Stability of Intravenous Nitroglycerin Solutions

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Abstract □ The stability of intravenous nitroglycerin solutions prepared from either sublingual tablets or a 10% nitroglycerin–lactose adsorbate (powder) was examined under various conditions. Nitroglycerin concentration was measured by high-pressure liquid chromatography. Nitroglycerin stock solutions (0.8–1.0 mg/ml) prepared from tablets or powder in 0.9% saline were stored upright in refrigerated multidose vials for 6 months without a significant decrease in concentration. Storage of the solutions at room temperature resulted in a 20% loss after 3 months. Intravenous nitroglycerin solutions (0.2 mg/ml) prepared from tablets or powder in either 0.9% saline or 5% dextrose in water were stored in glass intravenous bottles at temperatures between 6 and 38° for 24 hr with a maximum loss of 18%. Stability was not affected by light. Solutions in contact with rubber stoppers, plastic intravenous bags, or plastic administration sets exhibited decreased nitroglycerin concentration characteristic of sorption. Nitroglycerin concentrations decreased to a greater extent when the administration sets were equipped with plastic burets. Brief contact of nitroglycerin solutions with a plastic syringe did not result in decreased concentration. The stability of intravenous nitroglycerin solutions packaged in glass was not dependent on light, the vehicle, or the source of nitroglycerin. Contact with rubber or plastic surfaces should be minimized.

Keyphrases □ Nitroglycerin—intravenous solutions, stability, effect of temperature, light, source, and packaging □ Stability—effect of temperature, light, source, and packaging on intravenous nitroglycerin solutions □ Vasodilators—nitroglycerin, stability of intravenous solutions

Intravenous nitroglycerin is used clinically in various cardiovascular conditions (1–5). At present, only an investigational nitroglycerin formulation is commercially available for intravenous infusions. Consequently, many pharmacists prepare intravenous nitroglycerin solutions from sublingual nitroglycerin tablets (6, 7) or from a nitroglycerin–lactose adsorbate (8, 9). The stablity of nitroglycerin tablets was defined after the advent of single-tablet assays, particularly automated single-tablet assays (10–15). However, initial stability data on nitroglycerin in intravenous solutions were anecdotal (16) or conflicting (17, 18). Recently, the results of several investigations were reported (19–24).

This investigation examined the stability of nitroglycerin parenteral solutions under various conditions of temperature, exposure to light, packaging materials, nitroglycerin source, vehicle, administration set, and time.

EXPERIMENTAL

Assay—Nitroglycerin was measured by a modified high-pressure liquid chromatographic (HPLC) method (25). A high-pressure liquid chromatograph[1] equipped with a universal liquid chromatographic injector[2], UV absorbance detector[3] (254 nm), and a strip-chart recorder[4] was used for all analyses. Samples (25 μl) were chromatographed at room temperature on a microparticulate, reversed-phase, 30 cm × 4-mm i.d. column[5] with an eluting mobile phase of 60% methanol in water at a flow rate of 2 ml/min. The inlet pressure varied from 2400 to 3000 psi and was noted on a daily basis. The retention time of nitroglycerin was ~4 min, and samples could be injected every 5 min.

The technique was sensitive to injections of >100 ng of nitroglycerin. Precision was 1.0% over a solution range of 190–300 μg of nitroglycerin/ml. Standard solutions were prepared from 0.4-mg sublingual nitroglycerin tablets[6] and 10% (w/w) nitroglycerin–lactose adsorbate[7] (powder). Standard curves were linear ($r \geq 0.99$) over the concentration range used.

Stability Study—The stability of nitroglycerin solutions with initial concentrations of 0.8 or 1.0 mg/ml (stock) and 0.2 mg/ml (intravenous) was tested.

Stock Solutions—Nitroglycerin stock solutions were pipetted into 5-ml multidose vials[8] for stability testing. Rubber stoppers[9] (20 mm) were fitted to the vials with a metal tear-off seal[10].

Vials containing 5 ml of nitroglycerin solution (1.0 mg/ml) prepared from tablets in 0.9% saline were stored in groups of three under conditions of varied temperature, light, and contact with the rubber stopper (Solutions VRT, VU, VF, VO, and VR, Table I).

In addition, five vials containing 5 ml of nitroglycerin solution (0.8 mg/ml) prepared from tablets in 0.9% saline (Solution VT) and five vials containing 5 ml of nitroglycerin solution (0.8 mg/ml) prepared from powder in 0.9% saline (Solution VP) were stored under fluorescent light at 22–30° in an upright position.

Intravenous Solutions—Intravenous nitroglycerin solutions (0.2 mg/ml) were prepared in 250-ml plastic bags of 0.9% saline[11] or in 250-ml glass bottles of 0.9% saline[12] or 5% dextrose in water[13]. Initially, 50 ml of the saline or 5% dextrose solution was removed from the container; a glass syringe was then used to add 50 ml of freshly prepared nitroglycerin stock solution. Containers were inverted throughout the stability study. A tubing clamp attached to the bags and a glass rod inserted into the bottles sealed the administration ports.

Intravenous nitroglycerin solutions were first prepared in saline from a tablet nitroglycerin stock solution. Five bags and five bottles containing the nitroglycerin solutions were stored under each condition of light and temperature (Solutions PRT, PF, PR, PO, GRT, GF, GR, and GO, Table II).

Five solutions of tablet nitroglycerin in bottles of saline (Solution GT) were compared to five solutions of tablet nitroglycerin in bottles of 5% dextrose solution (Solution GD) and to five solutions of powder nitroglycerin in bottles of saline (Solution GP). These solutions were stored between 26 and 28° under fluorescent light. At the same time, solutions of tablet nitroglycerin were prepared in 10 bottles and five bags of saline. Administration tubing[14] (1.8 m) was connected to each bag (Solution PTu) and five bottles (Solution GTu). The tubing was immediately filled with solution and then continually perfused at 0.5 ml/min by gravity.

Administration tubing (2.1 m) with a buret[15] was connected to the remaining five bottles (Solution GBu) and was similarly filled and perfused. One hundred milliliters of solution remained within the buret chamber throughout the perfusion. Solutions PTu, GTu, and GBu were sampled simultaneously from the container and the terminal end of the administration set. All containers and tubing were stored between 26 and 28° under fluorescent light.

Two-tailed t tests (26) were used to compare the sample means. When

[1] Model ALC/GLC 204, Waters Associates, Milford, MA 01757.
[2] M-6000A, SDS-4126, Waters Associates.
[3] M-440, S-440-00634, Waters Associates.
[4] Recordal series 5000, Fisher Scientific, Pittsburgh, PA 15219.
[5] μBondapak C_{18}, P/N 27324, S/N 067552, Waters Associates.
[6] No. 161, lot 2AE55B, exp. Mar. 1, 1980, Eli Lilly and Co., Indianapolis, IN 46206.
[7] SDM No. 17, lot J17-H12, drum no. 2, ICI Americas, Inc., Specialty Chemicals Division, Wilmington, DE 19897.
[8] Serum bottle S-104E, No. 223738, Wheaton Industries, Millville, NJ 08332.
[9] No. 224124, Wheaton Industries.
[10] No. 224193, Wheaton Industries.
[11] No. 2B1322, lot CP412XO, exp. Mar., 1980, Travenol Laboratories, Deerfield, IL 60015.
[12] No. 2A1322, lot G431L2, exp. Nov., 1979, Travenol Laboratories.
[13] No. 2A0062, lot G454R6A, exp. Mar., 1980, Travenol Laboratories.
[14] Solution administration set, minidrip 60 drops/ml, no. 2C0002, lot H259W1, Travenol Laboratories.
[15] Buret solution administration set with ball valve, minidrip 60 drops/ml, No. 2C0132, lot U18X3, Travenol Laboratories.

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Table I—Nitroglycerin Stock Solutions [a]

Symbol	Initial Nitroglycerin Concentration, mg/ml	Nitroglycerin Source[b]	Storage		
			Position	Light Exposure	Temperature
VRT	1.0[c]	Tablets	Upright	Fluorescent	22–30°
VU	1.0[c]	Tablets	Inverted	Fluorescent	22–30°
VF	1.0[c]	Tablets	Upright	Dark (foil-wrapped)	22–30°
VO	1.0[c]	Tablets	Upright	Dark	38°
VR	1.0[c]	Tablets	Upright	Dark	6°
VT	0.8[d]	Tablets	Upright	Fluorescent	22–30°
VP	0.8[d]	Powder	Upright	Fluorescent	22–30°

[a] Containers were multidose vials (5 ml) with rubber stoppers, and the vehicle was (1.0 mg/ml) saline. [b] Tablets were 0.4-mg sublingual tablets, and powder was 10% (w/w) nitroglycerin–lactose adsorbate. [c] Vials were prepared from the same nitroglycerin solution. [d] The stability of nitroglycerin solutions (0.8 and 1.0 mg/ml) was measured at the same time.

Table II—Nitroglycerin Intravenous Solutions (Initial Concentration, 0.2 mg/ml)

Symbol[a]	Container[b]	Administration Set	Perfusion Rate, ml/min	Nitroglycerin Source[c]	Vehicle[d]	Storage	
						Light Exposure	Temperature
GRT	Bottle	—	—	Tablet	Saline	Fluorescent	28–30°
GF	Bottle	—	—	Tablets	Saline	Dark (foil-wrapped)	28–30°
GO	Bottle	—	—	Tablets	Saline	Dark	38°
GR	Bottle	—	—	Tablets	Saline	Dark	6°
PRT	Bag	—	—	Tablet	Saline	Fluorescent	28–30°
PF	Bag	—	—	Tablets	Saline	Dark (foil-wrapped)	28–30°
PO	Bag	—	—	Tablets	Saline	Dark	38°
PR	Bag	—	—	Tablets	Saline	Dark	6°
GT	Bottle	—	—	Tablets	Saline	Fluorescent	
GP	Bottle	—	—	Powder	Saline	Fluorescent	26–28°
GD	Bottle	—	—	Tablets	5% dextrose in water	Fluorescent	
GTu	Bottle	Tubing (1.8 m)	0.5	Tablets	Saline	Fluorescent	
PTu	Bag	Tubing (1.8 m)	0.5	Tablets	Saline	Fluorescent	26–28°
GBu	Bottle	Tubing (2.1 m) with buret	0.5	Tablets	Saline	Fluorescent	

[a] Stability of solutions GRT through PR was measured separately from that of solutions GT through GBu. [b] Bottle was inverted glass infusion bottle, 250 ml; bag was plastic infusion bag, 250 ml. [c] Tablets were 0.4-mg sublingual tablets; powder was 10% (w/w) nitroglycerin-lactose adsorbate. [d] Saline was 0.9% saline.

the data could be fitted to the equation of a straight line, slopes were statistically tested (27) for difference.

RESULTS

To assess the uniformity of the nitroglycerin source, solutions were prepared from different samples of tablets or powder (five tablets or ~20 mg of powder/sample). The HPLC peak height responses were 34.4 ± 1.5 cm/mg of tablet and 296 ± 14 cm/mg of powder.

Although a glass syringe was used in this study to transfer nitroglycerin solutions, hospital personnel often use plastic, disposable syringes. The concentration in 50 ml of a nitroglyerin solution (1.0 mg/ml) was measured before and after two successive 1-min exposures to a 50-ml plastic syringe. Concentration did not change significantly after contact with the syringe.

USP XX (28) specifications allow the average potency of sublingual nitroglycerin tablets to vary 20% from the labeled strength. The concentration of nitroglycerin stock solutions (1.0 mg/ml) prepared from tablets in saline and stored upright in multidose vials under fluorescent light at 22–30° decreased 20% after 87 days and 35% after 6 months (Solution VRT, Table III). When the vials were stored at 38° (VO), nitroglycerin concentration decreased 20% after 50 days and 67% after 6 months. Solutions that were protected from light (VF) showed decreases of 20% after 98 days and 31% after 6 months. When vials were stored inverted (VU), the concentration decreased 20 and 58% after 2 days and 6 months, respectively. In nitroglycerin solutions stored upright at 6° (VR), no change in concentration was observed over 6 months. Nitroglycerin stock solutions prepared from tablets at 0.8 mg/ml (VT) declined in concentration by 20% in 87 days and by 41% in 6 months. Similar solutions prepared from powder (VP) had concentration decreases of 20 and 43% after 82 days and 6 months, respectively.

The observed concentration changes were linear with time during the study for all solutions except those stored inverted (VU). The rate of concentration change in solutions stored at 22–30° under fluorescent light differed from that in solutions stored at 6 or 38° ($p < 0.001$, Fig. 1) but did not significantly differ from that in solutions protected from light. The rate of concentration change was independent of the initial concentration (0.8 or 1.0 mg/ml) and the source of the nitroglycerin (powder or tablet). The concentration of solutions stored inverted differed significantly from that in solutions stored upright after 1 month ($p < 0.001$, Fig. 2).

The concentration of intravenous nitroglycerin solutions (0.2 mg/ml) stored in plastic bags differed from the initial concentration after 1.3 hr, regardless of storage temperature or exposure to light ($p < 0.05$). After 8 hr, the concentration of solutions stored under fluorescent light at 28–30° (Solution PRT) in the dark at 28–30° (PF), 38° (PO), or 6° (PR)

Table III—Stability of Nitroglycerin Stock Solutions

Variables[a]	Predicted[b] Time for Nitroglycerin Concentration to Decrease 20%, days	Decrease in Nitroglycerin Concentration, %		
		1 Month	3 Months	6 Months
Tablet solutions, 1.0 mg/ml				
6°, dark, upright (VR)	—	−11	−5	−8
38°, dark, upright (VO)	50	23[c]	51[c]	67[c]
22–30°, light, inverted (VU)	2	39[c]	58[c]	58[c]
22–30°, dark upright (VF)	98	2	26[c]	31[c]
22–30°, light, upright (VRT)	87	5	29[c]	35[c]
0.8 mg/ml solutions				
22–30°, light, upright				
Tablets (VT)	87	5[c]	18[c]	41[c]
Powder (VP)	82	13[c]	28[c]	43[c]

[a] Nitroglycerin solutions were prepared in 0.9% saline and packaged in multidose vials. Variables included initial concentration; nitroglycerin source, and storage conditions. [b] Values were predicted by least-squares method except VU, which was estimated graphically. [c] Significantly different from initial ($p < 0.05$).

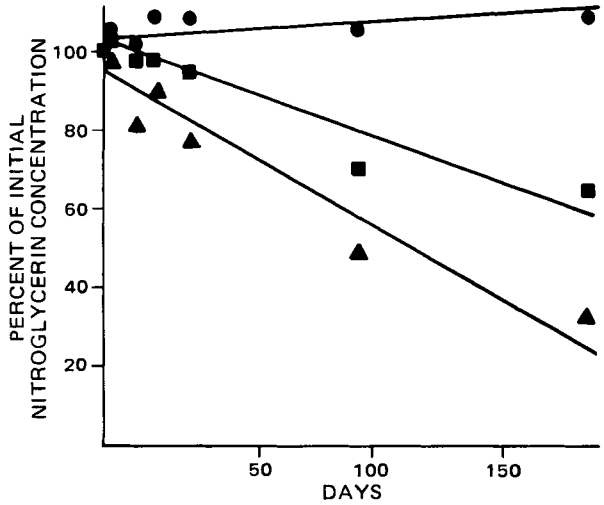

Figure 1—*Effect of temperature on nitroglycerin stock solutions, (p < 0.001). Solutions (1.0 mg/ml) were prepared from tablets in saline, packaged in multidose vials and stored upright. Key: ●, 6°, Solution VR; ■, 22–30°, Solution VRT; and ▲, 38°, Solution VO.*

decreased 44, 38, 46, and 14%, respectively. The concentration decrease of solutions stored at 28–30° under fluorescent light differed from that of solutions stored at 6° ($p < 0.001$) but did not differ from that of solutions protected from light for 52 hr. After 27 hr, the concentration decrease of solutions stored at 38° (68%) differed significantly ($p < 0.001$) from that of solutions stored at 28–30° (61%).

The concentration of intravenous nitroglycerin solutions (0.2 mg/ml) stored in glass bottles under fluorescent light at 28–30° (Solution GRT) or in the dark at 28–30° (GF), 38° (GO), or 6° (GR) did not differ significantly from the initial value after 52 hr. The rate of concentration change did not differ among these solutions. In a separate comparison, the concentration of nitroglycerin solutions stored in glass bottles decreased <18% after 24 hr at 26–28° under fluorescent light when solutions were prepared from powder in saline (GP), tablets in 5% dextrose solution (GD), or tablets in saline (GT). The rate of concentration change was independent of the vehicle (5% dextrose solution or saline) and of the source of nitroglycerin (tablet or powder).

At 1.3 hr, the nitroglycerin concentrations (expressed as a percentage of the initial value) in solutions stored in plastic bags were as follows:

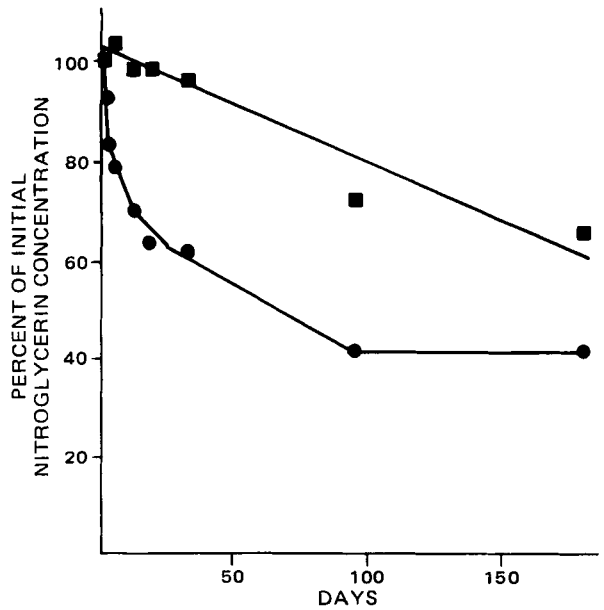

Figure 2—*Effect of contact with the rubber stopper of multidose vials on nitroglycerin concentration (p < 0.001). Solutions (1.0 mg/ml) were prepared from tablets in saline and stored at 22–30° under fluorescent light. Key: ●, stored inverted, Solution VU; and ■, stored upright, Solution VRT.*

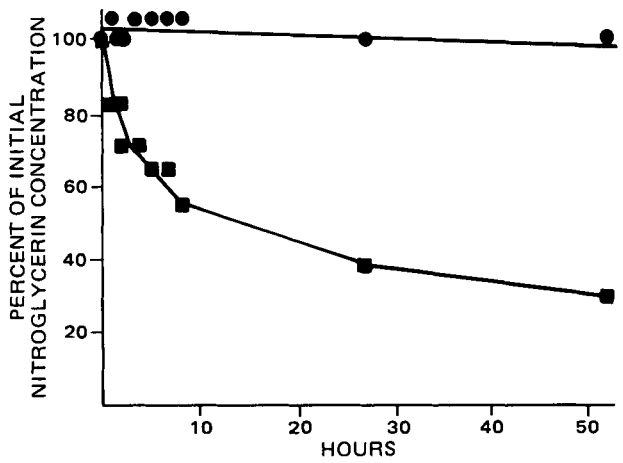

Figure 3—*Effect of glass and plastic intravenous containers on nitroglycerin concentration (p < 0.01). Solutions (0.2 mg/ml) were prepared from tablets in saline and stored at 28–30° under fluorescent light. Key: ●, glass bottles, Solution GRT; and ■, plastic bags, Solution PRT.*

under fluorescent light at 28–30°, 85%; in the dark at 28–30°, 87%; at 6°, 90%; and at 38°, 79%. Similarly, after 1.3 hr, solutions stored in glass bottles under identical conditions had concentrations that were 100, 103, 108, and 105% of the initial value, respectively. The values for solutions stored in plastic bags were different in all instances from the values for solutions stored in glass bottles ($p < 0.01$, Fig. 3).

When intravenous nitroglycerin solutions were packaged in glass (G) or plastic (P) containers and perfused through administration sets, concentration decreases occurred in the bulk solution remaining in the container and the solution perfusing the administration set. Concentration changes in the bulk solution were not significantly different from those in similar solutions without an administration set. However, concentration changes following perfusion of the administration sets were significant in all solutions ($p < 0.001$).

The mean concentration decrease of the solution perfusing administration tubing for 8 hr from a glass container (GTu) was 37% of nitroglycerin concentration in the container and differed ($p < 0.02$) from that of the solution perfusing tubing with a buret (50%, GBu). The mean decrease after perfusion of tubing from a glass container also differed from that of identical tubing attached to a plastic bag (27%, PTu, $p < 0.02$, Table IV). The largest decrease in nitroglycerin concentration occurred during the 1st hr of perfusion. After 4 hr, concentrations no longer changed with time and decreases in concentration remained as follows: tubing from glass bottle, 35%; tubing with buret from glass bottle, 55%; and tubing from plastic bag, 20% (Fig. 4).

Following an 8-hr perfusion, the mean decrease from the initial nitroglycerin concentration for the total administration system (container

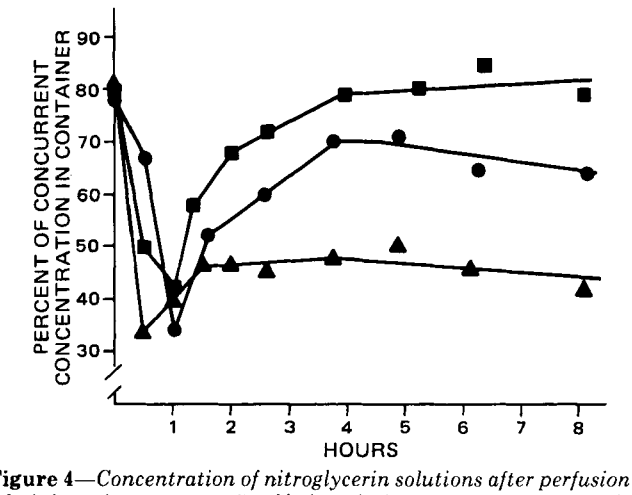

Figure 4—*Concentration of nitroglycerin solutions after perfusion of administration sets at 0.5 ml/min relative to concurrent container concentration (p < 0.001). Key: ■, plastic intravenous bag, tubing without buret, solution PTu; ●, glass intravenous bottle, tubing without buret, Solution GTu; and ▲, glass intravenous bottle, tubing with buret, Solution GBu.*

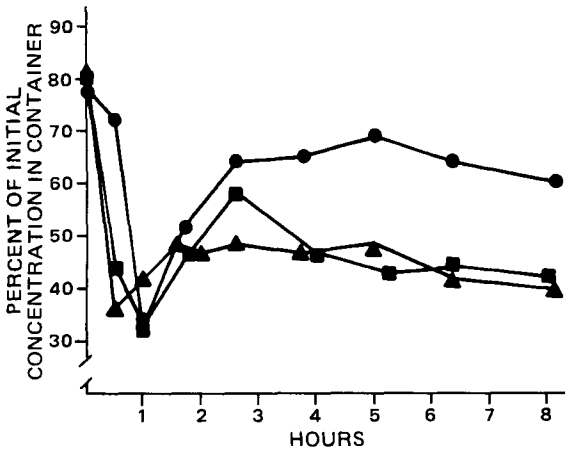

Figure 5—*Decrease from initial nitroglycerin concentration in container after perfusion of sets at 0.5 ml/min ($p < 0.001$). Key: ■, plastic intravenous bag, tubing without buret, Solution PTu; ●, glass intravenous bottle, tubing without buret, Solution GTu; and ▲, glass intravenous bottle, tubing with buret, Solution GBu.*

plus administration set) was 38% for tubing with a glass bottle (GTu), 51% for tubing with buret and a glass bottle (GBu), and 50% for tubing with a plastic bag (PTu). The decrease that occurred when tubing was used with a plastic bag differed ($p < 0.01$) from that of the system of tubing and a glass bottle but did not differ from that of the system of tubing with buret and a glass bottle (Table IV, Fig. 5).

DISCUSSION

The stability of nitroglycerin stock solutions (0.8–1.0 mg/ml) did not depend on exposure to light or the nitroglycerin source. However, nitroglycerin concentration significantly decreased with time in solutions stored at elevated temperatures or in contact with rubber stoppers (Figs. 1 and 2). Nitroglycerin stock solutions in upright multidose vials were refrigerated for ~6 months without a significant decrease in concentration. Storage of the vials at room temperature resulted in a 20% decrease in nitroglycerin concentration after ~3 months (Table III). The marked decrease in nitroglycerin concentration following contact of solutions with rubber stoppers suggests that any vial found inverted or on its side should be discarded or that an all-glass packaging system (*e.g.*, ampul) should be used.

The stability of intravenous nitroglycerin solutions (0.2 mg/ml) was not dependent on the vehicle, nitroglycerin source, or exposure to light. Storage in glass bottles for 24 hr at 6–38° resulted in a maximum loss of 18%. However, during storage in plastic infusion bags or during perfusion of plastic administration sets, nitroglycerin concentration decreased significantly with time (Figs. 3–5). Administration tubing with a buret removed more nitroglycerin from solution than did tubing without a buret. The increased stability realized by packaging nitroglycerin solutions in glass rather than plastic was negated when administration tubing with a buret was used instead of tubing without a buret (Table IV and Fig. 5).

Other studies have similarly reported minimal concentration changes in nitroglycerin solutions refrigerated in multidose vials for up to 6 months (19, 20). Autoclaving nitroglycerin solutions (400 μg/ml) at 121° for 20 min resulted in a 5% decrease in concentration (19). However, storage of nitroglycerin solutions in inverted multidose vials for 1 month resulted in a 45% decrease in nitroglycerin concentration (18).

Similar losses of nitroglycerin from solutions stored in plastic bags have been reported, but reports on the stability of nitroglycerin solutions stored in glass bottles were conflicting (17, 18, 20–23). However, stability in glass bottles was greater than that in plastic bags (18, 21–23). Contact of solutions with plastic administration sets resulted in 15–75% decreases in nitroglycerin content (21, 23, 24).

Nitroglycerin formulations may exhibit instability by degradation, volatilization (29, 30), intertablet migration (11, 30), and sorption by packaging materials (13, 15, 30, 32). Nitroglycerin degrades by hydrolysis to mono- or dinitroglycerin (15) and, at elevated temperatures, to nitric acid and glycerol (33). Microbial degradation also has been reported (34). Sorption of nitroglycerin by rubber surfaces was reported for aqueous solutions (18) and propylene glycol–ethanol solutions (35) of nitroglycerin. Nitroglycerin was recovered by methanolic extraction from plastic bags (22) and was reported to leave an oily residue on glass (36).

Table IV—Effect of the Administration Set or System on the Stability of Nitroglycerin Solutions

Administration System[a]	Mean Decrease in Nitroglycerin Concentration, %[b]	
	Administration Set Alone	Administration System
Glass bottle, tubing with buret (GBu)	50[c]	51[d]
Glass bottle, tubing without buret (GTu)	37	38
Plastic bag, tubing without buret (PTu)	27[c]	50[d]

[a] Container and administration set. [b] Percent decrease in the nitroglycerin concentration of solutions perfused through administration sets (0.5 ml/min). [c] Significantly different from GTu ($p < 0.02$). [d] Significantly different from GTu ($p < 0.01$).

The sorption of nitroglycerin during perfusion of the plastic administration sets in this study may have occurred by two processes. Nitroglycerin may have first adsorbed onto the tubing in a concentrated layer and then absorbed into the plastic matrix while nitroglycerin from the solution replenished the concentrated layer. Until the surface layer was saturated, adsorption was rapid with respect to the perfusion rate, and nitroglycerin was largely removed from solution. As saturation of the concentrated layer occurred, the extraction ratio of nitroglycerin declined; nitroglycerin concentration in the solution emerging from the tubing rose to a constant fraction of that in the container (Fig. 4). While adsorption may have accounted for the initially rapid clearance of nitroglycerin by the tubing, a greater quantity of nitroglycerin probably was removed by absorption (37).

Adsorption and absorption were capacitance (surface area) and perfusion rate limited. The nitroglycerin concentration decreased faster and remained lower when the surface area perfused by the solution was increased by the use of administration tubing with a buret rather than tubing without one (Fig. 4). Similarly, concentration decreases were more rapid and extensive at slower perfusion rates (24) as a result of the increased contact time between the solution and the surface of the administration set.

The reversible nature of nitroglycerin sorption to plastic could account for the observation that the tubing attached to bags removed a smaller percentage of nitroglycerin than did identical tubing attached to bottles (Table IV). Adsorption of the concentrated layer may have reached equilibrium during the first 1 or 2 hr of perfusion when the nitroglycerin concentration in the bag was relatively high. As the nitroglycerin level decreased in the bag, the solution perfusing the tubing was too dilute relative to the concentrated layer, and nitroglycerin desorbed into the solution. Consequently, the effect of the tubing on the nitroglycerin concentration was lessened.

The short contact of nitroglycerin solutions with a plastic syringe, unlike the longer contact with administration sets, was not associated with a decrease in nitroglycerin concentration. Plastic syringes may be used for the transfer of nitroglycerin solutions, but prolonged storage of nitroglycerin solutions in plastic syringes may result in a decreased concentration.

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Preparation and Screening of Some New Thioacetals, Sulfones, and Derivatives of 4-Dichloromethylbenzoyl and 4-Trichloromethylbenzoyl Chloride as Potential Antimalarials

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Abstract □ The preparation and screening of some potential antimalarials are reported. The new compounds which are inactive as antimalarials are several benzene-, benzyl-, and fluorene thioacetals, β-disulfones derived from these thioacetals, α-chlorobenzyl sulfones, amides, and thioesters derived from 4-dichloromethylbenzoyl chloride and 4-trichloromethylbenzoyl chloride. The known compounds bis(4-aminophenyl)sulfone and 4′-aminophenyl-4-aminobenzene thiolsulfonate also were prepared and showed some antimalarial activity.

Keyphrases □ Antimalarials—preparation of new thioacetals, sulfones, and 4-dichloromethylbenzoyl and 4-trichloromethylbenzoyl chloride derivatives □ Thioacetals—preparation of potential antimalarials □ Sulfones—preparation of potential antimalarials □ Derivatives—of 4-dichloromethylbenzoyl and 4-trichloromethylbenzoyl chloride, preparation of potential antimalarials

Malaria is still an important health problem in tropical areas. Various factors contribute to this situation including the development of malaria strains resistant to known antimalarials. This development has led to at least one recent antimalarial program (1). The purpose of the present work was to prepare potential antimalarials based on two model systems of known antimalarials, 1,4-bis(trichloromethyl)benzene which has been known as an active antimalarial for many years (2), and derivatives of bis(4-aminophenyl)sulfone which are more useful as suppressives than as therapeutic agents (3).

The synthesized compounds (Scheme I) share similarities with known antimalarials (2, 3). The trichloromethylaryl derivatives had no antimalarial activity, but the α-disulfone VIII*b* and the thiolsulfonate IX*b* showed some antimalarial activity.

RESULTS AND DISCUSSION

Thioacetals may be prepared by various methods (4–6) among which the reaction of *gem*-dihalides with sodium thiolates is a convenient one. Compound I*a* (Table I) was prepared from benzal chloride and a triethylammonium thiophenolate whereas VII*a* was formed easily from the *gem*-dihalide and a thiophenol. Acid-catalyzed reactions between 4-(trichloromethyl)benzaldehyde and various thiophenols gave the thioacetals I*c*, I*d*, and III*a*.

Two methods considered for the preparation of β-disulfones were a reaction of triethylammonium sulfinates with *gem*-dihalides or an oxi-

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