Loss of Nitroglycerin from Aqueous Solution into Plastic Intravenous Delivery Systems

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Received September 28, 1978, from the *Divisions of Pharmaceutics and Pharmaceutical Chemistry and Pharmacology, College of Pharmacy, Ohio State University, Columbus, OH 43210.* Accepted for publication March 22, 1979.

Abstract □ The mechanism of potential loss of nitroglycerin stored in plastic and glass containers was studied from an equilibrium and kinetic approach. Plastic strips equilibrated with dilute aqueous solutions of neat nitroglycerin showed that the drug was lost by absorption. Drug loss was followed by an electron-capture GLC assay. The same assay of control solutions in glass showed no drug loss in 48 hr at pH 5.7. The kinetics of nitroglycerin absorption and desorption were determined using synthesized ^{14}C-labeled drug. Absorption can be quantified using a diffusion model, where the concentration in the aqueous phase falls with time. Curve fitting yielded an average diffusion coefficient in plastic of 2.05×10^{-9} cm^2/sec and a partition coefficient of 104 (plastic–water) at 30°. Temperature-dependence studies of absorption showed that the diffusion coefficient followed an Arrhenius relationship with an energy requirement of 19.6 kcal/mole, whereas effects on the partition coefficient were negligible. Nitroglycerin desorption from plastic disks under sink conditions into water can be quantified by assuming a diffusion model where the concentration at the surface of a plane sheet remains constant. Nonlinear least-squares curve fitting generated a diffusion coefficient of 1.14×10^{-9} cm^2/sec for the desorption process at 30°.

Keyphrases □ Nitroglycerin—intravenous delivery systems, loss from aqueous solution into plastics □ Plastics—loss of nitroglycerin from aqueous solution into intravenous delivery system components □ Drug delivery systems, intravenous—loss of nitroglycerin from aqueous solution into plastics

Nitroglycerin in tableted dosage forms has been studied extensively from the standpoint of stability and packaging (1–7). In the past few years, considerable interest has centered on the clinical use of intravenous nitroglycerin solutions for myocardial infarction and in open heart surgery (8, 9). The intravenous solutions are prepared extemporaneously by pharmacists, usually from sublingual tablets. Two recent studies (9, 10) raised questions concerning the potency and stability of such solutions.

An editorial pointed out that there are certain agreements in the results of these studies but that there are also certain significant differences (8). Both papers reported some nitroglycerin loss from intravenous solutions stored in glass and plastic containers and suggested that the drug loss might be consistent with sorption to container or delivery units. However, the two studies differed in those results concerned with the apparent actual drug chemical stability and the relative amounts of drug lost to plastic containers. Two letters appearing subsequent to these studies corroborated nitroglycerin loss from intravenous solution to plastic (11, 12).

The purposes of this study were to define the mechanism of nitroglycerin loss to a plastic intravenous container material[1] using equilibrium and kinetic studies and to reevaluate nitroglycerin stability in glass containers. This information seemed to be a necessary requisite to an understanding of factors affecting the potency and stability of intravenous nitroglycerin solutions. Solutions were prepared using freshly synthesized nitroglycerin to obviate any effects of adjuvants present in formulations. This possibility was pointed out by Pikal *et al.* (7). Potential adjuvant effect is another complicating factor in comparing the results of previous studies. Moreover, the assays used in this study for nitroglycerin were different from those used previously and provide an additional basis for evaluation of stability and potency problems associated with intravenous nitroglycerin solutions.

EXPERIMENTAL

In equilibrium studies, strips of a plastic[1] intravenous container (17.88 × 4.98 × 0.04075 cm; volume 3.63 cm^3) were equilibrated with 200 ml of normal saline solutions[2] containing various initial nitroglycerin concentrations (8–90 μg/ml). The dilute solutions were kept in aluminum foil-stoppered 250-ml erlenmeyer flasks at 35 ± 1° [3]. The solution pH was ~5.7 and remained constant throughout the study. Separate studies over a 2-week period showed that equilibrium essentially occurred in 2 days.

The nitroglycerin was synthesized using the method of Dean and Baun (13), where the ratio of reactants was varied to increase the nitroglycerin yield[4]. A 1.05% stock solution of the synthesized nitroglycerin in ethyl acetate was used as a nitroglycerin source for the solutions in this study. The stock solution was standardized using the phenol disulfonic acid method of Dean and Baun (13).

The nitroglycerin content of the aqueous phase in equilibrium with plastic was determined using a GLC procedure[5] based on the work of Rosseel and Bogaert (14). The assay is stability indicating, since hydrolysis products of nitroglycerin are separated and detected. Isosorbide dinitrate was used as the internal standard[6]. Standard curves for nitroglycerin were constructed by plotting the ratio of the area under the nitroglycerin chromatogram to that of isosorbide dinitrate as a function of the nitroglycerin concentration. These standard curves were used to determine the nitroglycerin concentration initially and after equilibrium with plastic in the following way. A 100-μl sample was taken and extracted with 500 μl of benzene containing a known amount of isosorbide dinitrate. The extraction removed 98+% of both nitrates. After extraction, the organic layer was removed and refrigerated until a portion of it was injected on the column. The nitroglycerin concentration was determined from the ratio of nitroglycerin areas to standard isosorbide chromatograms.

Control studies were conducted at the same time as the equilibrium studies under identical conditions. The only difference was the absence of plastic.

In kinetic sorption studies, two strips cut from plastic intravenous containers[1] (4 × 4 × 0.04075 cm; volume 0.652 cm^3) were placed in a 100-ml water jacketed beaker, kept at constant temperature[7], containing

[1] Viaflex, lot HP05 × 7, Travenol.

[2] Lot G446 × 4A, Travenol.

[3] Water controlled shaker bath, Research Specialties model 2156, operated at 25 rpm.

[4] Sulfuric acid (2.17 moles) and nitric acid (2.27 moles) were cooled to 25°. Then 0.130 mole of glycerin (Eaton-Colby) was slowly added, keeping the temperature below 16°. The mixture was then added to 1.5 liters of distilled water at 10°, and the congealed nitroglycerin was collected and purified by repeated washing with water. Purity was established by TLC and GLC (9).

[5] Hewlett-Packard model 5730A with a ^{63}Ni-electron-capture detector. A glass column (1.8 m × 2 mm i.d.) was used with 3.5% QF-1 on Gas Chrom Q (Supelco D3550). The carrier gas (argon–methane, 95:5) had a flow rate of 30 ml/min; the injection port and detector were at 200°, and the column was at 120°.

[6] Stuart Pharmaceuticals AN00983, 25% adsorbate on lactose. The isosorbide dinitrate was extracted with hot acetone, and the acetone was then removed over a nitrogen stream. Standard solutions were prepared by accurately weighing known amounts and dissolving them in chromatographic grade benzene.

[7] Haake model FK circulating water bath at 30, 35, 40, and 45 ± 0.5°.

0022-3549/79/0900-1163$01.00/0

Table I—Recovery of Initial Concentration of Nitroglycerin Stored in Glass at 35° in Normal Saline Solution, pH 5.7

Initial Concentration, μg/ml	Percent Found	
	24 hr	48 hr
95	99	104
15	104	107
15	98	107
3.8	87	105
3.6	101	107
0.2	90	87
Average	96.5	102.8

aqueous solutions of constant labeled[8] drug (61.06 μg/ml, 38,212 dpm/ml) together with nonlabeled drug in various total concentrations. In studies at 30°, four different initial concentrations were used (61–473 μg/ml), and each concentration study was run in duplicate. Temperature-dependence studies (30–45°) were run in duplicate with a single initial concentration of 473 μg/ml.

The solutions were prepared from ethanol stock solutions of both labeled and nonlabeled drug. The cold stock solution contained 205.91 mg of nitroglycerin/ml, and the labeled drug stock solution contained 152.65 mg/ml[9]. At appropriate time intervals, 50 μl of aqueous sample was placed in a vial containing 10 ml of counting cocktail[10] and 4 ml of water. The radioactivity was determined by liquid scintillation counting[11] for 20 min (counting efficiency 86.35%, background 46 cpm).

The initially clear strips became opaque when exposed to water. To determine if the imbibed water affected sorption, the following experiment was run. Plastic strips were presoaked in distilled water for more than a day and immediately immersed in a solution of the radioactive drug (473 μg/ml total, 61.06 μg/ml labeled, 38,212 dpm/ml). Sorption studies using the presoaked strips were carried out as were those described for nonpresoaked strips.

In desorption studies, 40 disks cut from the same plastic intravenous bags (1.503 cm in diameter, 0.0407 cm thick; volume 0.0723 cm^3) were equilibrated 1 week with 300 ml of a 442-μg/ml (43.19 dpm/μg) nitroglycerin solution. Two disks were collected and counted to determine the initial amount of nitroglycerin sorbed (1652.1 and 1644.9 μg/disk were found). The desorption studies, run in duplicate, were conducted at 30° using 19 disks in 300 ml of stirred water. Sink conditions were maintained by replacing the water at a rate of 5 ml/min with a peristaltic pump[12].

In the desorption studies, a disk was removed from solutions in the jacketed beaker at appropriate intervals, rinsed in water, blotted on paper, and placed in a counting vial containing 10 ml of cocktail. The disk was allowed to stand in the cocktail for a few hours to enhance the leaching of ^{14}C-nitroglycerin, thus increasing counting efficiency. Four milliliters of water was then added to form a gel, permitting suspension of the disk horizontally and halfway from the bottom of the vial. The radioactivity was determined by liquid scintillation counting for 20 min.

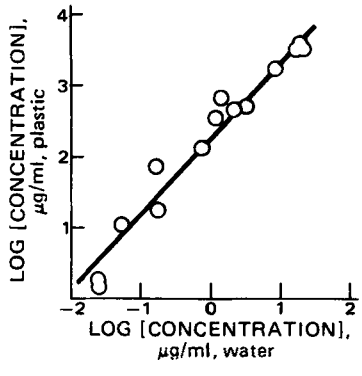

Figure 1—*Log-log relationship between nitroglycerin equilibrium concentration (micrograms per milliliter) in plastic and concentration in normal saline solution at 35°. The circles are experimental values, and the line was generated by least-squares regression, giving a slope of 1.09 ± 0.07 SD.*

[8] Prepared from 500 μCi of 1,3-^{14}C-glycerol (New England Nuclear, 1.64 mg/10 ml, specific activity 55.7 mCi/mmole). Water in the labeled sample was removed by storage over phosphorus pentoxide for 1 day. One gram of cold glycerin was added, and nitroglycerin was synthesized as indicated in footnote 4. The yield was 70%, and the product had a specific activity of 69.02 μCi/mmole.

[9] The initial concentrations were determined by an HPLC method (15) using a DuPont model 830 chromatograph with a Tracor model 970 variable-wavelength detector at a wavelength of 210 nm. A 25-cm Partisil ODS (Whatman) column was used. The assay separates and detects hydrolysis products of nitroglycerin.

[10] PCS cocktail, Amersham/Searle.

[11] Beckman model 345.

[12] Harvard model 500 1200.

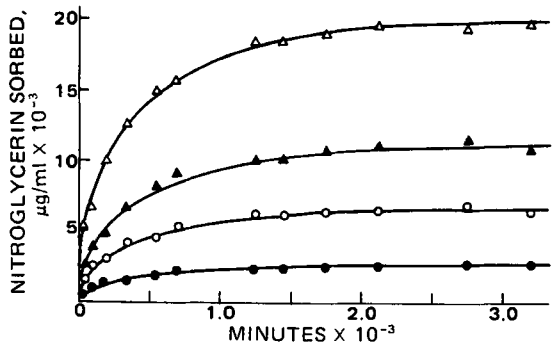

Figure 2—*Relationship between the amount (micrograms per cubic centimeter) of nitroglycerin adsorbed by plastic strips and time from a solution initially at 61 (●), 143 (○), 267 (△), and 472 (▲) μg of nitroglycerin/ml at 30°. The symbols are experimental data, and the line was generated by nonlinear least-squares fitting based on Eq. 1.*

RESULTS AND DISCUSSION

In the studies where plastic strips were permitted to equilibrate with aqueous nitroglycerin solutions, the amount of drug in the plastic was calculated from the difference between the measured initial concentration and the concentration found at equilibrium in the aqueous phase. The concentration in plastic was calculated using the measured volume of the strip. The calculation is valid because control studies showed no drug loss through either hydrolysis or sorption to glass in 48 hr.

Table I presents the nitroglycerin recovery from solutions stored in aluminum foil-stoppered 250-ml erlenmeyer flasks at 35°. Over a concentration range of 0.2–95 μg/ml, assay of the solution showed 97% nitroglycerin remaining after 24 hr and 103% after 48 hr. The drug is apparently stable over a 2-day period in aqueous solution. This finding is in agreement with the results of many investigators (12–18) but not with those of others (9, 10). Sturek *et al.* (9) found a 13% loss after 50 hr, which may have been the result of adjuvants in the sublingual tablets used to prepare the solutions. It is difficult to speculate about the 25% loss in 5 hr reported by Ludwig and Ueda (10) since the contents of their nitroglycerin stock solution are not known.

When the logarithm of the concentration found in plastic at equilibrium is plotted as a function of the logarithm of the concentration in the aqueous phase at equilibrium, a linear relation is found (Fig. 1) with a slope of 1.09 ± 0.15 (95% confidence limit) as generated by linear regression. This result shows that nitroglycerin loss to plastic is an absorption or partitioning process and that the role of adsorption, if present, is minor. When the apparent partition coefficient is calculated from the slope of a regression of concentration in plastic on the concentration in the aqueous phase at equilibrium, the value obtained is 166 ± 14. There is little doubt that nitroglycerin preferentially distributes into the plastic from its aqueous solution.

In kinetic sorption studies, the amount of nitroglycerin taken up by

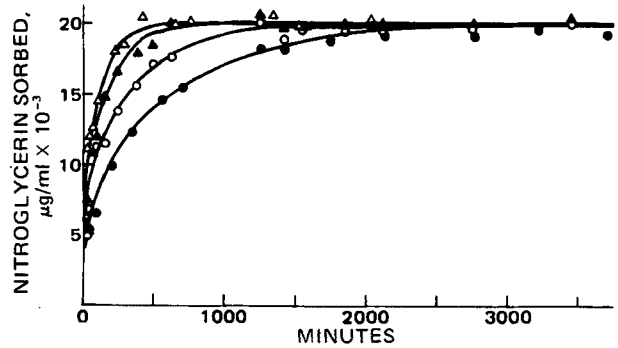

Figure 3—*Relationship between the amount of nitroglycerin adsorbed per cubic centimeter of plastic strips and time from solutions initially at 473.0 μg/ml at 45° (△), 40° (▲), 35° (○), and 30° (●). The symbols are experimental data, and the lines were generated by nonlinear least-squares fitting of Eq. 1.*

Table II—Amount Adsorbed, Diffusion Coefficient, Partition Coefficient, and Time for 0.5 Fractional Sorption for Nitroglycerin in Solution at Different Initial Concentrations Exposed to Plastic Strips at 30°

Initial Concentration, μg/ml	Amount Adsorbed at Equilibrium, M_∞, μg/cm³	Diffusion Coefficient[a], D, cm²/sec × 10⁹ (±SD × 10¹⁰)	Partition Coefficient	Time for 0.5 Fractional Sorption, min[b]
61.1	2,404.0	1.75 (1.58)	91.3	180
61.1	2,690.8	1.88 (1.30)	111.1	200
143.4	5,876.2	2.01 (1.74)	96.9	210
158.7	6,703.5	1.96 (1.29)	101.6	175
266.9	11,300.8	2.06 (1.23)	105.7	200
266.9	11,674.8	1.83 (1.47)	106.4	220
470.9	21,359.7	2.68 (2.25)	111.2	190
470.9	19,956.6	2.22 (1.31)	103.8	175

[a] Obtained by nonlinear least-squares fitting of amount adsorbed by plastic (micrograms per cubic centimeter) at time t (M_t) and the time using Eq. 1. [b] Interpolated from nitroglycerin sorbed-time profiles (Fig. 2).

the plastic strips was followed by measuring the solution loss of radioactivity as a function of time. Since equilibrium studies indicated that a sorption process was taking place, the data were treated using a model describing sorption by a plane sheet immersed in a limited volume of solution where the solute concentration in an aqueous solution falls as the solute enters the sheet. In such a system, the equation relating fractional equilibration, M_t/M_∞, and time is (19):

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n^2} \exp(-Dq_n^2 t/h^2) \qquad \text{(Eq. 1)}$$

where M_t is the total amount of solute in the sheet at time t, M_∞ is the corresponding amount after infinite time, h is the half film thickness, and D is the diffusion coefficient. The value of α is the ratio of the final concentration to the total concentration drop in the aqueous solution (initial concentration, C_0, minus final concentration, C_∞):

$$\alpha = \frac{C_\infty}{C_0 - C_\infty} \qquad \text{(Eq. 2)}$$

The values of q_n are the nonzero positive roots of:

$$\tan q_n = -\alpha q_n \qquad \text{(Eq. 3)}$$

and can be obtained from published tables (19) or with a suitable programmable hand calculator.

The amount of nitroglycerin adsorbed by the plastic at time t, M_t (micrograms per disk), was fitted to Eq. 1 using a nonlinear least-squares fitting technique[13] (NONLIN). The values for α ranged from 0.69 to 0.82, and six terms under the summation were used. The total amount of nitroglycerin in the strips at infinite time, M_∞ (micrograms per cubic centimeter), and the diffusion coefficient (square centimeters per second) were estimated by the computer program. Figure 2 represents the fit obtained for data at initial concentrations of 61–473 μg/ml at 30°. The symbols are data points, and the line was generated by nonlinear least-squares fitting.

Table II lists the values of M_∞, the diffusion coefficient, the partition coefficient calculated from M_∞ and C_∞, and the time for 0.5 fractional attainment of sorption at the four different initial solution concentrations used. The studies were run in duplicate. The accuracy obtained, as reflected in the standard deviation for the diffusion coefficient, was good and the precision between duplicate runs was ±5% or better. Because of the constant half-life for sorption (Table II) at the several concentrations used, it is concluded that the diffusion coefficient is independent of concentration over a 61–473-μg/ml range, giving an average value of 2.05×10^{-9} ($SD = 0.29 \times 10^{-9}$) cm²/sec at 30°. The average partition coefficient obtained from the kinetic studies, 103.5 (SD = 6.82), is of the same order of magnitude as that found in the equilibrium studies run at 35° in normal saline solution. A log–log plot of the concentration in plastic *versus* aqueous concentration at equilibrium agrees well with the conclusion reached from the equilibrium studies that absorption, and not adsorption, is the major cause for nitroglycerin loss.

Data obtained from sorption kinetic studies using presoaked plastic strips were also fitted to Eq. 1 and showed excellent conformance. The diffusion coefficients generated, 2.27×10^{-9} ($SD = 0.163 \times 10^{-9}$) and 1.76×10^{-9} ($SD = 0.132 \times 10^{-9}$) cm²/sec, are not significantly different from those found using nonpresoaked strips.

In absorption temperature-dependence studies, the initial nitroglycerin solution concentration bathing the strips was held constant at 473 μg/ml and the temperature was held constant at 30, 35, 40, or 45°. The relation between the amount of nitroglycerin taken up per cubic centimeter of strip and the time at each temperature is presented in Fig. 3. The figure gives data for one of the duplicate trials used. When the data are fitted to Eq. 1, the result obtained is given by the solid lines in Fig. 3, showing excellent compliance with the diffusional model selected. The computer-generated diffusion coefficients for nitroglycerin in the plastic as well as the amount of nitroglycerin taken up at equilibrium are given in Table III for both experimental trials. The diffusion coefficient is dependent on temperature. Plotting the diffusion coefficient–temperature data in the Arrhenius manner:

$$D = D_0 e^{-E/RT} \qquad \text{(Eq. 4)}$$

gives an excellent linear relation between the logarithm of the diffusion coefficient, D, and the reciprocal of absolute temperature, $1/T$. The energy term, E, has a value of 19.6 kcal/mole (1.59 SD), and the preexponential term, D_0, is 3.24×10^5 cm²/sec.

Although the diffusion coefficient is temperature sensitive, the calculated partition coefficient does not change with temperature (Table III).

Studies directed toward measuring the desorption kinetics of nitroglycerin from the container material were intended to establish the reversibility of the interaction. The amount of nitroglycerin remaining per disk under sink conditions was measured by scintillation counting over 8000 min. The nitroglycerin lost per disk, L_t, at each sampling time was determined by taking the difference between the amount initially present (1652 and 1645 μg/disk in two trials) and the amount found at each time.

The relation between the amount lost and time for one trial is given in Fig. 4. The symbols represent experimental values, and the line joining them was generated by NONLIN[13] from a diffusion model describing diffusion through a plane sheet where the concentration throughout the sheet is initially uniform and where the concentration at the surface remains constant during the time course of desorption (19). The relation between fractional loss, L_t/L_∞, and time, t, under these conditions is:

$$\frac{L_t}{L_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp[-D(n+\tfrac{1}{2})^2\pi^2 t/h^2] \qquad \text{(Eq. 5)}$$

where L_∞ is the amount lost at long time (equal to the amount present initially), D is the diffusion coefficient, and h is the half thickness of the

Table III—Effect of Temperature on the Diffusion Coefficient and Partition Coefficient of Nitroglycerin Sorption from Aqueous Solution by a Plastic Intravenous Container Material

Temperature	Amount Adsorbed at Equilibrium, M_∞, μg/cm³	Diffusion Coefficient[a], D, cm²/sec × 10⁹ (±SD × 10¹⁰)	Partition Coefficient
30°	21,359.7	2.68 (2.25)	111.2
30°	19,956.6	2.22 (1.31)	103.8
35°	18,154.6	4.53 (2.86)	92.4
35°	19,982.9	4.28 (2.80)	102.4
40°	20,118.2	8.61 (6.30)	94.6
40°	19,774.2	8.06 (5.46)	93.8
45°	21,718.3	9.82 (9.74)	106.7
45°	21,818.3	11.8 (13.8)	104.1

[a] Obtained by nonlinear least-squares fitting of amount adsorbed by plastic at time t (M_t) and the time using Eq. 1.

[13] Unit 7292, The Upjohn Co., Kalamazoo, Mich.

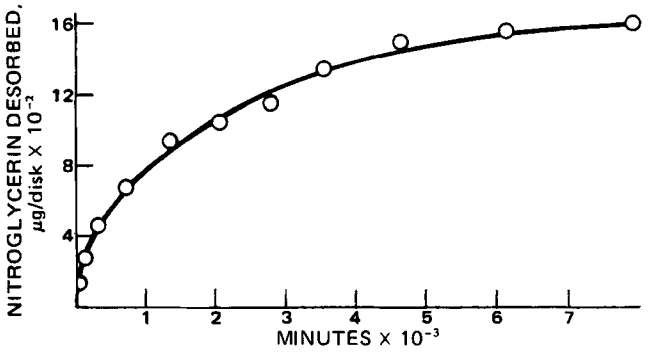

Figure 4—*Relationship between the amount of nitroglycerin lost from a plastic disk initially containing 1652 μg and time under sink conditions at 30°. The symbols are experimental data, and the line was that generated by nonlinear least-squares fitting of Eq. 4.*

sheet. Equation 5 is a reduced form of the more general Eq. 1, where α equals ∞ and where the roots of Eq. 3 are:

$$q_n = (n + \tfrac{1}{2})\pi \qquad \text{(Eq. 6)}$$

Equation 5 was used by Pikal *et al.* (7) in describing nitroglycerin desorption from two packaging materials. The computer-generated values for the diffusion coefficient using Eq. 5 are 1.17×10^{-9} (4.63×10^{-11} *SD*) and 1.10×10^{-9} (4.62×10^{-11} *SD*) cm²/sec at the two initial amounts of nitroglycerin per disk used (1652 and 1645 μg/ml, respectively). These values agree well with each other and with those generated in sorption studies at 30°: 2.05×10^{-9} cm²/sec (average value from Table II) and 2.45×10^{-9} cm²/sec (average value from Table III). Thus, the loss of nitroglycerin to the plastic intravenous container apparently is a reversible sorption process.

SUMMARY

Under the experimental conditions used, both equilibrium and kinetic studies showed that nitroglycerin is removed from aqueous solution by the plastic container material through an absorption process. The partition coefficient of nitroglycerin between plastic and aqueous solutions is ~104 at 30°. The time course for the absorption can be described as diffusion through a sheet where the concentration in the aqueous solution phase falls with time, with a diffusion coefficient of about 2.1×10^{-9} cm²/sec. Nitroglycerin loss from aqueous solution does not occur through hydrolysis since solutions stored in glass containers at pH 5.7 and 35° retained potency for at least 48 hr.

Although the experimental data support the thesis that the uptake of nitroglycerin is migration of the drug into the plastic matrix, this finding does not exclude the possible adsorption of the drug on the surface. Conceivably, the quantity of solute adsorbed may be insignificant when compared with the amount absorbed and the rate of adsorption may be much faster than the rate of absorption, with the result that any adsorption is obscured. Thus, the experimental conditions employed as well as the physical and chemical properties of the drug molecule and the plastic could affect conclusions reached regarding the rate-limiting mechanisms and the equilibrium distribution of drugs exposed to plastic.

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ACKNOWLEDGMENTS

Presented at the APhA Academy of Pharmaceutical Sciences, Hollywood, Fla., meeting, November 1978.

Supported in part by a grant from Eli Lilly Co. and the Public Health Service, National Heart, Lung, and Blood Institute (1R01 HL 23303-01).