Stability Study of Nitroglycerin Sublingual Tablets

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Abstract □ Nitroglycerin sublingual tablets were studied over a 1-year period to determine tablet stability in terms of loss of strength, uniformity of tablets, and degradation of the drug itself. Tablets from six different firms were analyzed by a semiautomated procedure. The samples included two molded tablets and four compressed tablets, ranging in age at the time of initial assay from 40 days to over 1 year. The results indicated that there is a loss of strength of nitroglycerin tablets and that refrigeration slows down this loss. The study also indicated that these tablets were stable during the year of testing in terms of tablet uniformity and degradation of nitroglycerin.

Keyphrases □ Nitroglycerin sublingual tablets—stability study, loss of strength, uniformity of tablets, and degradation of drug □ Tablets, sublingual nitroglycerin—stability □ Content uniformity—nitroglycerin sublingual tablets □ Stability—nitroglycerin sublingual tablets, loss of strength, uniformity of tablets, and degradation of drug

Much recent research has been devoted to the tableting, packaging, storage, and analysis of sublingual nitroglycerin tablets. In 1973, Fusari (1) reported that tablets that were uniform when manufactured developed increased individual tablet variation upon storage because of the volatilization and subsequent intertablet migration of nitroglycerin. It has been reported (1–3) that packing materials, such as cotton and rayon, in contact with nitroglycerin tablets absorb varying amounts of nitroglycerin.

In light of all that has been reported about the problems of packaging and storage of sublingual nitroglycerin, a study was carried out to determine the stability of sublingual nitroglycerin in tablets in terms of loss of strength, uniformity of tablets, and degradation of the drug itself.

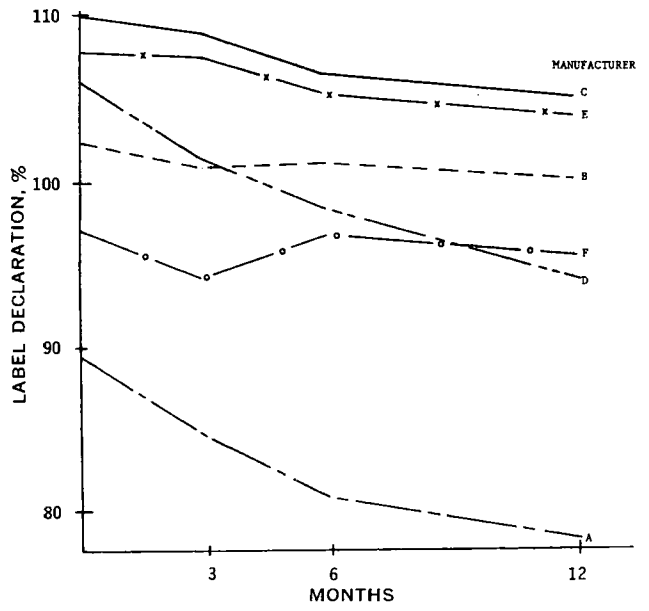

Figure 1—*Average of the 180 individual tablet assays (in percent of label declaration)* versus *time of storage after receipt.*

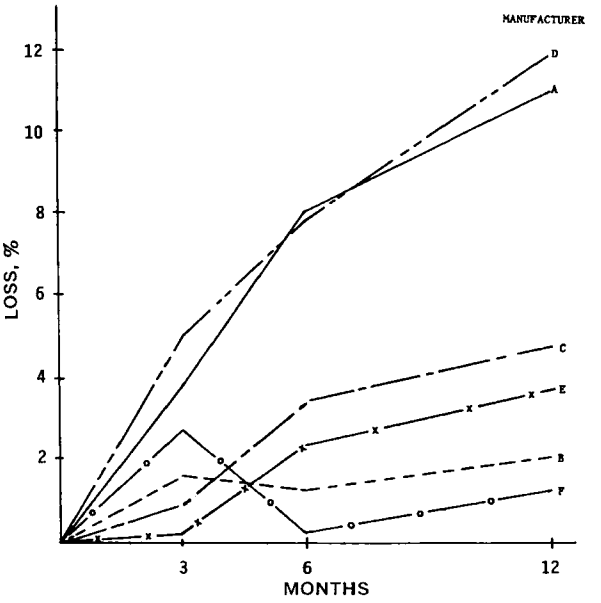

Figure 2—*Loss in percent of label declaration* versus *time of storage in this laboratory.*

One batch was sampled from each manufacturer of sublingual nitroglycerin. This sample consisted of 24 bottles from the batch most recently released by the firm's quality control department. The samples used were as follows.

Manufacturer A: 0.65-mg ($\frac{1}{100}$-gr) compressed tablets, manufactured December 24, 1971; 1000-tablet amber glass bottle, metal cap with paper liner either waxed or plastic covered, shrink-fit seal over bottle mouth, and cotton packing in bottle.

Manufacturer B: 0.6-mg molded tablets, manufactured November 16 to December 10, 1971; 100-tablet amber glass bottle, metal cap, and rayon packing.

Manufacturer C: 0.6-mg molded tablets, manufactured November 22 to December 7, 1971; 100-tablet linear polyethylene bottle, tin-plated screw cap with linear paraffin wax on liner, glassine paper seal on bottle, and rayon packing.

Manufacturer D: 0.4-mg compressed tablets, manufactured February 22 to February 26, 1971; 100-tablet amber plastic bottle, metal screw cap with liner, and cotton packing.

Manufacturer E: 0.43-mg ($\frac{1}{150}$-gr) compressed tablets, manufactured July 19 to August 9, 1971; 1000-tablet bottle; nine amber plastic with metal cap and 15 amber glass with plastic cap, both with shrink-fit seal and all with cotton packing.

Manufacturer F: 0.6-mg compressed tablets, released by quality control October 11, 1971; 1000-tab-

Table I—Average of 180 Tablets[a]

Manufacturer	Dosage	Approximate Age of Sample at Assay, days	Percent of Label Declaration		
			Average of 180 Tablets	Coefficient of Variation, %	Range
A	0.65 mg ($^1/_{100}$ gr)	40	89.4	5.0	77.3–109.2
			89.5 (T)	4.6	
			88.9 (M)	4.2	
			89.6 (B)	6.2	
		130	84.5	5.0	71.8–96.4
			84.1 (T)	5.7	
			84.8 (M)	5.3	
			84.5 (B)	4.1	
		220	81.4	5.9	70.8–97.3
			80.9 (T)	5.9	
			83.3 (M)	5.6	
			80.1 (B)	5.7	
		405	78.4	5.2	70.4–94.1
			79.0 (T)	5.3	
			78.4 (M)	4.9	
			77.7 (B)	5.5	
B	0.6 mg	72	102.4	4.9	89.2–115
			101.8 (T)	4.6	
			102.1 (M)	5.4	
			103.4 (B)	4.6	
		162	100.8	4.9	87.3–114.8
			101.9 (T)	4.6	
			100.1 (M)	5.2	
			100.6 (B)	5.2	
		252	101.2	5.2	86.1–117.1
			101.8 (T)	6.1	
			101.4 (M)	4.8	
			100.5 (B)	4.8	
		435	100.4	4.6	88.5–112.4
			100.8 (T)	4.7	
			100.9 (M)	4.5	
			99.4 (B)	4.7	
C	0.6 mg	80	110.0	7.7	74.5–134.0
			111.7 (T)	8.4	
			108.8 (M)	8.7	
			109.5 (B)	6.0	
		170	109.1	7.3	86.6–129.2
			108.8 (T)	8.0	
			110.3 (M)	5.8	
			108.1 (B)	8.0	
		260	106.5	8.0	78.7–134.8
			108.7 (T)	7.3	
			106.1 (M)	7.7	
			104.6 (B)	9.1	
		448	105.2	7.5	82.6–121.9
			104.9 (T)	8.1	
			104.5 (M)	6.9	
			106.0 (B)	7.5	
D	0.4 mg	387	106.5	6.1	89.3–129.7
			107.0 (T)	5.9	
			105.3 (M)	5.9	
			107.3 (B)	6.4	
		473	101.4	5.5	90.0–120.5
			101.7 (T)	6.1	
			100.9 (M)	5.2	
			101.5 (B)	5.1	
		568	98.6	5.2	88.9–117.4
			97.7 (T)	5.2	
			99.1 (M)	5.3	
			99.1 (B)	5.1	
		746	94.6	5.3	79.6–111.6
			94.8 (T)	5.5	
			93.6 (M)	5.4	
			95.4 (B)	5.0	
E[b]	0.43 mg ($^1/_{150}$ gr)	243	107.8	4.0	94.5–117.1
			107.4 (T)	4.1	
			107.8 (M)	3.8	
			108.3 (B)	4.0	
		334	107.6	3.5	103.2–127.4
			107.7 (T)	4.0	

(*continued*)

Table I—(*Continued*)

Manufacturer	Dosage	Approximate Age of Sample at Assay, days	Percent of Label Declaration		
			Average of 180 Tablets	Coefficient of Variation, %	Range
			108.0 (M)	4.7	
			107.1 (B)	3.7	
		426	105.4	4.2	87.0–117.2
			104.2 (T)	4.4	
			105.7 (M)	4.3	
			106.3 (B)	4.0	
		608	104.1	5.0	91.6–127.7
			101.6 (T)	4.5	
			104.5 (M)	5.1	
			106.2 (B)	5.4	
F[c]	0.6 mg	209	97.0	21.8	50.5–200.4
			96.7 (T)	17.7	
			94.9 (M)	23.2	
			99.4 (B)	24.6	
		302	94.2	18.8	54.5–145.7
			87.8 (T)	16.8	
			97.6 (M)	18.4	
			97.1 (B)	21.1	
		393	96.8	21.0	51.8–167.8
			97.1 (T)	22.6	
			92.6 (M)	19.7	
			100.8 (B)	21.1	
		577	95.8	22.9	47.3–167.6
			92.2 (T)	21.8	
			96.6 (M)	23.3	
			98.6 (B)	23.3	

[a] Sixty each from top (T), middle (M), and bottom (B) of the bottle at 0, 3, 6, and 12 months after receipt in this laboratory. [b] Batch failed USP XVIII tablet disintegration test. [c] Batch failed USP XVIII content uniformity requirement.

let amber glass bottle, metal screw cap with shrink-fit seal-closures, and cotton packing.

EXPERIMENTAL

Analytical Protocol—Six of the 24 bottles in each batch were analyzed within 1 month of receipt. From each of the six freshly opened containers, 10 tablets were sampled from the top layer, 10 from the middle layer, and 10 from the bottom layer (180 tablets total). These 18 groups of tablets were kept discrete and traceable to the point of sampling (bottle and layer).

The remaining 18 bottles from the batch were divided into three groups of six each for subsequent analyses. The subsequent analyses were performed 3, 6, and 12 months after the date of the original analysis and utilized the identical sampling technique.

Table I shows the average of these 180 assay results together with the averages of the 60 tablets from the top, middle, and bottom of the six bottles. Figure 1 is a graphic representation of the average assay of the 180 tablets in relation to the time of storage of the samples after receipt. Figure 2 shows the percent loss of the six products based on the average of the 180 individual tablet assays.

The six containers opened for the original analyses (zero time) *only* were treated additionally as follows. After initial analysis, the bottles were tightly reclosed. Three bottles were stored at 5°, and the remaining three bottles were stored at ambient temperatures ranging from 15.5 to 33°. After 3, 6, and 12 months, 11 tablets were sampled at random from each of six containers, and the containers were tightly reclosed after each withdrawal.

Ten of the 11 tablets from each container were individually analyzed by the same procedure used for the original analysis; the remaining tablet from each bottle was analyzed by TLC. Table II shows the average assays for tablets from the three bottles stored at 5° (10 from each bottle) and the three bottles (10 from each bottle) stored at 12.8–29.4°. These analyses were made on the same bottle of tablets each of the assay times of 0, 3, 6, and 12 months. Figure 3 shows the difference in percent of label claim between the averages of those stored at 5° and those stored at room temperature.

Bottle packing material and cap liners were analyzed for nitroglycerin by quantitative TLC to see if the loss in strength could be attributed to adsorption onto the packing material. Table III shows the results of the TLC analysis performed on freshly opened bottles.

Principles—The nitroglycerin tablet is disintegrated with a small amount of water and then extracted with a suitable aliquot of isooctane. A portion of the isooctane extract is sampled by an automated analyzer system, which hydrolyzes the nitroglycerin with tetramethylammonium hydroxide in 1-propanol, yielding 2 moles of nitrite ion from each mole of nitroglycerin (4).

p-Chloroaniline in propanol is diazotized by the nitrite formed; the diazotized product is then coupled with *N*-(1-naphthyl)ethylenediamine in 1-propanol. The absorbance of the resultant color is determined at 550 nm.

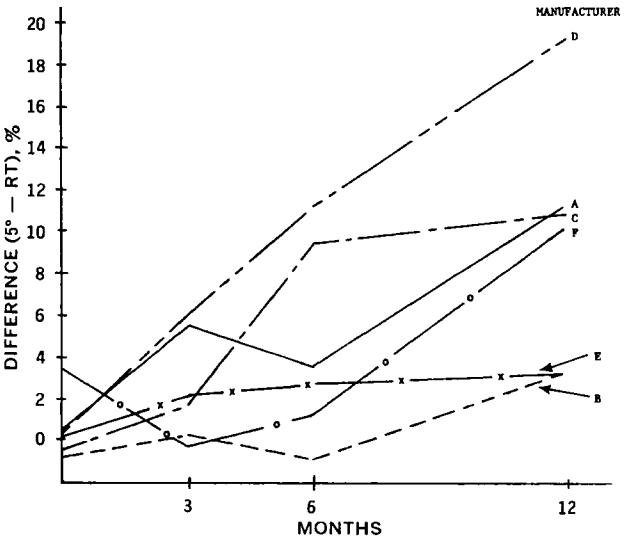

Figure 3—*Difference in percent of label declaration between tablets stored at 5° and room temperature (RT) versus time of storage in this laboratory.*

Table II—Summary of Analysis of Subsamples 1–3 (Refrigerated) and 4–6 (Room Temperature)

Manufacturer	Dosage	Approximate Age of Sample at Assay, days	Subsample	Percent of Label Declaration: Average (Number of Tablets)	Percent of Label Declaration: Coefficient of Variation, %
A	0.65 mg ($^1/_{100}$ gr)	40	1–3	89.6 (90)	5.3
			4–6	89.1 (90)	4.8
		130	1–3	90.6 (30)	6.5
			4–6	85.1 (30)	5.3
		220	1–3	87.8 (30)	6.3
			4–6	84.3 (30)	5.5
		405	1–3	87.5 (30)	4.3
			4–6	76.3 (30)	5.1
B	0.6 mg	72	1–3	102.0 (90)	4.8
			4–6	102.8 (90)	4.6
		162	1–3	101.8 (30)	6.5
			4–6	101.6 (30)	3.6
		252	1–3	99.3 (30)	4.3
			4–6	100.2 (30)	5.3
		435	1–3	101.0 (30)	6.6
			4–6	97.9 (30)	4.6
C	0.6 mg	80	1–3	109.7 (90)	7.6
			4–6	110.2 (90)	8.1
		170	1–3	107.3 (30)	7.7
			4–6	105.6 (30)	10.2
		260	1–3	113.7 (30)	7.9
			4–6	104.3 (30)	10.7
		435	1–3	103.3 (30)	10.0
			4–6	92.3 (30)	13.5
D	0.4 mg	22	1–3	106.7 (90)	6.1
			4–6	106.3 (90)	6.0
		108	1–3	105.3 (30)	5.2
			4–6	99.4 (30)	5.0
		203	1–3	103.1 (30)	5.9
			4–6	92.0 (30)	5.0
		381	1–3	101.7 (30)	5.5
			4–6	82.7 (30)	5.7
E	0.43 mg ($^1/_{150}$ gr)	243	1–3	107.9 (90)	3.5
			4–6	107.7 (90)	4.4
		334	1–3	108.9 (30)	3.5
			4–6	106.8 (20)	4.0
		426	1–3	109.3 (30)	4.0
			4–6	106.6 (20)	4.3
		608	1–3	107.8 (30)	3.2
			4–6	104.6 (20)	2.9
F	0.6 mg	209	1–3	99.7 (90)	22.1
			4–6	94.3 (90)	21.5
		302	1–3	96.5 (30)	22.8
			4–6	96.8 (30)	24.7
		393	1–3	97.0 (30)	20.7
			4–6	95.8 (30)	17.1
		577	1–3	101.7 (30)	25.7
			4–6	91.7 (30)	17.9

Apparatus—The automated analyzer[1] system consisted of a liquid sampler II equipped with stainless steel cover plate[2], a proportioning pump I, a colorimeter equipped with either an 8- or a 15-mm tubular flow cell (depending on drug dosage level) and 550-nm filters, and a single-pen recorder[3], linear in transmittance and provided with paper printed in absorbance units, moving at 46 cm (18 in.)/hr. Figure 4 is a manifold diagram showing the coils, tubing, and fittings.

Reagents—The following were used:

Nitroglycerin Adsorbate—About 10% nitroglycerin adsorbed on lactose, standardized against potassium nitrate using the AOAC total nitrate method (5).

Isooctane—ACS reagent grade 2,2,4-trimethylpentane.

1-Propanol—ACS reagent grade.

Tetramethylammonium Hydroxide Solution—Prepared by diluting 25 ml of aqueous 10% tetramethylammonium hydroxide to 1000 ml with 1-propanol.

p-*Chloroaniline Solution*—Prepared by adding 500 mg to 100 ml of hydrochloric acid, shaking the mixture to disperse, diluting to 1000 ml with 1-propanol, and shaking to dissolve. A fresh solution should be prepared weekly.

N-*(1-Naphthyl)ethylenediamine Dihydrochloride Solution*—Prepared by adding 1 g to 5 ml of water, shaking the mixture to disperse, adding 5 ml of hydrochloric acid, diluting to 1000 ml with 1-propanol, and shaking to dissolve. A fresh solution should be prepared weekly.

Nitroglycerin Standard Solution—(a) For analysis of 0.3 and 0.6 mg/tablet: An amount of adsorbate equivalent to approximately 12 mg of nitroglycerin is accurately weighed, transferred to a 1000-ml volumetric flask containing 400 ml of isooctane, shaken intermittently for 15 min, diluted to volume with isooctane, and

[1] AutoAnalyzer, Technicon Corp., Tarrytown, NY 10591
[2] Technicon No. 127-B029.
[3] Bristol.

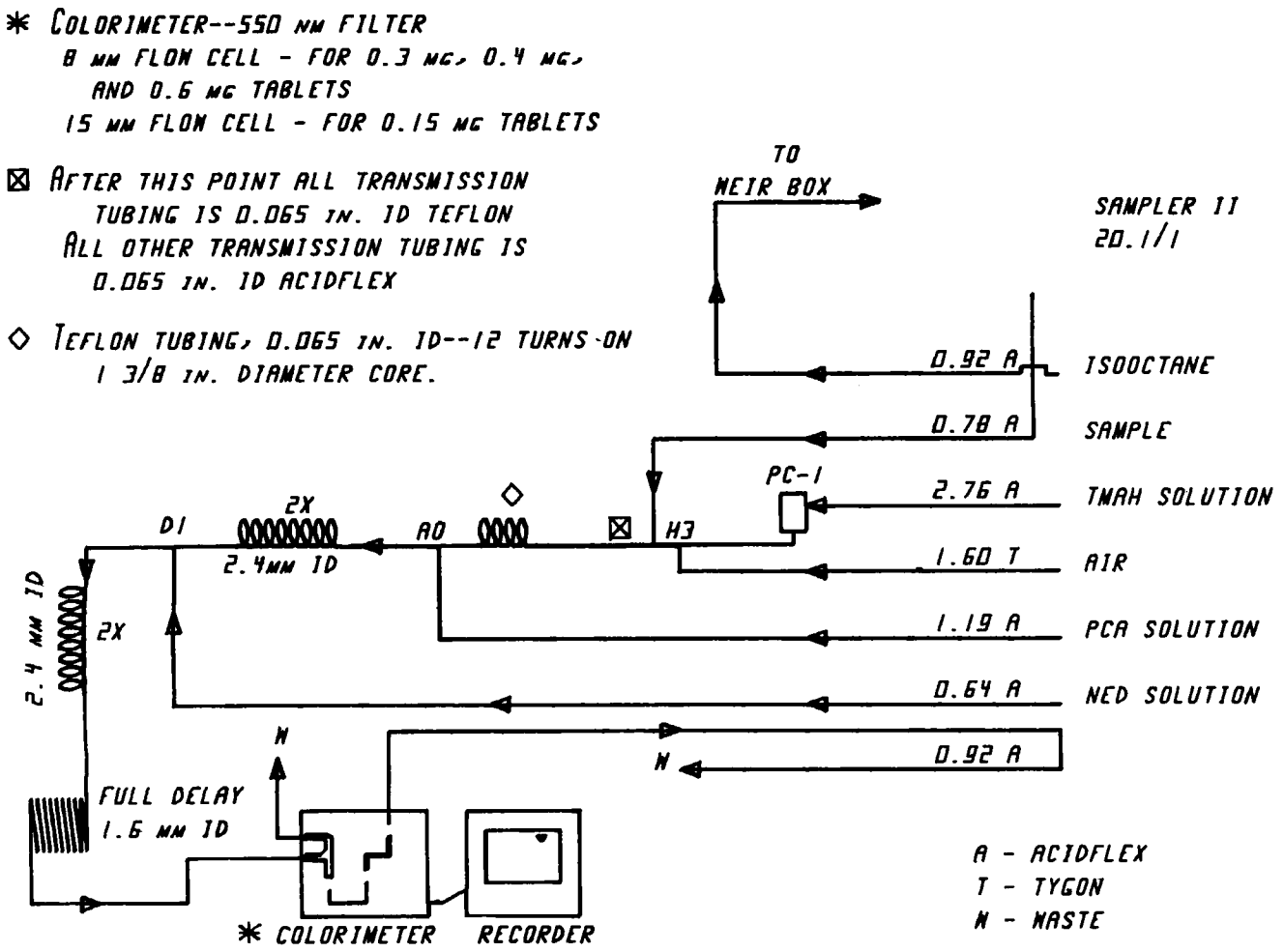

Figure 4—*Manifold diagram for semiautomated method of analysis for nitroglycerin tablets.*

mixed. Just before use, a 50-ml aliquot is shaken with 1 ml of water for 1 min, and the clear isooctane layer is decanted into the automated analyzer cup.

(b) For analysis of 0.4 mg/tablet: An amount of adsorbate equivalent to 16 mg of nitroglycerin is accurately weighed and treated as in *(a)*.

(c) For analysis of 0.15 mg/tablet: Solution *a* (25.0 ml) is transferred to a 125-ml glass-stoppered erlenmeyer flask; then 25.0 ml of isooctane is added, and the solution is mixed. Just before use, it is shaken for 1 min with 1 ml of water, and the clear isooctane layer is decanted into the automated analyzer cup. The dry isooctane solutions are stable for at least 2 months if kept tightly stoppered.

Sample Preparation—Single tablets are disintegrated with 0.5 or 1.0 ml of water in a glass-stoppered flask, 25 or 50 ml of isooctane is added, and the solution is shaken mechanically for 15 min. The amounts of solvents necessary per dosage level are:

dosage, mg	water, ml	isooctane, ml
0.6	1.0	50
0.4	0.5	25
0.3	0.5	25
0.15	0.5	25

The decanted isooctane extract is sampled from 8.5-ml polyethylene cups by the sampler at a rate of 20 samples/hr with a sample-to-wash ratio of 1:1. The sample stream is mixed with a stream of tetramethylammonium hydroxide solution and air in a Teflon coil; *p*-chloroaniline solution is added and mixed into the resulting stream, followed by *N*-(1-naphthyl)ethylenediamine dihydrochloride solution. The stream is delayed with a full delay coil and then passed through a colorimeter having 550-nm filters.

An 8-mm flow cell is used for dosage levels of 0.3, 0.4, and 0.6 mg; a 15-mm flow cell is used for a dosage level of 0.15 mg. The sampling pattern is two standards, five samples, one standard, five samples, one standard, five samples, *etc.* The first standard on each sample wheel is ignored in calculations because some absorption takes place in the tubing. A stainless steel sample cover plate must be used, and the sample solutions should not stand in the cups any longer than necessary before sampling because of evaporation of solvent.

TLC—*TLC Plates*—Silica gel G[4] (20 × 20 cm) plates were prepared (for the quantitative visual estimation method) by scooping out nine channels (2 mm wide) to give 10 bands of thin layer 18 mm wide.

Silica gel GF[4] (20 × 20 cm) prescored plates were prepared (for the quantitative colorimetric estimation by TLC) by scooping out three channels (2 mm wide, each channel at score mark on glass plate) to give four bands of thin layer 38 mm wide.

Developing Solution—Benzene–ethyl acetate–acetic acid (16:4:1) (6) was used.

Spray Reagent—A solution of 1% *N*-(1-naphthyl)ethylenediamine dihydrochloride in methanol was prepared. Visualization was achieved by exposing the plates to UV light after spraying.

Standard—Potassium nitrate standard solution and standard preparation were prepared according to USP XVIII.

Plate Standard[5]—A mixture of nitroglycerin, 1,3-dinitroglycerin, 1,2-dinitroglycerin, and mononitroglycerin in alcohol was prepared and applied to the TLC plates using disposable pipets.

Packing Material—The plugs of packing material from the bot-

[4] Supplied by Analtech, Brinkmann Instruments, Inc., Westbury, NJ 11590

[5] Supplied by Dr. Philip Needleman, Washington University School of Medicine.

Table III—Results of TLC Analysis of Packing Material and Cap Liners

Manufacturer	Approximate Age of Material at Assay, days	Material	Found, mg		
			Nitroglycerin	1,3-Dinitroglycerin	1,2-Dinitroglycerin
A	220	Cotton packing	1.03	0.07	0.05
		Liner	—	—	—
	405	Cotton packing	1.1	0.17	0.06
		Liner	0.01	—	—
B	252	Rayon packing	0.03	—	—
		Liner	0.003	—	—
	435	Rayon packing	0.05	—	—
		Liner	0.01	—	—
C	260	Rayon packing	0.26	0.05	0.01
		Liner	0.01	—	—
	448	Rayon packing	0.31	0.098	0.02
		Liner	0.004	—	—
D	203	Cotton packing	1.4	0.01	0.01
		Liner	0.27	—	—
	381	Cotton packing	2.0	0.04	0.03
		Liner	0.22	—	—
E	243	Cotton packing	0.274	0.01	0.01
		Liner	0.014	—	—
F	302	Cotton packing	2.8	0.08	0.63
		Liner	0.05	—	—
	393	Cotton packing	7.1	0.12	0.1
		Liner	0.02	—	—
	577	Cotton packing	8.8	0.22	0.2
		Liner	Trace	Trace	Trace

tles were placed in a 5-ml hypodermic syringe with about 3 ml of methanol and agitated by rotating between the fingertips. They were then injected into disposable pipets containing a small amount of powder[6] to control the flow of liquid to the TLC plate. Pipets were standing at right angles to the plate with their tips touching the plate. Four replacement washes with methanol were applied.

Wax Paper Liners—The wax paper liners from the bottles in the sample were attached to wires (by rolling them around the wire) and churned up and down in the disposable pipets containing about 0.5 ml of methanol (pipet tips were plugged with small amounts of powder[6] to control the flow of liquid to the TLC plate). Pipets were standing at right angles to the TLC plate with their tips touching the plate. Four replacement washes were applied.

Plate Development—The plate was developed to about 4 cm in methanol, air dried, developed an additional 10 cm with developing solution, and air dried again.

Quantitative Visual Estimation—The developed unscored TLC plates were sprayed and visualized after exposure to UV light for several minutes and by visual comparison with standards on the same plate.

Colorimetric Estimation by Quantitative TLC—Each of the developed, scored TLC plates was snapped along score marks into four sections. Sections containing standards were sprayed and visualized under UV light. The broken plates were reassembled, and the thin-layer areas on sample and blank sections corresponding to the visualized standard nitroglycerin spot were removed and placed in 100-ml volumetric flasks with 1 ml of acetic acid and allowed to stand for 30 min. Two milliliters of phenoldisulfonic acid was added and the flask was allowed to stand another 15 min; then 50 ml of water and 10 ml of ammonium hydroxide were added.

After cooling to room temperature, the solution was diluted to 100 ml with water and scanned in a spectrophotometer from 600 or 550 nm to 350 nm against a reagent blank. Blank solutions of adsorbent were carried through the analysis and subtracted.

Quality Control of Analytical System—It was imperative that some quality assurance checks be made on the automated method during the year of testing. The 10% nitroglycerin adsorbate was used throughout the study and was assayed periodically to ensure that it had not lost nitroglycerin. It first assayed (January 1972) at 10.1%. Subsequent assays in June 1972 and February 1973 were also 10.1%. In each case the total nitrate method was used with potassium nitrate as the standard.

To ensure that the system was performing satisfactorily, a composite of 0.6-mg nitroglycerin tablets consisting of ground tablet material was analyzed throughout the year. This composite was kept in a refrigerator at 5°. It was analyzed 10 times before the start of the study, and the percent coefficient of variation of the system was 0.50. As can be seen from the data in Table IV, the system had good precision and gave essentially the same assay results over the year.

Table IV—Analysis of 0.6-mg Quality Control Composite

Date	Percent Found[a]	*SD*	Coefficient of Variation, %
January 1972	106.4 (10)[b]	0.53	0.50
February 4, 1972	106.1	—	—
February 22, 1972	108.2	—	—
February 23, 1972	108.6 (2)	—	—
May 3, 1972	105.0 (3)	—	—
May 9, 1972	106.1	—	—
August 10, 1972	106.7 (3)	—	—
November 27, 1972	107.1 (8)	0.78	0.73
December 11, 1972	106.2 (8)	0.82	0.77
February 1, 1973	104.7 (4)	—	—
February 7, 1973	107.0 (5)	—	—
February 14, 1973	106.1	—	—
February 20, 1973	104.9 (7)	—	—
May 8, 1973	106.0 (7)	—	—
Average of assays during study of February 4 to May 8	106.2 (51)	1.26	1.19

[a] Based upon label declaration. [b] Values in parentheses are numbers of assays performed on that date.

[6] SilicAR TLC 4 GF, Mallinckrodt Chemical Works, St. Louis, MO 63160

Table V—Analysis of Variance on Averages of 180 Assays

Months	Manufacturer A	B	C	D	E	F
0	89.4	102.4	110.0	106.5	107.8	97.0
3	84.5	100.8	109.1	101.3	107.6	94.2
6	81.4	101.2	106.5	98.6	105.4	96.8
12	78.4	100.4	105.1	94.6	104.1	95.8
Observed F ratio	200.54	5.12	13.15	144.42	26.70	0.74
Significant	Yes	Yes	Yes	Yes	Yes	No
Critical value $F_{0.95}$ (3, ∞) = 2.60						

Table VI—Analysis of Variance on Room Temperature Average Assay (RTA) *versus* Refrigerated Average Assay (RFA)

	Manufacturer A	B	C	D	E	F
3 Months						
RTA	85.1	101.6	105.6	99.4	106.8	96.8
RFA	90.6	101.8	107.3	105.3	108.9	96.5
Observed F	16.51	0.0102	0.452	19.9	3.153	0.0025
Difference significant	Yes	No	No	Yes	No	No
6 Months						
RTA	84.3	100.2	104.3	92.0	106.6	95.8
RFA	87.8	99.3	113.7	103.1	109.3	97.0
Observed F	6.83	0.618	12.830	62.94	4.513	0.0562
Difference significant	Yes	No	Yes	Yes	Yes	No[a]
12 Months						
RTA	76.3	97.9	92.3	82.7	104.6	91.7
RFA	87.5	101.0	103.3	101.7	107.8	101.7
Observed F	127.91	4.481	16.511	204.6	11.379	2.5996
Difference significant	Yes	Yes	Yes	Yes	Yes	No[a]
Critical value $F_{0.95}$ (1, 60) = 4.00						

[a] Note large coefficient of variation percent in Table II for this batch.

RESULTS AND DISCUSSION

The results shown in Table I indicate a loss in strength of the nitroglycerin with age, with Manufacturers A and D's products showing substantial losses (Figs. 1 and 2). A one-way analysis of variance (one variable) (7) was performed to test if the difference in the results between the time periods was significant. Table V shows the averages for the 180 assays for that time period and the observed F ratio calculated using one-way analysis of variance. The only sample that did not show a statistical difference in the means was Manufacturer F's product.

The data in Tables I and II also indicate that there was no increase in intertablet variation throughout the year in samples stored in the refrigerator and at room temperature, as evidenced by the coefficient of variation of the tablets analyzed for the test period. The range of the assays remained about the same for each assay period, with the highs being no higher or the lows lower. These results are not in direct conflict with the findings in the recent publications of Fusari (1, 8). Fusari's data indicate that the increase in variability develops within 1 month of manufacture. The batches used in this study were more than 1 month old before the authors' initial assay. In addition, four of the six batches under study here were compressed tablets. Fusari referred only to molded tal ets.

The results shown in Table II indicate a difference in analysis of tablets from bottles stored at 5° and at room temperature (Fig. 3). An analysis of variance was performed to test if the difference between the average assays at each time was statistically significant. Table VI shows the averages of the 30 assays from the three bottles stored in the refrigerator and the three bottles stored at room temperature, as well as the observed F ratio. Only Manufacturer F's product failed to show a significant difference at 12 months. Manufacturers A and D showed a statistically significant difference as early as 3 months, Manufacturers C and E showed a statistically significant difference at 6 months, and Manufacturer B did not show a difference until 12 months.

An additional statistical analysis of variance was performed on the data in Table I to determine whether the drug stratified between different levels in the bottles. No stratification was found. No degradation of nitroglycerin to 1,3-dinitroglycerin, 1,2-dinitroglycerin, or the mononitroglycerins was observed in the tablets by TLC.

Table III shows the results of the analysis for the nitroglycerin in the cap liners and packing materials. As reported earlier, the bottle packing absorbed varying amounts of nitroglycerin; cap liners absorbed a lesser amount.

In summary, the data presented here show:

1. There is a loss of strength of nitroglycerin tablets from previously unopened bottles upon storage.
2. Refrigeration of nitroglycerin tablets slows down the loss of nitroglycerin.
3. The nitroglycerin tablets used in this study, four compressed tablets and two molded tablets, were stable during the year of testing in terms of uniformity of tablets and degradation of the drug.

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Automated Conductimetric Titrimeter: Use in Studying Ionic Solute–Solute Interactions

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Abstract □ An automatic conductimetric titration apparatus is described in which the delivery of titrant is effected using a motorized automatic syringe having a wide range of injection rates. Two applications of the apparatus are described: *(a)* determination of the CMC of cationic and anionic surfactants, and *(b)* study of the interaction of an organic anion (sodium lauryl sulfate) and organic cations (phosphonium salts). The accuracy and precision of results using this apparatus are superior to results obtained by the tedious manual method.

Keyphrases □ Titrimeter, automated conductimetric—design, application to studying solute–solute interactions □ Syringe, motorized automatic—component of automatic conductimetric titration apparatus, application to solute–solute interactions □ Conductimetric titrations—automatic apparatus described, applied to solute–solute interactions

The physical property of solution conductance is well established, and conductimetric titration measurements can be used for various purposes. In pharmacy such measurements find application in studies on association and micellization, interaction (*i.e.*, complexation) between species of opposite charge, and analytical quality control. However, the usual method of addition of titrant or complexing agent to the titration vessel is tedious, and the results are often subject to experimental inaccuracies.

A conductimetric titration of one ion against another of opposite charge will provide information on ion-pair formation, complexation (as described by the solubility product), and, if one ion is surface active, the effect of the added species (counterion) on micelle formation. In addition, a study of the interaction of a large organic ion with congeneric members of a series of ions of opposite charge can lead to the calculation of thermodynamic quantities and, subsequently, the derivation of extrathermodynamic parameters (1) for use in linear free energy relationships to examine structure–activity correlations by regression analysis.

Studies on the variation of the free energy term with temperature should lead to an insight into enthalpy and entropy contributions to the interaction and, in consequence, the processes responsible for such complex formation. Because small errors in measurement of the solubility product (and any association constant) will lead to greater errors when the free energy–temperature relation is differentiated (2), an essential requirement of measurement is that the experimental data are of high accuracy. Such accuracy cannot be obtained with manual or semiautomatic methods.

Thus, an accurate automatic conductimetric titration apparatus was developed, using commercially available components, which is suitable for pharmaceutical systems. Semiautomatic conductimetric titrimeters for use in analytical measurements were described previously (3, 4).

EXPERIMENTAL

Apparatus (Fig. 1)—A conductivity bridge[1], which is continuously and automatically balanced, is connected to a dip-type conductivity cell contained in a thermostated beaker. The temperature is maintained constant by water pumped from a water bath and cooler unit. The titration mixture is agitated constantly by a magnetic stirrer. The measured conductivity, which can be read directly from the bridge, is normally recorded in the form of a continuous trace on a chart recorder.

In titrations where an external standard is used, a similar thermostated beaker is connected to the water bath; a dip cell, which has a comparable cell constant (±0.01) to the other cell, is connected to the external standard terminal of the bridge. The stirring conditions in the external standard are maintained the same as in the unknown during the titration.

The delivery of the titrant is maintained constant using a motorized automatic syringe[2], which has a wide range of delivery rates according to the capacity of the special syringes used. Where an external standard is used, two syringes of the same capacity are employed and driven simultaneously at the same rate.

Calibration—The conductivity bridge was trimmed and calibrated as described in the instrument manual.

The automatic motorized syringe equipment is supplied with special syringes, consisting of a calibrated glass barrel and a steel plunger fitted with a rubber gasket. The accuracy and reproducibility of the volume delivered from the syringes were tested by two techniques: *(a)* the syringe was allowed to drain into a dry, previously calibrated volumetric flask of a suitable volume; and *(b)* the syringe was filled with a potassium chloride solution of known conductivity and this was titrated into a blank of double-distilled water of known volume. The conductivity was recorded as a func-

[1] Wayne-Kerr B642 universal bridge, Wayne-Kerr, Surrey, England.
[2] R. Braun, Melsungen, West Germany.