cut into four equal wedge-shaped pieces. [b] Standard deviation of fit for 10^4 P (Torr) *versus* t. [c] Slope for 10^4 P (Torr) *versus* t (minutes). Slope is assigned a value of zero when the standard deviation of the slope is larger than the slope. When using $a = 4$ μm, the theoretical slope (14) for nonequilibrium effects is −0.0006. The uncertainty given for a slope is the standard deviation of the slope.

Fresh Conventional Tablets—If the migration effect is real, a lack of equilibrium must exist in freshly prepared tablets, and differences in vapor pressure should exist. In an attempt to observe anomalous behavior in vapor pressure data that could be attributed to a lack of equilibrium, vapor pressure measurements were made on two lots of conventional 0.3-mg tablets using identical experimental procedures and data analysis. One lot (Lot C) was aged 2 years, and the fresh lot (Lot D) was 1 month old.

The only factor affecting the *precision* of vapor pressure data is the reproducibility of the background corrections (14), which is known from experiment. Thus, the expected standard deviation in a set of measurements of P/P° is calculated to be $\pm 0.04_1$ for the conditions of this experiment. Moreover, theoretical considerations (14) indicate that the observed vapor pressure should be essentially independent of time over the time range of this experiment; *i.e.*, the theoretical slope (14) of 10^4 P (Torr) *versus* t (minutes) is calculated as -0.000_6.

The data obtained are summarized in Table III. The second column gives the standard deviations in 10^4 P (Torr) for the linear fit. The observed scatter is typical for measurements with Cell 2 and is roughly the same for both aged and fresh tablets. The third column gives the apparent relative vapor pressure at zero time, which is the equilibrium relative vapor pressure for the tablet if the tablet is initially in internal equilibrium. For aged tablets, the precision (*i.e.*, standard deviations in P/P°) is consistent with the expected precision of the measurement. However, the standard deviation in P/P° for fresh tablets is about a factor of 2 larger than expected.

The time dependence is given in the last column in Table III in the form of the slope of the linear 10^4 P (Torr) *versus* time (minutes) curve. For aged tablets, the time dependence is too small to be consistently observed above the scatter in the data, as expected. However, fresh tablets show a decrease in vapor pressure with time that is much larger than can be accounted for by theory (14). Moreover, at least for Tablets 5 and 8, the slope appears far too large to be rationalized in terms of experimental error. Thus, the vapor pressure results for fresh tablets are anomalous, and the anomaly has physical meaning.

These results may be interpreted as evidence for a lack of equilibrium in fresh tablets. If a given tablet is not in internal equilibrium, the tablet approaches equilibrium at some finite rate upon aging. Transfer of nitroglycerin occurs from a state of higher chemical potential to a state of lower chemical potential. Data presented earlier in this report suggest that the state of low chemical potential is nitroglycerin condensed in small capillary pores which, by virtue of the concave liquid–vapor interface, has a relative vapor pressure less than unity (20). The state of higher chemical potential is probably that of nitroglycerin coated on lactose fines (Fig. 1A).

As the sample ages and equilibrium is approached, the "average"

Table IV—Vapor Pressures of Nitroglycerin in Conventional Sublingual Tablets

Tablet Sample	Mean Tablet Potency, μg	Relative Vapor Pressure[a], $P/P^{\cdot}$ Uncertainty, ±0.05	
		25.0°	36.9°
0.6 mg, aged (Lot A)	625	0.97[b]	0.88
0.4 mg, aged (Lot B)	400	1.01	0.88
0.3 mg, aged (Lot C)	262	0.90	0.88
0.3 mg, fresh (Lot D)	316	0.98	—

[a] $P^{\cdot}$ ≡ vapor pressure of liquid state nitroglycerin at temperature t. At 25°, $P^{\cdot} = 5.5 \times 10^{-4}$ Torr; at 36.9°, $P^{\cdot} = 21.9 \times 10^{-4}$ Torr. [b] Crushed tablets yielded $P/P^{\cdot} = 0.97$.

nitroglycerin vapor pressure decreases. The rate of approach to equilibrium is slow under ambient conditions and probably is limited by gas phase diffusion. However, at low pressure (~5×10^{-4} Torr), diffusion can no longer be rate limiting, and the sample approaches equilibrium at a significant rate during the effusion experiment, resulting in a decrease in apparent vapor pressure with time. The wide range of slopes for fresh tablets suggests that the tablets are not uniform in their displacement from equilibrium. Thus, a larger standard deviation in $P/P^{\cdot}$ is expected for fresh tablets than for tablets at equilibrium, as observed.

Aged Conventional Tablets—Vapor pressure data for aged conventional tablets of varying potency are given in Table IV. The fresh tablet (Lot D) data from Table III are included for comparison. At 36.9°, each entry represents the mean of two tablets; at 25°, each entry is the mean of at least four tablets.

The nitroglycerin adsorption isotherm (Fig. 2) indicates that a conventional molded tablet containing more than 0.3 mg of nitroglycerin at equilibrium should have a relative vapor pressure, $P/P^{\cdot}$, of unity within the accuracy of the Knudsen experiment. This conclusion is rigorous only near 25°, but it should also be a good approximation at other temperatures. In general, the vapor pressure data are consistent with the adsorption data. The relative vapor pressures at 25° for Lots A and B are unity well within experimental error, and the value for Lot C is slightly less than unity. The vapor pressures at 36.9° show no evidence of a dependence on tablet potency. However, the deviation from unity is somewhat larger than expected, an observation for which no explanation is obvious.

Stabilized Tablets—The effects of sample form (tablet *versus* powder) and "free water" content were investigated for nitroglycerin–povidone systems[11] (Fig. 3). Each experimental point is a mean of at least two, and normally more than four, replicate measurements. The data for crushed 0.4-mg tablets at povidone–nitroglycerin weight ratios higher than 0.87 are real time data (see *Experimental*). The solid curve represents the mean of all nontablet samples. The estimated uncertainty in relative vapor pressure is indicated by vertical lines.

As an excellent first approximation, the vapor pressure of a sample depends only on the povidone–nitroglycerin weight ratio. An order of magnitude increase in the ratio of free water to nitroglycerin does not significantly affect the vapor pressure. Moreover, the differences between tablet samples and nontablet samples are small and probably not significant. In particular, while the point for 0.3-mg tablets (weight ratio 1.15) appears somewhat lower than the solid curve, the vapor pressure for the same lot of tablets, when crushed, is also lower by nearly the same amount.

The effects of different additives on nitroglycerin vapor pressure are compared in Fig. 4. The povidone data refer to the smoothed nontablet data taken from Fig. 3. Although bis(2-ethylhexyl) phthalate is not used as a stabilizer, bis(2-ethylhexyl) phthalate–nitroglycerin data are included for purposes of comparison. Within experimental error, the two polyethylene glycols are identical in their

[11] The level of sucrose was varied between 0 and 1.4% for several tablet and powder samples with no apparent effect on the vapor pressure. Since sucrose is not soluble either in nitroglycerin or in the additives considered here, this result was expected.

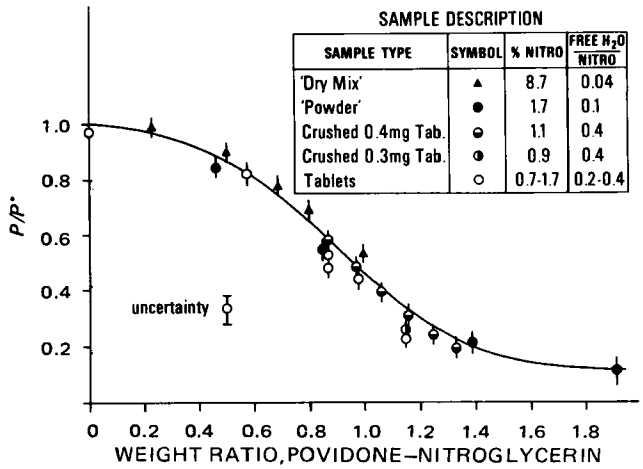

Figure 3—*Effects of sample type and free water on vapor pressure for nitroglycerin–povidone systems at 25°. P· ≡ vapor pressure of pure nitroglycerin.*

effects on the vapor pressure of nitroglycerin. The vapor pressure of a polyethylene glycol 400 stabilized tablet[12] is in excellent agreement with the powder curve. Both povidone and the polyethylene glycols significantly reduce the vapor pressure of nitroglycerin at weight ratios higher than 0.5. At high weight ratios, povidone is more effective in reducing the vapor pressure of nitroglycerin. Crude solubility measurements on microscopic samples indicate that all additives considered in Fig. 4 are soluble in nitroglycerin at weight ratios below ~1. Thus, the differences between bis(2-ethylhexyl) phthalate and the other additives are due to differences in the effective nitroglycerin–additive interaction in solution.

Vapor pressures at 37° were measured for povidone–nitroglycerin systems over a weight ratio range of 0.2–1.0. When the data are expressed in terms of relative pressure, $P/P^{\cdot}$, where $P^{\cdot}$ is the vapor pressure of pure nitroglycerin at 37°, the 37° data fall on the povidone curve in Fig. 4 (25° data) within the uncertainty of the data. Thus, the heat of vaporization of nitroglycerin is not greatly changed by the presence of povidone, indicating that the magnitude of the enthalpy change for the transfer process, nitroglycerin (pure liquid) → nitroglycerin (povidone–nitroglycerin system), is about 1 kcal/mole or less.

MIGRATION MECHANISMS

On the basis of the data, the following mechanism for the migration effect is proposed. Freshly prepared tablets exhibit significant and variable deviations from equilibrium due to a number of empty or partially filled small pores. As the tablet system (*e.g.*, 100 tablets in a bottle) approaches equilibrium, nitroglycerin is transferred from

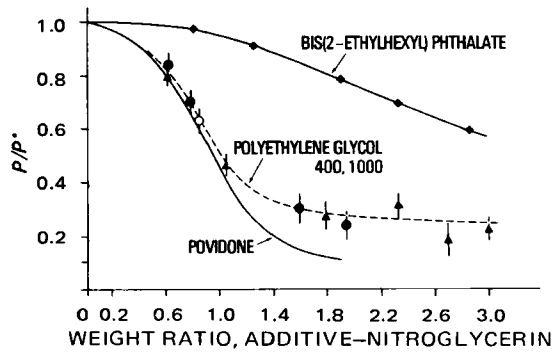

Figure 4—*Nitroglycerin vapor pressure reduction by additives at 25°: comparison of povidone, polyethylene glycols, and bis(2-ethylhexyl) phthalate. Key: ●, polyethylene glycol 400 powder sample; ○, polyethylene glycol 400 tablet; and ▲, polyethylene glycol 1000 powder sample.*

[12] Nitrostat, Parke-Davis and Co.

regions of high chemical potential (*i.e.*, coated on the lactose surface as shown in Fig. 1A) to the empty or partially filled small pores, which are states of lower chemical potential. When all pores small enough to condense nitroglycerin at the prevailing vapor pressure are filled, the surface-to-pore transfer stops. Since a given tablet is not an isolated system, intertablet as well as intratablet transfer takes place, resulting in potency variations of the same order of magnitude as variations in the volume of small pores.

The role of the stabilizing additive is *not* to minimize the migration effect by slowing the *rate* of volatilization. First, although the reduction in vapor pressure achieved in commercial formulations slows the rate of volatilization, the magnitude of the reduction is not sufficient to delay the development of poor content uniformity by more than a few months. For commercial polyethylene glycol 400 tablets[12], the reduction is about 35%; these stabilized tablets would be stable (*i.e.*, maintain good content uniformity) only about 35% longer than conventional tablets. Thus, an additive would not minimize the migration effect but would only moderately slow its development.

Second, if the additive minimized the migration effect by slowing the rate of volatilization, the formulation that produced the lowest vapor pressure would be superior. However, in spite of a higher vapor pressure (a factor of 2.5), 0.3-mg tablets stabilized with polyethylene glycol 400[12] appear equivalent to 0.3-mg tablets stabilized with povidone.

The role of the additive is clearly to lower the vapor pressure. However, the vapor pressure must be lowered *only enough to make it thermodynamically impossible for a significant quantity of nitroglycerin to be transferred from the lactose surface to a small pore.* Thus, for thermodynamic reasons, most of the permanent intertablet nitroglycerin migration occurring with conventional tablets will never occur in a closed system of stabilized tablets.

Reduction of the rate of volatilization is not particularly important within the context of the migration effect. Adsorption data imply that if the vapor pressure is reduced by more than about 15%, pore condensation is negligibly small. Thus, an additive prevents transfer to an empty pore if P/P° is less than about 0.85 in the additive–nitroglycerin phase. If the potential transfer is to a pore *partially filled* with the nitroglycerin–additive phase, transfer takes place until the composition changes are sufficient to result in about a 15% decrease in vapor pressure. Here, the parameters for nitroglycerin in the Kelvin equation (20) are assumed to be not greatly changed by the additive.

Thus, for povidone and polyethylene glycol 400 systems, transfer takes place until the concentration differences between the surface and pore are about 5%. With no additive present, this type of transfer takes place until either the small pore is filled or the surface is essentially devoid of nitroglycerin. The effectiveness of the additive in reducing this type of transfer depends on the slope of the vapor pressure *versus* weight ratio curve. For both povidone and polyethylene glycol 400, this slope becomes particularly large in the region where $P/P^{\circ} < 0.85$. Therefore, the use of these additives to achieve a vapor pressure reduction of about 15% is sufficient to prevent significant intertablet migration.

Finally, it should be emphasized that stabilized formulations are stabilized only with respect to intertablet nitroglycerin migration. The volatility is decreased, not eliminated, and losses of nitroglycerin arising from improper storage are decreased but not, in general, eliminated. At 25°, the air space above nitroglycerin tablets contains less than 7 μg of nitroglycerin/liter. Consequently, losses to the atmosphere are small, even if the container is not tightly closed or is repeatedly opened. Nitroglycerin sorption by polymeric packaging materials is a more serious problem[13]. Even stabilized tablets suffer severe sorption losses when in vapor contact with some polymers.

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[13] A study of nitroglycerin sorption by polymers will be the subject of a future report.