Nitroglycerin Sublingual Tablets II: Preparation and Stability of a New, Stabilized, Sublingual, Molded Nitroglycerin Tablet

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Abstract □ A new, molded, stabilized, sublingual nitroglycerin tablet was prepared. This tablet shows the same bioavailability as conventional tablets but has the advantage of markedly improved stability. In contrast to conventional tablets, which often develop marked intertablet dose variation within 1 month, the stabilized tablet maintains its content uniformity for long periods, even at 37 and 45°, thus assuring a more uniform and predictable dose to the patient.

Keyphrases □ Nitroglycerin sublingual tablets—preparation, stability analysis of molded tablets containing polyethylene glycol as a fixative □ Sublingual nitroglycerin tablets—preparation, stability analysis of molded tablets containing polyethylene glycol as a fixative

Many papers have reported the instability of conventional molded sublingual tablets (1–7), and all have noted that the volatilization of nitroglycerin plays a part in this instability. However, it has only recently been recognized that one fundamental change accompanying volatilization is intertablet migration of nitroglycerin, leading to large intertablet dose variation. A report (8) showed that conventional nitroglycerin tablets are unstable, not in the usual sense of chemical breakdown but with respect to (a) slow loss of potency due to volatilization of nitroglycerin, and (b) maintenance of content uniformity.

Since this instability could not be controlled by manipulating the container and cap liner, it was decided that the best solution involved reformulation of the tablet to minimize volatilization and subsequent intertablet migration of nitroglycerin.

As shown in the first paper of this series (8), all results indicated that the problem with conventional sublingual nitroglycerin tablets starts with the manufacturing process[1]. During this procedure, a mixture of alcohol and water is added to a blended mixture of nitroglycerin, lactose, and sucrose. After molding, the tablets are air dried. It is postulated that nitroglycerin can be brought to the tablet surface during the drying process by the evaporation of alcohol and water, where it becomes available for loss and/or migration by slow volatilization, depending on the character of the immediate environment. If this hypothesis is correct, the addition of a "fixing" agent to the tablets should inhibit the volatilization of nitroglycerin and help solve the problems of potency loss and intertablet dose variation caused by the migration of nitroglycerin.

This paper describes the preparation of a stabilized tablet and its properties, followed by a description of the experiments that confirmed its superior stability.
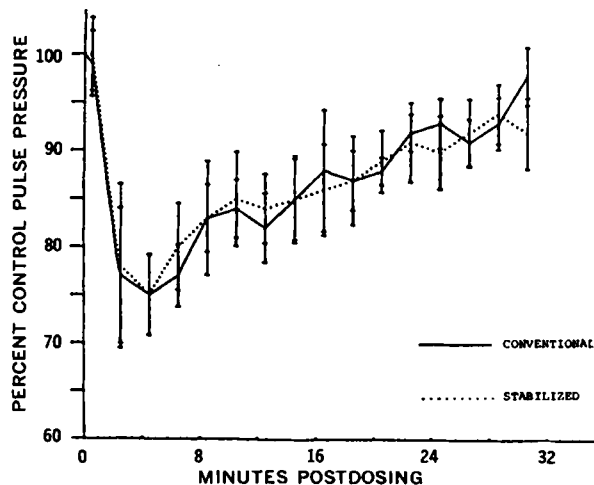

Figure 1—*Comparative bioavailability of conventional and stabilized nitroglycerin tablets in dogs.*

Both short-term stress experiments and long-term stability studies were included. While some short-term stress experiments have no necessary parallel in a real life situation, they illustrate the regulated or controlled behavior of the stabilized tablet, which is in marked contrast to the irregular behavior exhibited by the conventional tablet. The long-term stability studies are still in progress; data up to 25 months will be given.

EXPERIMENTAL

Tablet Manufacture

Molded, stabilized, sublingual tablets[2] were made in exactly the same way as conventional sublingual tablets, except that a water-soluble, nonvolatile fixing agent[3] was added to the formulation. The fixative was added as a constant percentage of the nitroglycerin present in our three different formulations (0.3, 0.4, and 0.6 mg. nitroglycerin per tablet). The lactose, sucrose, and 10% nitroglycerin tablet mixture[4] was blended in a 142-l. blender (PK), equipped with a liquid feed bar (intensifier bar), for 10 min. The granulating fluid, consisting of water, alcohol, and fixative, was added through the intensifier bar over 3 min., after which the mixture was blended for another 12 min. The intensifier bar operated continuously throughout the entire 25-min. blending period. The blended mixture was then stored overnight in a refrigerator. The molded[5] tablets were then air dried for about 20–48 hr. before bottling and packaging.

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[2] Nitrostat; Parke, Davis brand of stabilized, molded, sublingual nitroglycerin tablets.

[3] Polyethylene glycol 400 was used for the tablets described in this paper, but polyethylene glycol 4000 has also been used successfully. The amount used was 85% (w/w) of the nitroglycerin in the tablet formula.

[4] E. I. duPont de Nemours supplies this as a 10% nitroglycerin–90% β-lactose (w/w) mixture.

[5] Molding was accomplished using a Colton tablet molding machine, model 720.

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[1] This possibility was also suggested by M. D. Richman *et al.* (1).

Table I—Properties of Stabilized Sublingual Tablets[a]

	Stabilized Tablet	Conventional Tablet
Physical properties		
Disintegration	Not >45 sec.	Not >45 sec.
Wickability	Average (20 tablets): not >20 sec., no tablet >40 sec.	Average (20 tablets): not >20 sec., no tablet >40 sec.
Chemical properties		
Assay (as is):		
Average (30 tablets): 99.7% label claim		
Range: 92.1–108.1%		
SD: 4.0%		
SD σ (corrected for tablet weights): 1.3%		

[a] Nitrostat.

Table II—Transfer of Nitroglycerin from Conventional Tablets to Stabilized Tablets from Open Dishes

	Stored in Same Glass Desiccator under Vacuum for 24 hr.					
	Before Vacuum			After Vacuum		
Tablet	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
Stabilized tablet, 432 mcg. (¹⁄₁₅₀th gr.)[b]	102.8	92.6–109.9	3.3	138.5	127.8–151.6	3.8
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	96.4	71.6–115.8	9.6	73.2	43.0–108.2	25.1
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	104.1	88.6–126.8	9.1	74.1	55.0–101.0	16.1
Stabilized tablet, 432 mcg. (¹⁄₁₅₀th gr.)[b]	104.1	95.9–111.6	3.7	125.7	119.1–135.2	3.7
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	102.5	70.9–115.9	11.0	89.5	40.7–113.7	16.7
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	104.1	88.6–126.8	9.1	75.7	63.4–89.4	8.4
Stabilized tablet, 432 mcg. (¹⁄₁₅₀th gr.)[b]	102.8	92.6–109.9	3.3	111.0	101.4–124.2	4.5
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	102.5	70.9–115.9	11.0	93.9	61.8–113.6	15.1
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	104.1	88.6–126.8	9.1	91.7	72.9–108.7	8.7
Stabilized tablet, 432 mcg. (¹⁄₁₅₀th gr.)[b]	105.3	93.5–114.3	3.7	146.9	130.5–162.4	5.8
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	102.5	70.9–115.9	11.0	83.4	37.8–111.3	23.9
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	104.1	88.6–126.8	9.1	71.2	51.6–94.5	16.9
Stabilized tablet, 0.6 mcg.[b]	103.9	95.0–112.0	4.1	123.3	111.6–132.5	4.8
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	102.5	70.9–115.9	11.0	84.8	48.6–107.6	19.2
Conventional tablet, 432 mcg. (¹⁄₁₅₀th gr.)	104.1	88.6–126.8	9.1	79.1	54.0–106.0	15.8

[a] Label claim. [b] These samples were in the same desiccator.

Biopharmaceutical Equivalence

An experimental model using dogs was developed to compare bioavailability of stabilized and conventional tablets. Six non-anesthetized adult beagle dogs, weighing 12 kg., were used. Tablets were given sublingually, and peripheral pulse pressure was monitored using an on-line computer[6] (9).

Short-Term Experiments—*Exposure to High Vacuum from Open Dishes*—Stabilized and conventional tablets were placed close to each other in open 7.62-cm. (3-in.) watch glasses or 5.3-cm. petri dishes in glass vacuum desiccators and were exposed to pump vacuum for 24 hr. This procedure was repeated three times.

Exposure to High Vacuum in Opened Commercial Containers—The caps and stuffing were removed from stabilized and conventional tablets in their commercial containers, and the bottles were placed as far away from each other as possible in *glass* vacuum desiccators. Vacuum, from a vacuum pump, was continuously

[6] EMR.

applied for 24 hr., after which the vacuum (about 1 torr) was released and 30 tablets from each bottle were assayed. Four separate experiments were run.

Exposure to High Vacuum on Open Dishes in Plastic Desiccator—Two 7.62-cm. (3-in.) petri dishes were placed in a 25.40-cm. (10-in.) plastic desiccator. One dish contained stabilized tablets and the other contained conventional tablets. Pump vacuum (about 1 Torr) was applied for 23 hr., after which the vacuum was disconnected and 30 tablets from each dish were assayed. The experiment was repeated.

Storage in Polystyrene Boxes (Patient-Type Containers) for 1 Month at 37°—One hundred stabilized and conventional tablets were placed in separate polystyrene boxes, 3.81 × 5.71 × 1.58 cm. (1.5 × 2.25 × 0.625 in.), with hinged lids; two sets of boxes were used for each type of tablet. In addition, tablets of each type were stored in closed, regular amber-glass containers as controls. After obtaining an "initial time" assay, all samples were stored at 37°. One box of each set was opened twice a day for 2 min. and the other was kept closed. After 1 month, 30 individual tablets were assayed.

Table III—Effect of Storage of Stabilized Tablets and Conventional Tablets in Open Commercial Containers under Vacuum in Glass Desiccators for 24 hr.

Tablet	Diameter of Desiccator (in.)	Before Vacuum			After Vacuum		
		Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
Stabilized tablet, 432 mcg. (1/150th gr.)[b]	25.40 cm. (10)	102.8	92.6–10?.9	?.3	101.6	?2.2–112.2	5.1
Conventional tablet, 432 mcg. (1/150th gr.)		102.5	70.9–115.9	11.0	95.6	65.6–115.9	13.9
Conventional tablet, 432 mcg. (1/150th gr.)		104.1	88.6–126.8	9.1	96.8	65.5–130.9	16.7
Stabilized tablet, 648 mcg. (1/100th gr.)[b]	20.32 cm. (8)	102.8	?3.3–112.8	5.0	123.4	106.6–138.5	5.7
Conventional tablet, 648 mcg. (1/100th gr.)		100.4	75.1–117.9	11.5	53.1	24.2–82.0	33.9
Stabilized tablet, 648 mcg. (1/100th gr.)[b]	25.40 cm. (10)	102.8	93.3–112.8	5.0	122.0	105.5–137.2	7.1
Conventional tablet, 648 mcg. (1/100th gr.)		100.4	75.1–117.9	11.5	59.6	23.6–109.5	41.3
Stabilized tablet, 0.4 mg.[b]	20.32 cm. (8)	102.8	92.(–109.9	3.3	133.3	114.1–145.1	5.9
Conventional tablet, 648 mcg. (1/100th gr.)		89.6	?2.0–119.6	18.?	21.7	4.1–71.8	85.2

[a] Label claim. [b] These tablets were run simultaneously in the same desiccator.

Table IV—Comparison of Loss of Nitroglycerin from Stabilized Tablets and Conventional Tablets from Open Dishes under Vacuum in 25.40-cm. (10-in.) Plastic Desiccator for 23 hr.

Tablet	Before Vacuum			After Vacuum		
	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
Stabilized tablet, 432 mcg. (1/150th gr.)[b]	102.8	92.6–109.9	3.3	91.5	82.2–99.0	5.0
Conventional tablet, 432 mcg. (1/150th gr.)	104.1	88.6–126.8	9.1	40.3	19.9–58.3	21.1
Stabilized tablet, 432 mcg. (1/150th gr.)[b]	102.8	92.6–109.9	3.3	84.9	76.6–94.3	5.5
Conventional tablet, 432 mcg. (1/150th gr.)	104.1	88.6–126.8	9.1	37.9	27.5–57.6	19.5

[a] Label claim. [b] These dishes were in same vacuum desiccator.

Table V—Comparison of Stabilized Tablets and Conventional Tablets Stored in Polystyrene Boxes at 37°

Sample	Stabilized Tablets, 432 mcg. (1/150th gr.)			Conventional Tablets, 432 mcg. (1/150th gr.)		
	Average As ay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
Glass control						
Initial time	103.2	94.7–111.3	3.3	104.7	9?.5–111.2	3.1
After 1 month	99.9	94.9–107.5	3.1	98.3	80.3–137.0	11.6
Polystyrene "opened" twice a day, after 1 month	93.4	87.2–102.9	3.2	82.6	61.1–103.1	11.0
Polystyrene "closed," after 1 month	92.7	82.6–101.8	5.1	94.4	64.6–119.5	13.1

[a] Label claim.

Storage in Cardboard Boxes (Patient-Type Containers) at 37° for 1 Month—Cardboard boxes are easily available to patients. The box[7] selected measures 6.98 × 8.25 × 0.15 cm. (2.75 × 3.25 × 0.06 in.) and has an inner compartment which is completely covered over by a sliding outer shell in the manner of a safety match box. Since these boxes are not as tight as polystyrene boxes, three sets of boxes, plus a glass bottle control, were used. One box was opened two times

a day for 1 month, another was kept closed, and the third box was sealed with wax. The glass bottle controls for stabilized and conventional tablets served to give the initial time assay for each set. Boxes and bottles, each containing 100 tablets, were stored at 37°. After 1 week and again after 1 month, 30 individual tablets were assayed from each box and the glass bottle.

Effect of Storage with Different Liners, Rayon Stuffing, and Periodic Bottle Opening (Closed Environment)—One lot of stabilized tablets was compared to a lot of conventional tablets. Tablets were

[7] Parke, Davis "Medicated Throat Disc" package.

Table VI—Comparison of Stabilized Tablets and Conventional Tablets Stored in Cardboard Boxes for 1 Month at 37°

	Stabilized Tablets, 432 mcg. ($^1/_{150}$th gr.)			Conventional Tablets, 432 mcg. ($^1/_{150}$th gr.)		
Sample	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
Glass bottle						
Initial	103.2	93.5–111.4	3.6	110.7	99.1–119.8	4.1
After 1 month	101.4	95.1–110.5	3.3	105.7	95.4–119.2	5.6
Box, "open"						
1 week	77.0	59.0–95.1	11.4	70.7	38.5–101.8	26.2
1 month	28.2	24.6–31.7	7.1	5.4	3.6–7.6	16.9
Box, "closed"						
1 week	87.4	72.9–98.2	5.6	62.8	26.6–94.7	26.0
1 month	32.0	20.3–47.4	24.1	5.3	2.7–9.7	30.8
Box, "wax"						
1 week	84.6	64.5–97.2	8.0	82.3	10.5–123.7	27.8
1 month	40.8	28.9–46.5	12.3	7.9	4.5–29.6	68.0

[a] Label claim.

Table VII—Effect of Immediate Environment on Stabilized Tablets and Conventional Tablets at 37°, Opened and Closed Bottles

	Unopened Controls						Opened Bottles[a]					
	With Rayon; % of L.C.[b]			Without Rayon; % of L.C.[b]			With Rayon; % of L.C.[b]			Without Rayon; % of L.C.[b]		
Sample	Average	Range	SD	Average	Range	SD	Average	Range	SD	Average	Range	SD
Conventional tablet, 432 mcg. ($^1/_{150}$th gr.), liner I[c]												
Initial assay	104.7	98.5–111.2	3.2	—	—	—	—	—	—	—	—	—
1 month	100.8	67.9–135.1	15.5	98.8	82.0–119.8	9.7	99.1	83.9–136.4	11.7	102.3	82.2–134.4	12.2
Stabilized tablet, 432 mcg. ($^1/_{150}$th gr.)												
Initial assay	103.2	94.7–111.3	3.4	—	—	—	—	—	—	—	—	—
Liner I[c], 1 month	99.5	87.8–108.4	5.1	98.8	88.5–112.1	4.3	100.3	95.0–108.9	3.1	104.5	96.8–111.5	3.5
Liner II[d], 1 month	102.0	87.5–116.1	6.8	101.7	92.1–109.0	2.9	102.0	94.9–108.5	3.8	104.6	97.6–117.7	4.9
Polyethylene terephthalate[e], 1 month	104.9	92.1–111.1	4.0	103.4	95.7–114.1	4.4	101.4	91.5–108.9	3.9	101.6	93.3–109.3	3.7
Tinfoil, 1 month	103.0	95.0–111.9	4.5	102.1	94.5–112.3	4.4	101.1	90.1–113.5	4.3	100.8	93.8–116.9	4.3

[a] Opened 2 min. a day for a month, weekends excepted, for a total of 21 openings. [b] Label claim. [c] Excelloseal. [d] Esterfoil 50. [e] Mylar.

Table VIII—Comparison of Nitroglycerin Transfer from Stabilized Tablets and Conventional Tablets to Placebo Tablets at 37°[a]

	Tablet Assays, 432 mcg. ($^1/_{150}$th gr.)			Placebo Assays	
Sample and Time Interval	Average Assay, % of L.C.[b]	Range of Assays, % of L.C.[b]	Percent Relative Standard Deviation	Average Assay, % of L.C.[b]	Range of Assays, % of L.C.[b]
Stabilized tablet					
Initial	103.2	94.7–111.3	3.4	—	—
8 days	—	—	—	1.6	—
1 month	99.0	92.3–105.9	3.5	2.0	—
Conventional tablet 1					
Initial	106.0	78.5–129.0	13	—	—
8 days	—	—	—	21.6	—
1 month	86.4	38.0–121.9	16.4	26.6	20.4–35.3
Conventional tablet 2					
Initial	104.7	98.5–111.2	3.2	—	—
8 days	—	—	—	6.6	—
1 month	99.1	83.0–117.0	7.4	8.4	5.6–14.2

[a] These results are not as dramatic as those described earlier (8) using the 648-mcg. ($^1/_{100}$th-gr.) tablet; however, since this was a side-by-side comparison, the results are indicative of the differences in the tablets. [b] Label claim.

placed in amber-glass bottle containers; half of the bottles had a small pledget of rayon stuffing inserted and the other half had no stuffing. One liner[8] was used for the conventional tablets, and several liners[9] were used for the stabilized tablets. After capping, all bottles were stored at 37° for 1 month. Half of the bottles of each type were used as closed bottle controls, while the remaining bottles were opened once a day, except weekends, for 2 min. for a total of 21 openings.

Effect of Storing in Presence of Placebo Tablets (Closed Environment)—This experiment was performed to compare the behavior of two types of tablets when stored with placebos. The tablets used were 432 mcg. ($^1/_{150}$th gr.). Three separate runs were made, two involving conventional tablets and one involving the stabilized tablet. After initial assays were run, 69 nitroglycerin-containing

[8] Excelloseal (Kerr and Owens Illinois).
[9] Excelloseal, tinfoil, Esterfoil, and polyethylene terephthalate (Mylar).

Table IX—Comparison of Retention of Original Potency for Stabilized Tablets and Conventional Tablets Exposed on Open Dishes at Room Temperature

Lot	Time	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Percent of Original Potency Retained
Stabilized tablet 1, 0.4 mg.	Initial	104.4	91.7–112.9	5.7	—
	2 Days	96.7	81.8–107.3	6.8	93
	5 Days	84.6	68.0–101.6	10.5	81
	7 Days	66.1	41.0–88.5	20.0	63
Stabilized tablet 2, 0.4 mg.	Initial	106.4	99.6–112.5	3.1	—
	7 Days	65.1	32.8–85.5	22.3	61
Conventional tablet 1, 432 mcg. (1/150th gr.)	Initial	102.6	84.0–119.5	7.4	—
	3 Days	72.9	37.0–122.2	30.3	71
	5 Days	67.6	30.4–100.8	24.0	66
Conventional tablet 2, 432 mcg. (1/150th gr.)	Initial	96.4	71.6–115.8	9.6	—
	3 Days	68.1	34.7–111.8	27.3	71
	6 Days	45.8	8.1–84.3	44.5	48
Conventional tablet 3, 432 mcg. (1/150th gr.)	Initial	97.4	60.1–110.8	11.4	—
	3 Days	73.9	39.4–100.9	21.4	76
	6 Days	54.5	13.7–83.2	31.2	56
Conventional tablet 4, 648 mcg. (1/100th gr.)	Initial	94.9	61.9–122.2	17.1	—
	3 Days	78.2	43.6–130.6	31.3	82
	5 Days	64.7	35.6–93.9	24.9	68

[a] Label claim.

Table X—Effect of Storage in Open Commercial Containers at Room Temperature in Draft-Free Area

Tablet	Days	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Standard Deviation
Stabilized tablet, 432 mcg. (1/150th gr.)	0	100.5	90.0–107.7	4.5
	22	99.8	90.6–107.3	4.0
Stabilized tablet, 648 mcg. (1/100th gr.)	0	104.4	91.7–112.9	5.9
	26	101.4	91.2–114.4	4.5
	41	101.0	80.5–114.1	6.6
Conventional tablet, 432 mcg. (1/150th gr.)	0	96.4	71.6–115.8	9.3
	28	95.3	65.8–109.8	11.0
Conventional tablet, 432 mcg. (1/150th gr.)	0	97.4	60.1–110.8	11.1
	28	97.9	73.7–113.8	12.0
Conventional tablet, 432 mcg. (1/150th gr.)	0	102.6	84.0–119.5	7.6
	28	98.3	73.1–134.7	12.0
Conventional tablet, 432 mcg. (1/150th gr.)	0	101.3	85.9–122.8	8.0
	28	97.9	78.6–137.4	12.0

[a] Label claim.

tablets were mixed with 30 placebo tablets in amber-glass or high density polyethylene containers and stored at 37° for 1 month. At the end of 8 days, five placebo tablets were removed from the container and assayed. At the end of 1 month, 10 placebos were removed for assay.

Complete Exposure of Tablets to Surrounding Air on Watch Glasses (Open Environment)—Stabilized and conventional tablets were applied to watch glasses, which were stored side-by-side without covering at room temperature for 5–7 days. At given intervals, 30 individual tablets were assayed.

Effect of Storage in Open Commercial Containers (Open Environment)—Stabilized and conventional tablets in bottles of 100 were obtained in-house or commercially; the caps, liners, and stuffing were removed and the containers were stored at room temperature without caps in an area free from drafts. There was a 3–4-cm. distance between the top of the tablets and the lip of the container. At given intervals, 30 tablets from a bottle were assayed; a different bottle was used at each assay period.

Long-Term Stability[10] of Conventional and Stabilized Tablets in Glass Bottles with Polyethylene Terephthalate Liners at 25, 37,

and 45°—Two lots of conventional tablets were packaged exactly as were the stabilized tablets, *i.e.*, amber-glass bottle with rayon stuffing and a polyethylene terephthalate cap liner. These lots were stored under the same conditions as the stabilized tablets to obtain comparable stability data.

RESULTS AND DISCUSSION

Tablet Manufacture and Bioavailability—The stabilized tablet was designed to keep the good physical characteristics of the ordinary sublingual tablet such as ready disintegration, dissolution, and "wickability"[11], while at the same time reduce the intertablet migration of nitroglycerin by volatilization. Easy disintegration and wickability are related to the release rate of nitroglycerin and were desirable in the stabilized tablet (Table I). The stabilized and conventional tablets were required to meet the same specifications for disintegration and wickability. In actual practice, the disintegration time generally falls between 10 and 30 sec.

The average assay for stabilized tablets was 99.7% of label claim, with a range of 92.1–108.1% and a standard deviation of 4.0%;

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[10] Long-term stability studies on stabilized tablets are still in progress on many lots of tablets and include storage at 4°, room temperature, 37°, and 45°.

[11] Defined as the time in seconds required for water to wet the tablet completely by capillary action under controlled conditions.

Table XI—Long-Term Stability of Stabilized Tablets, 432 mcg. ($^1/_{16}$th gr.), at 25, 37, and 45° with 19-hr. Drying Period

	25°			37°			45°		
Months	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD
0	103.7	89.7–113.0	5.6	103.7	89.7–113.0	5.6	103.7	89.7–113.0	5.6
1	103.9	92.9–111.1	4.7	106.0	91.3–113.9	6.1	102.6	92.1–114.5	5.5
2	104.6	95.5–121.9	5.8	103.9	89.8–114.8	6.2	104.6	93.6–116.7	6.4
3	102.0	90.1–115.9	5.5	101.1	88.8–111.7	5.6	102.6	91.4–114.4	5.6
4	99.8	85.8–108.6	5.6	99.5	87.7–112.8	6.9	101.8	87.8–124.1	8.0
5	99.5	88.3–110.4	5.2	—	—	—	101.0	81.4–114.0	7.7
6	98.7	85.2–108.7	6.4	99.9	79.3–106.2	7.1	—	—	—
7	100.6	87.3–111.9	6.8	99.3	82.6–111.6	6.1	93.0	75.7–104.5	6.8
10	99.4	79.5–111.5[b]	6.5	93.6	80.6–104.0	6.3	88.9	76.1–105.7	6.4
13	100.0	87.2–112.5	7.5	92.4	75.8–103.6	5.6	86.2	63.8–100.3	8.9
25	95.6	78.6–108.8	6.8	—	—	—	—	—	—

[a] Label claim. [b] Only one tablet at 79.5; next tablet was assayed at 88.8.

Table XII—Stability Data on Clinical Lots of Stabilized Tablets at 25, 37, and 45°

Stabilized Tablet	Elapsed Time, Months	25°			37°			45°		
		Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD	Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	SD
324 mcg.	0	107.3	98.4–117.4	4.0	107.3	98.4–117.4	4.0	107.3	98.4–117.4	4.0
	1	106.7	97.2–117.0	3.9	103.7	95.0–115.8	4.4	104.3	89.2–119.2	6.6
	2	103.8	94.0–117.6	4.3	102.7	94.5–114.3	4.7	101.9	90.8–117.1	5.1
	3	109.1	93.0–122.6	5.8	98.4	85.6–108.6	4.9	96.6	79.4–105.9	5.8
	4	104.3	94.7–115.3	5.9	99.2	92.6–119.4	5.2	99.0	88.8–110.8	4.9
	5	100.6	91.1–114.1	5.3	99.2	87.7–110.0	4.9	95.9	84.7–111.6	4.9
	6	103.8	92.6–114.7	4.9	—	—	—	—	—	—
	11	101.3	94.0–114.3	4.8	99.7	87.8–110.0	5.1	99.0	89.0–119.4	6.3
	18	102.6	91.6–119.3	6.4	—	—	—	—	—	—
	22	96.7	84.0–110.9	5.3	—	—	—	—	—	—
432 mcg.	0	106.5	101.8–110.5	2.0[b]	106.5	101.8–110.5	2.0	106.5	101.8–110.5	2.0
	1	104.8	91.3–112.3	5.2	108.2	92.4–114.3	6.0	106.1	98.5–121.8	4.9
	2	102.8	95.2–120.5	5.7	101.0	87.2–114.7	5.5	101.5	91.3–112.9	4.9
	3	101.3	88.0–113.5	4.6	100.9	87.5–113.8	5.6	100.6	92.4–110.0	5.1
	4	102.0	94.8–110.3	4.5	100.5	92.3–110.1	3.8	100.6	90.5–118.4	6.7
	5	103.5	92.5–119.0	5.5	98.8	81.0–113.3	6.1	100.2	91.7–111.0	4.9
	6	100.9	90.6–110.4	4.5	—	—	—	—	—	—
	11	104.1	99.2–112.7	3.4	102.0	90.0–122.6	7.3	94.6	74.4–119.3	8.6
	18	104.4	84.2–122.3	7.7	—	—	—	—	—	—
	22	101.1	89.6–115.0	5.7	—	—	—	—	—	—
648 mcg.	0	103.4	96.7–110.2	2.7	103.4	96.7–110.2	2.7	103.4	96.7–110.2	2.7
	1	101.0	88.4–120.8	6.7	98.7	92.1–110.3	4.5	99.3	90.2–117.8	5.3
	2	104.1	92.2–123.3	5.6	102.7	86.0–117.5	6.3	102.2	78.6–126.9	9.8
	3	96.8	89.8–113.7	4.7	—	—	—	—	—	—
	4	97.4	83.7–112.5	6.2	94.6	81.8–111.4	6.6	95.4	79.7–115.2	7.1
	5	95.2	78.0–117.0	7.0	94.2	72.0–107.1	7.6	91.2	78.2–110.6	7.0
	6	97.3	81.0–114.6	5.7	—	—	—	—	—	—
	11	98.8	75.8–113.5	8.1	101.4	88.4–120.1	7.9	86.6	70.1–106.4	8.3
	18	95.1	81.2–114.0	7.5	—	—	—	—	—	—
	22	94.3	77.7–102.9	4.5	—	—	—	—	—	—

[a] Label claim. [b] A lot better than normal; 3–4 is more normal; the jump to 5.2 in 1 month probably indicates this was an exceptional bottle.

when the assays were corrected for the weight of the tablets, the standard deviation of the assays fell to 1.3%. This indicates a satisfactory blending operation and shows that the initial variability in the tablet assays is largely due to tablet weight differences. The latter are more difficult to control in a molded tablet than in a compressed tablet.

The chief virtue of molded sublingual nitroglycerin tablets has been their ability to release nitroglycerin readily. Figure 1 shows a comparison of the bioavailability of nitroglycerin from conventional and stabilized tablets in dogs. The stabilized and conventional tablets were comparable in pharmacological effect; both caused a marked fall in pulse pressure within 3 min. of sublingual administration. There was a partial return to normal over the next 10 min., but lesser effects could be seen for up to 30 min. Although not shown in Fig. 1, it was observed that the pulse pressure returned to pretest levels within 50 min. Human clinical trial followed the dog experiments and confirmed that the stabilized tablet gives the same phar-

macological effect as the conventional tablet.

Effects of High Vacuum—Many different experiments were carried out under pump vacuum for 20–24 hr. at about 1 Torr to compare the behavior of the stabilized and conventional tablets. These experiments involved exposure of the different tablets either in their opened, commercial containers or in uncovered petri dishes. Both glass and plastic vacuum desiccators were used without internal drying agents[12]. In general, these experiments showed that the stabilized tablet is more retentive of its nitroglycerin than is the

[12] No phosphorus pentoxide was used in these desiccators. Two separate experiments, using phosphorus pentoxide in the bottom of glass desiccators, showed that both stabilized and conventional tablets lost large amounts of nitroglycerin. The stabilized tablets retained 70–80% of their original potency, while the conventional tablets retained only 16–30%. Moreover, the loss from the stabilized tablets was in a much more even or controlled manner than from the conventional tablets.

Table XIII—Comparison of Long-Term Stability of Conventional and Stabilized Tablets, 432 mcg. ($^{1}/_{150}$th gr.), at Various Temperatures Using Glass Bottles and Polyethylene Terephthalate Cap Liners

Temperature	Elapsed Time, Months	Conventional Tablets Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation	Conventional Tablets Average Assay, % of L.C.[a]	Range of Assay, % of L.C.[a]	Percent Relative Standard Deviation	Stabilized Tablets Average Assay, % of L.C.[a]	Range of Assays, % of L.C.[a]	Percent Relative Standard Deviation
25°	0	103.8	94.9–113.5	3.9	104.7	98.5–111.2	3.1	103.7	89.7–113.0	5.4
	1	102.0	76.6–122.1	12.7	103.3	64.7–129.8	14.1	103.9	92.9–111.1	4.5
	2	102.1	84.9–131.2	10.6	102.2	83.7–119.6	7.9	104.6	95.5–121.9	5.5
	3	100.3	74.5–120.7	12.4	102.9	84.9–121.0	9.4	102.0	90.1–115.9	5.4
	4	101.2	79.5–128.6	12.6	99.9	80.5–131.0	11.7	99.8	85.8–108.6	5.6
	5	101.4	85.9–123.2	10.7	103.1	79.2–127.9	10.7	99.5	88.3–110.4	5.2
	6	101.1	81.6–127.0	12.5	104.9	79.7–132.7	14.3	98.7	85.2–108.7	6.5
	7	—	—	—	—	—	—	100.6	87.3–111.9	6.8
	10	—	—	—	—	—	—	99.4	79.5–111.5[b]	6.5
	13	—	—	—	—	—	—	100.0	87.2–112.5	7.5
37°	0	103.8	94.9–113.5	3.9	104.7	98.5–111.2	3.1	103.7	89.7–113.0	5.4
	1	107.6	72.0–147.2	15.6	101.8	69.5–143.3	17.4	106.0	91.3–113.9	5.8
	2	100.0	73.1–130.7	12.9	101.8	86.1–117.0	8.3	103.9	89.8–114.8	6.0
	3	99.8	76.7–137.6	13.9	103.7	86.7–113.5	7.2	101.1	88.8–111.7	5.5
	4	96.4	76.2–127.6	10.0	99.9	73.5–124.7	12.9	99.5	87.7–112.8	6.9
	5	100.1	76.5–142.4	16.7	104.6	73.8–137.1	16.4	—	—	—
	6	—	—	—	—	—	—	99.9	79.3–106.2	7.1
	7	—	—	—	—	—	—	99.3	82.6–111.6	6.1
	10	—	—	—	—	—	—	93.6	80.6–104.0	6.3
	13	—	—	—	—	—	—	92.4	75.8–103.6	5.6
45°	0	103.8	74.9–113.5	3.9	104.7	98.5–111.2	3.1	103.7	89.7–113.0	5.4
	1	102.3	71.8–142.9	13.9	101.6	74.6–124.3	12.7	102.6	92.1–114.5	5.4
	2	97.2	77.5–116.1	10.7	101.8	86.1–117.0	8.3	104.6	93.6–116.7	6.1
	3	100.4	76.5–119.4	11.7	97.7	73.7–140.9	12.4	102.6	91.4–114.4	5.5
	4	97.3	69.1–120.4	10.4	96.1	62.7–113.9	13.7	101.8	87.8–124.1	7.9
	5	98.2	79.0–133.1	10.9	99.7	78.7–119.6	10.0	101.0	81.4–114.0	7.6
	6	—	—	—	—	—	—	92.1	79.0–111.9	8.9
	7	—	—	—	—	—	—	93.0	75.7–104.5	7.3
	10	—	—	—	—	—	—	88.9	76.1–105.7	7.2
	13	—	—	—	—	—	—	86.2	63.8–100.3	8.9

[a] Label claim. [b] Only one tablet at 79.5; next tablet was assayed at 88.8.

conventional tablet and that plastic desiccators cause a much greater loss of nitroglycerin than do glass desiccators.

The most interesting results, however, were obtained when stabilized and conventional tablets were placed in the same glass vacuum desiccator and then exposed to vacuum. The results always showed a substantial transfer of nitroglycerin from the conventional tablets to the stabilized tablets when the vacuum exposure was from open petri dishes (Table II). The results were slightly more variable in the case of the commercial containers. In one experiment, both the stabilized and conventional tablets showed a small net loss of nitroglycerin; in three other experiments there was a large transfer of nitroglycerin from the conventional to the stabilized tablets (Table III). These observations further substantiate the fact that nitroglycerin can and does migrate; they also demonstrate the high affinity of fixative for nitroglycerin. In practice, this is demonstrated by the better stability profile shown by stabilized tablets. The stabilized tablets absorbed the nitroglycerin in a controlled manner (Tables II and III); that is, there was little change in the percent relative standard deviation of the tablets after the absorption of nitroglycerin. The conventional tablets, by contrast, lost nitroglycerin very irregularly.

The experiment using plastic desiccators was prompted by an article (6) reporting FDA removal of plastic pen containers from the market because of the very high loss of nitroglycerin from these containers. The losses described were so severe, i.e., 50% in 1 day, 80% in 3 days, and 93% in 30 days, as to be unexplainable on the basis of volatilization alone. It appeared that some active transport had to be involved. Observations in Table IV are in keeping with the results observed by the FDA. The results showed severe losses of nitroglycerin from the conventional tablets and much smaller losses of nitroglycerin from the stabilized tablets. These losses were far greater than those experienced in glass desiccators. Although the stabilized tablet lost nitroglycerin, it did so in a well-regulated

manner as opposed to the large, irregular loss shown by the conventional tablets.

Effects of Patient-Type Container Storage—To duplicate actual patient use, nitroglycerin tablets were stored in hinged polystyrene and cardboard boxes (Tables V and VI). Table V indicates the sharp difference in behavior between the stabilized and conventional tablets stored in the hinged polystyrene boxes. Stabilized tablets lose considerably less potency from the open box; moreover, the potency loss occurred with much less spreading in the range of assays, i.e., the content uniformity was maintained. The unopened glass bottle controls illustrate a point made previously; i.e., there is considerable spreading in the range of assays for conventional tablets stored even in closed bottles (8).

Table V shows that cardboard boxes are extremely poor containers for nitroglycerin tablets. Nevertheless, the data point out that stabilized tablets lose less of their original potency than conventional tablets in the same period. The conventional tablets retained only 5–8% of their original potency, whereas the stabilized tablets retained 28–41%.

Effects of Immediate Closed Environment—The first paper of this series (8) reported that conventional nitroglycerin tablets were affected by their immediate environment and that they behaved differently in the presence of different cap liners[13].

Two experiments were performed to illustrate that stabilized tablets are more independent of their immediate closed environment than are conventional tablets. To some extent, this was al-

[13] Excelloseal retained the average potency but was unsuitable for maintenance of content uniformity. Polyethylene terephthalate (Mylar), tinfoil, fluorohalocarbon film (Aclar), and Esterfoil (supplied by Owens Illinois) liners were better than Excelloseal for conventional nitroglycerin tablets, but even they did not hold much promise for long-term maintenance of content uniformity.
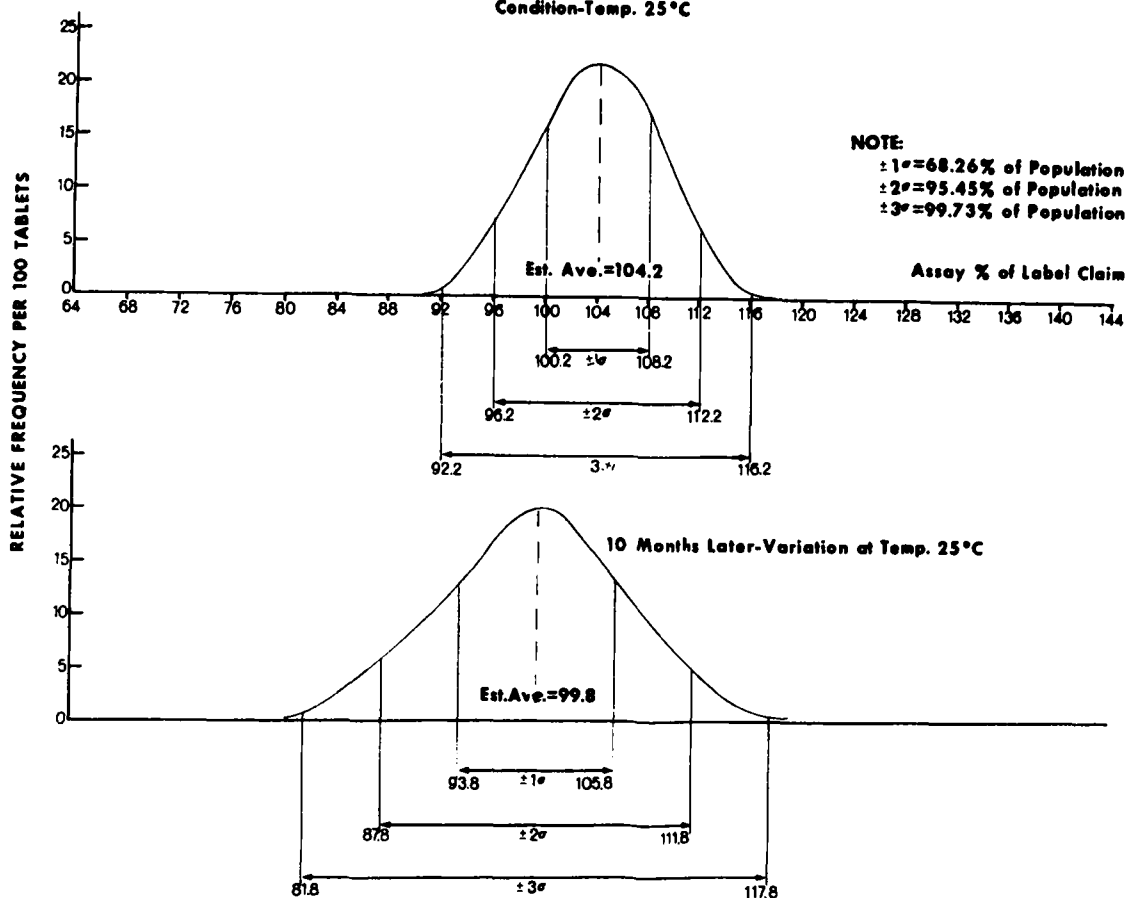
Figure 2—*Distribution curves for stabilized sublingual nitroglycerin tablets at the time of manufacture and after being packaged for 10 months.*

ready demonstrated by the polystyrene and cardboard box experiments. The two experiments were carried out in screw-capped glass bottles, which are a much preferred container to hinged polystyrene boxes. The results (Table VII) show that stabilized tablets, in contrast to conventional tablets, are little affected by their immediate container and/or the presence of rayon stuffing material, as shown by the values for average potency and standard deviation. Furthermore, daily bottle openings had little to no effect on the stabilized tablets; the latter fact is considerably important to a patient.

Table VIII shows the effect of storing stabilized and conventional tablets in the presence of placebo tablets. This experiment used different nitroglycerin-containing tablets and compressed lactose placebo tablets than were used previously (8). The results show that the stabilized tablet is more retentive of its nitroglycerin than is the conventional tablet; consequently, it maintains its content uniformity better than the conventional tablet. Recently, this same effect was also demonstrated by Shangraw and Contractor (7).

Effects of Immediate Open Environment—Two experiments were done to check the effects of an immediate open environment (Tables IX and X). Both types of tablets lost substantial amounts of nitroglycerin from open dishes (Table IX), but the stabilized tablets lost activity more slowly than the conventional tablets. After 5 days, the stabilized tablet lost the same amount or less nitroglycerin than the conventional tablets lost in 3 days. These results are, in essence, an extension of similar results obtained using cardboard boxes for storage. In the latter case, the boxes offered some protection so that the rate of loss was slower, but the results parallel each other.

The results using open commercial bottles stored in a draft-free area are in marked contrast to the results obtained on open dishes exposed to room temperature air. Very little potency was lost from either type of tablet under these circumstances. This is probably due to two factors:

1. The 3–4-cm. "dead space" above the tablets which acts as insulation from the surrounding air. In essence, the tablets are surrounded by a relatively quiescent, stagnant atmosphere instead of being swept by air currents.

2. The small surface area exposed from commercial containers compared to the larger area exposed from dishes.

Long-Term Stability—Long-term stability studies on stabilized tablets are still in progress, but some of the long-term data are summarized in Tables XI and XII. The stabilized tablets maintain both average potency and content uniformity even at 37 and 45°, thus assuring a more uniform and predictable dose to the patient.

Table XIII shows a comparison of the stability of both conventional and stabilized tablets when both types of tablets were stored under identical conditions using the same bottle and liner used for stabilized tablets. The conventional tablets develop marked inter-tablet dose variation within 1 month, whereas the stabilized tablets maintain their content uniformity at all temperatures tested. The stability exhibited by the stabilized tablets is a marked improvement over the stability shown by conventional sublingual nitroglycerin tablets.

Figures 2–4 give a graphical summary of the stability profiles of both stabilized and conventional tablets at room temperature. These figures show that the stabilized tablets maintain their content uniformity (Fig. 2) while the conventional tablets develop considerable intertablet dose variation (Figs. 3 and 4).

Disintegration times and wickability were also monitored during all stability studies. Although not shown in any of the tables, the values obtained were within the specification limits shown in Table I.

SUMMARY

A new, molded, stabilized, sublingual nitroglycerin tablet was prepared. This tablet shows the same bioavailability as conventional

CONVENTIONAL TABLET — S.T. 86 1/150gr. (1 Lot)

Initial Assay Variation (Estimated)
Temp. 25°C

NOTE:
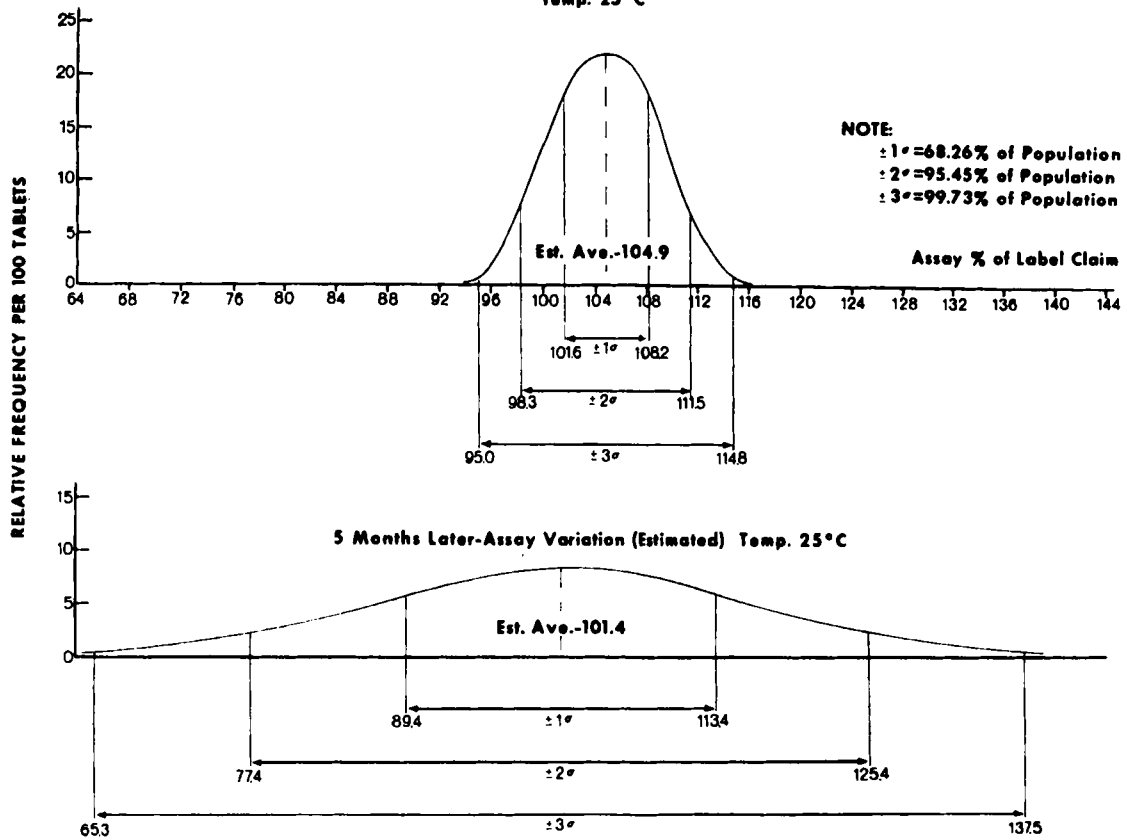±1σ =68.26% of Population
±2σ =95.45% of Population
±3σ =99.73% of Population

Assay % of Label Claim

Est. Ave.-104.9

101.6   ±1σ   108.2

98.3   ±2σ   111.5

95.0   ±3σ   114.8

5 Months Later-Assay Variation (Estimated)   Temp. 25°C

Est. Ave.-101.4

89.4   ±1σ   113.4

77.4   ±2σ   125.4

65.3   ±3σ   137.5

Figure 3—Distribution curves for conventional sublingual tablets at the time of manufacture and after being packaged for 5 months.

CONVENTIONAL TABLET — 1/150gr. (1 Lot)

Approx. Mfg. Period May 1971
Listed Exp. Date 6/1/76
Estimated Assay Variation
Dates of Assay 9/30/71 to 1/12/72
Temp. 25°C

NOTE:
± 1σ =68.26% of Population
±2σ=95.45% of Population
± 3σ =99.73% of Population

Assay % of Label Claim

Est. Ave. - 98.2

87.3   ±1σ   109.1

76.4   ±2σ   119.9

65.5   ±3   130.9
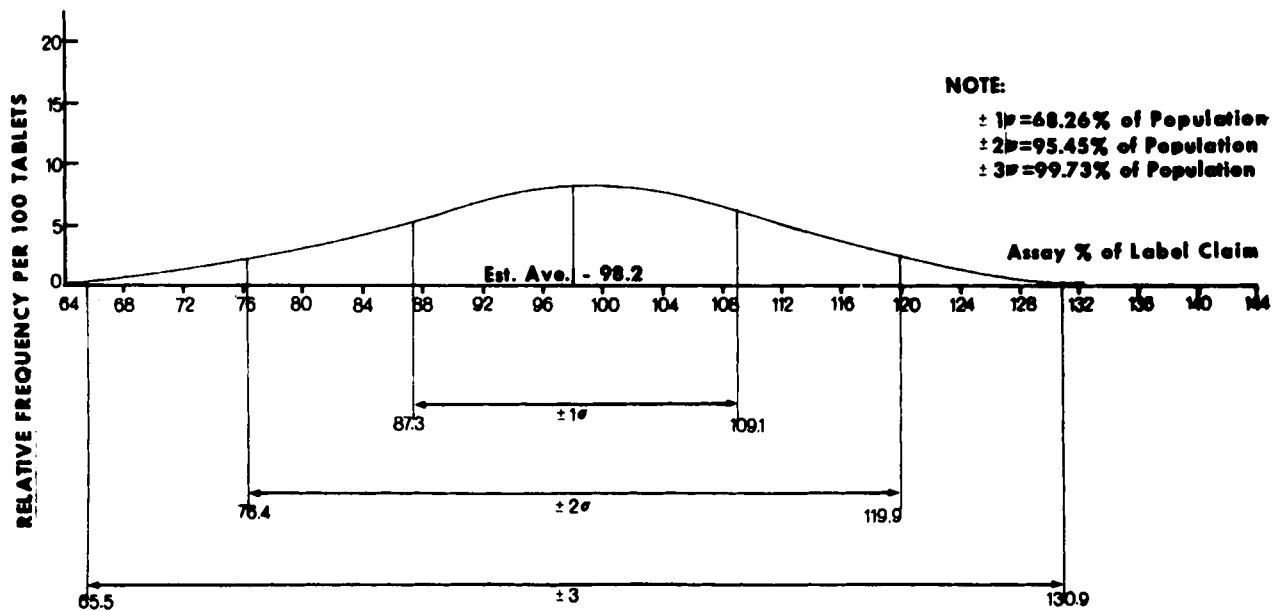
Figure 4—Distribution curve for conventional sublingual nitroglycerin tablets after being packaged for about 7 months.

tablets but has the advantage of markedly improved stability. In contrast to conventional tablets, which often develop marked intertablet dose variation within 1 month, the stabilized tablet maintains its content uniformity for long periods, even at 37 and 45°, thus assuring a more uniform and predictable dose to the patient.

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NOTES

Synthesis of Analogs Related to Pilocarpine

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Abstract ☐ Pilocarpine analogs with modification of the lactone ring were synthesized, and preliminary pharmacological evaluations indicate that several of the synthesized compounds possess interesting cholinergic activity.

Keyphrases ☐ Pilocarpine analogs—synthesized and screened for cholinergic activity ☐ Cholinergic activity—pilocarpine analogs with modified lactone rings synthesized and screened ☐ Structure–activity relationships—pilocarpine analogs synthesized and screened

Several naturally occurring alkaloids, *e.g.*, pilocarpine and muscarine, have been shown to possess potent cholinergic activity. This activity has been associated with the direct action of these substances on cholinergic receptors at synaptic junctions in target organs.

The nature of the cholinergic receptor is still not well understood. Presumably, acetylcholine must geometrically orient itself in such a manner that it binds to the receptor group at two points—the cationic and esteratic sites. Waser (1) postulated that the attachment of muscarinic agents to cholinergic receptors in smooth muscle involved two oxygen atoms and a quaternary nitrogen, having an optimum distance of approximately 4 Å separating the quaternary nitrogen from the ether or carbonyl oxygen. Jones (2) proposed that pilocarpine could assume a conformation similar to that of the active group postulated for the muscarinic receptor in ganglia.

A review of the literature indicates that structural requirements for cholinergic activity in pilocarpine analogs have not been studied adequately. It has been reported that an intact lactone ring is essential for activity. Moreover, the C-2 ethyl substitution on the lactone ring also has been reported as necessary for activity. Demethylation of pilocarpine on the imidazole moiety (pilocarpidine) showed reduced physiological activity (3). Brochmann-Hanssen *et al.* (4) found that various amine analogs, substituted for the imidazole moiety of pilocarpine, produced compounds with reduced activity. Quaternization of the imidazole ring giving the methyl iodides of both pilocarpine and isopilocarpine were synthesized (5) but their biological activity has not been reported. Ben Bassat *et al.* (6) presented data indicating that quaternization of pilocarpine derivatives on the imidazole moiety with a benzyl group possessed anticholinergic activity. This activity was augmented by the addition of *para*-substituents such as bromo, chloro, and methyl groups.

It appears that compounds possessing parasympathomimetic activity must contain a cationic site in the form of either a protonated tertiary or quaternary nitrogen separated from a region of high electron density approximately 4 Å away. Whether this site of high electron density in pilocarpine analogs is located about the carbonyl oxygen or the ether oxygen has not been determined. It appeared that minor alterations in the