Nitroglycerin Sublingual Tablets I: Stability of Conventional Tablets

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Abstract □ Nitroglycerin in molded sublingual tablets volatilizes and undergoes intertablet migration. Consequently, tablets that are uniform when manufactured develop enough intertablet dose variation that they frequently fail the USP XVIII content uniformity test. Factors influencing volatilization and migration are discussed.

Keyphrases □ Nitroglycerin tablets—stability, volatilization, and intertablet migration □ Tablets, nitroglycerin—stability, volatilization, and intertablet migration □ Content uniformity, nitroglycerin tablets—volatilization and intertablet migration

In recent years, a growing body of evidence has accumulated which shows that conventional nitroglycerin tablets lose potency if stored improperly (1–5). A little-known fact is that the stability of nitroglycerin tablets is complicated by the development of intertablet dose variation caused by the volatilization and subsequent intertablet migration of nitroglycerin[1]. Tablets that are uniform when manufactured develop increased individual tablet variation upon storage, even when little potency loss is observed and even if the tablets are refrigerated. This seeming anomaly was observed in this laboratory, and supporting data are given here.

Banes (2) reported an almost total loss of nitroglycerin from tablets stored in blister packs; most of this nitroglycerin was recovered from the adhesive used to cement the blister pack laminate together. Earlier, at least one manufacturer[2] found that nitroglycerin tablets, dried on brown Kraft paper, transferred substantial amounts of nitroglycerin to the paper. The present author found that stuffing materials in contact with nitroglycerin tablets readily absorb varying amounts of nitroglycerin from the tablets.

Bell (6) examined 55 lots of nitroglycerin tablets from four different manufacturers. Ten individual tablets were assayed per lot. His results showed that 101 of the 550 tablets assayed fell outside of the USP XVI limits of 80–112%. Although Bell made no mention of instability, it is now clear that his data reinforce the finding in this article.

The observation that nitroglycerin readily migrates through the bottle space into cotton stuffing offered a possible explanation for the instability of sublingual nitroglycerin tablets. Consequently, this study was undertaken to define the nature of the problems associated with the instability of nitroglycerin tablets. This information would be fundamental to the development of methods for stabilizing the tablets through either modification of the immediate container or reformulation.

[1] During the remainder of this article, the term stability will encompass both potency loss and lack of content uniformity.

[2] Personal communication, Warner-Chilcott Laboratories.

Table I—Assay of Placebos and Tablets[a] in Contact with Each Other at 25° for 1 Month

	Average Assay in Percent —of Label Claim— Placebos	Tablets
Placebos mixed with nitroglycerin tablets	93.3	34.7
Placebos above nitroglycerin tablets	12.4	91.1
Placebos below nitroglycerin tablets	29.1	90.1

[a] 600 mcg. (1/100 gr.).

EXPERIMENTAL

Assay Procedure—The assay procedure was an automated adaptation of the method of Bell (6). Previous experience showed that this method is stability indicating[3]. Tablets (0.3 mg.) were dissolved in 10 ml. of water in a glass-stoppered 50-ml. centrifuge tube; 0.4- and 0.6-mg. tablets required 15 and 20 ml. of water, respectively. The tubes were shaken vigorously initially and after two 5-min. intervals to ensure solution of the nitroglycerin. After solution was accomplished, the samples were placed in sample cups for the Sampler II using an Auto Analyzer[4] set at a rate of 30 samples/hr. At least 30 individual tablets were assayed per lot of product. Standards preceded and followed every 10 samples to allow close monitoring of the assay procedure. Calculations for each set of assays included the average, the range, and the standard deviation in order to facilitate comparisons among lots. The standard deviation was calculated, although normal distributions were probably not obtained due to large, irregular losses of nitroglycerin from the tablets. However, it serves as a convenient method for comparison.

Transfer of Nitroglycerin from Sublingual Tablets to Placebo Tablets—Placebo tablets were prepared using a rotary press[5]. The physical specifications for these tablets were as follows: 55–60-mg. weight, 0.48-cm. (0.19-in.) diameter, 0.29-cm. (0.115-in.) thickness, flat-faced, and beveled-edge punches. These tablets were purposely made larger than commercial nitroglycerin tablets to permit ease of sorting for assay purposes.

Three separate experiments were performed to evaluate if drug migration would occur, and whether the position of the placebo relative to the nitroglycerin tablets in the container had any effect.

In each experiment, 25 placebo tablets and 50 600-mcg. (1/100-gr.) nitroglycerin tablets were placed in normal commercial bottles[6] and allowed to stand at room temperature for 1 month. Four bottles were set up for each experiment. The results, which were obtained by one analyst and confirmed independently by another on a separate set of bottles, are shown in Table I.

Comparison of Content Uniformity at Time of Release and after Aging—All samples checked were in commercial bottles containing 100 tablets, and all had been stored at ambient room temperature. Sixty lots of tablets of various ages and dosage sizes were assayed. Fifty-six of these lots had already been marketed and four were new lots pending release. Comparisons of the "release" assays and aged assays are given in Tables II–IV.

Content Uniformity of Freshly Manufactured Lots—Four lots of newly manufactured 400-mcg. (1/150-gr.) tablets were assayed to

[3] To be submitted for publication.

[4] Technicon.

[5] Stokes B-2.

[6] Six-milliliter, round, amber bottle with screw cap containing an Excelloseal liner.

Table II—Comparison of "Release" and "Aged" Assays of Nitroglycerin Tablets [600 mcg. (1/100 gr.)] with Ambient Room Temperature Storage

Average Assay at Time of Manufacture	Range of Assay	σ[a]	Elapsed Time for "Aged" Assay, Months	Average Assay of 30 "Aged" Tablets	Range	σ
			Passes[b]			
101.8 (10)	93.3–109.0	4.5	14	95.0	75.5–122.1	9.8
101.1 (10)	96.6–109.2	3.5	14	100.3	78.5–116.1	11.0
102.4 (20)	96.7–109.3	3.8	13	98.2	77.0–121.1	13.4
103.1 (20)	89.4–115.0	5.1	12	97.9	83.2–123.9	8.7
111.4 (10)	101.1–116.8	4.2	11	96.3	84.1–114.9	6.7
106.1 (10)	98.3–111.9	3.9	8	98.0	78.7–120.3	9.0
103.6 (10)	96.6–109.8	3.6	8	95.0	81.1–116.6	8.4
105.0 (10)	98.9–112.7	4.9	7	96.0	81.7–113.8	9.3
98.0 (10)	90.2–111.0	5.9	6	98.0	77.7–117.5	11.3
104.1 (10)	96.1–112.2	4.9	6	98.1	78.9–121.0	9.9
93.5 (10)	90.7–101.2	3.0	5	94.2	78.0–110.5	8.3
96.2 (10)	91.7–102.4	3.5	5	99.8	79.5–115.6	10.0
			Fails[b]			
100.6 (10)	92.2–106.3	3.6	10	87.3	66.6–106.7	8.9
104.9 (10)	101.6–110.0	2.4	7	94.2	72.7–110.4	8.5

[a] Standard deviation. [b] Refers to passing or failing the content uniformity test in USP XVIII prior to the allowance of one "flyer" in 30 tablets.

Table III—Comparison of "Release" and "Aged" Assays of Nitroglycerin Tablets [400 mcg. (1/150 gr.)] with Ambient Room Temperature Storage

Average Assay at Time of Manufacture	Range of Assay	σ	Elapsed Time for "Aged" Assay, Months	Average Assay of 30 "Aged" Tablets	Range	σ
			Passes			
108.4 (40)	95.4–126.5	6.3	11	99.6	88.8–117.6	7.4
106.8 (10)	99.9–113.1	4.8	10	96.1	81.0–116.1	8.6
101.7 (10)	94.2–112.1	5.5	10	96.2	87.0–111.7	6.0
105.9 (10)	100.2–114.0	5.0	8	103.9	83.7–122.8	7.5
100.1 (10)	94.6–107.9	3.9	8	101.2	75.6–130.0	10.5
101.9 (10)	95.7–106.5	3.5	8	96.4	86.5–107.1	5.8
109.0 (10)	102.3–114.9	4.3	7	95.8	78.3–115.2	9.3
93.8 (10)	83.8–104.6	7.8	7	99.5	84.9–115.6	7.4
99.0 (10)	78.6–110.1	8.5	7	97.3	84.3–107.7	5.6
107.0 (10)	90.9–108.0	6.2	5	99.1	82.8–115.5	9.3
102.3	96.5–113.0	4.7	3	102.1	88.7–119.1	8.5
103.1 (10)	99.3–109.4	3.5	2	103.9	83.7–135.2	10.3
104.4 (10)	99.5–108.8	3.6	2	98.6	75.9–131.7	15.6
105.4 (10)	97.4–110.5	3.8	1	102.0	82.5–120.6	9.5
103.9 (10)	95.5–111.2	5.2	1	102.0	76.2–129.2	10.7
101.4 (10)	95.1–107.8	4.1	1	98.2	80.9–120.6	9.0
98.9 (30)	87.2–109.8	5.3				
103.6 (30)	93.7–114.8	4.9				
102.8 (30)	95.5–111.1	4.0				
102.7 (30)	92.2–112.7	4.6				
			Fails			
95.9 (10)	90.3–110.8	6.6	11	97.3	72.5–124.7	9.7
105.3 (10)	99.3–109.6	4.2	8	101.1	74.3–120.4	10.7
108.9 (40)	99.5–116.9	4.5	7	102.0	72.2–121.9	13.5
104.7 (10)	96.1–108.2	3.8	7	100.1	69.0–123.8	11.5
105.4 (10)	98.6–111.9	3.6	5	95.0	53.1–121.4	13.9
105.4 (10)	100.1–109.5	3.3	5	96.6	71.4–119.3	13.5
102.8 (10)	97.9–112.8	4.4	5	91.6	65.9–113.9	11.2
102.9 (20)	96.5–113.0	3.8	4	95.3	68.7–131.9	16.6
103.1 (10)	96.7–107.1	3.4	3	99.5	62.5–131.0	15.0
103.8 (10)	103.7–109.8	3.8	3	97.7	59.4–135.3	15.8
99.3 (10)	90.3–109.5	4.9	2	92.1	66.3–115.2	11.7
101.7 (10)	98.2–104.8	2.4	1	101.9	72.3–113.6	11.2

show the manufacturing process capability and to establish a baseline for additional experimental work. The results are shown in Table V.

Effect of Room Temperature Storage for 1 Month with and without Rayon Stuffing and Wax Seals—The four new lots of nitroglycerin tablets described above were placed in containers for this experiment while the assays described in Table V were being performed. Tablets were put into 120 commercial bottles[6]. Sixty of the bottles were "stuffed" with rayon and the other half were not. After storage for 1 month at room temperature, 30 tablets from each set were reassayed (Table VI).

Effect of Stuffing and Cap Liners at 37 and 45° for 1 Month—Tablets from Lot 345906 (Table V) were placed in amber glass bottles with screw caps. Seven different cap liners were used, both with and without a wax seal and without stuffing. Rayon, tissue, or cotton stuffing was used with each of the different cap liners in bottles without wax seals. The 136 bottles were stored at 37 and 45° for 1 month. At the end of this time, a bottle of each type was removed from storage and 30 tablets from each bottle were assayed individually (Table VII).

Comparison of Storage at Room and Refrigerator Temperatures—

Table IV—Comparison of "Release" and "Aged" Assays of Nitroglycerin Tablets [300 mcg. (1/200 gr.)] with Ambient Room Temperature Storage

Average Assay at Time of Manufacture	Range of Assay	σ	Elapsed Time for "Aged" Assay, Months	Average Assay of 30 "Aged" Tablets	Range	σ
			Passes			
100.7 (10)	92.0–105.1	5.0	9	93.3	77.6–108.6	6.6
105.9 (10)	98.5–113.8	5.1	8	94.2	77.7–129.2	11.4
102.8 (10)	97.3–111.7	5.0	7	95.6	76.9–112.2	8.3
103.1 (10)	98.5–108.8	4.7	7	94.7	81.8–120.1	11.1
104.5 (10)	100.6–109.4	2.4	7	99.4	79.9–128.4	12.5
106.3 (10)	102.5–112.0	3.2	4	104.1	80.2–128.2	13.0
102.6 (10)	96.4–107.7	3.8	3	95.3	84.9–104.9	6.3
			Fails			
100.9 (20)	89.1–111.2	6.2	11	75.2	39.6–91.0	11.8
93.8 (20)	83.3–102.5	3.6	10	88.5	71.3–105.3	8.1
103.6 (10)	94.1–113.0	6.4	7	102.1	63.5–132.9	13.6
101.9 (10)	98.5–105.8	3.2	7	95.3	67.4–121.8	13.8
103.8 (10)	100.8–108.4	2.3	4	88.3	69.2–125.0	14.3
104.8 (10)	97.7–110.8	4.1	4	95.5	63.3–152.6	17.0
98.0 (10)	78.6–105.2	8.2	4	89.4	56.6–131.8	18.7

Table V—Assay of Freshly Manufactured Nitroglycerin Tablets [400 mcg. (1/150 gr.)]

Lot Number	Assay in Percent of Label Claim: Average of 30 Tablets	Range of Assays	Standard Deviation
345903	98.9	87.2–109.8	5.3
345904	103.6	93.7–114.8	4.9
345905	102.8	95.5–111.1	4.0
345906	102.7	92.2–112.7	4.6

Tablets in commercial packages were stored at 4, 25, 37, and 45° and at 37° and 85% relative humidity. Data accumulated for 600-, 400-, and 300-mcg. (1/100-, 1/150-, and 1/200-gr.) tablets at 4 and 25° (room temperature) are given in Table VIII for comparison.

Stability of Nitroglycerin Tablets [400 mcg. (1/150 gr.)] at 25, 37, and 45° at Monthly Intervals—After preliminary experiments showed that polyethylene terephthalate[7] was a better cap liner than Excelloseal for nitroglycerin tablets, two lots of tablets were placed in commercial bottles with screw caps containing polyethylene terephthalate[7] liners. Initial assay values were obtained and the bottles were then stored at 25, 37, and 45°. At monthly intervals, one bottle of each lot stored under each of the three conditions was removed and 30 tablets were assayed (Table IX).

RESULTS AND DISCUSSION

Until recently, analytical techniques did not lend themselves to large numbers of individual tablet assays of low drug dosage forms. This situation improved dramatically with Bell's (6) publication of an individual tablet assay and the advent of automated analytical methodology. A combination of these two techniques has enabled the present author to assay many individual tablets, both rapidly and accurately, thus avoiding the "leveling" effect obtained from composite assays. As a result, greater insight was gained concerning the causes of the instability of nitroglycerin tablets. The tremendous amount of work involved in both stability and formulation studies on nitroglycerin tablets would have been physically impossible without the use of an automated analytical system.

The results shown in Table I clearly demonstrate that nitroglycerin can and does migrate from tablet to tablet. The migration occurs because of the inherent volatility of nitroglycerin[8] and must occur through the vapor phase. This migration is mediated by the stresses applied to the tablet by its immediate environment. Placebos that were physically intermixed with the nitroglycerin tablets received the most transfer of nitroglycerin, while those striated either above or below the nitroglycerin tablets received the least (Table I and Figs. 1 and 2). Many of the placebos that were intermixed with the nitroglycerin tablets contained more nitroglycerin than a tablet containing 100% of the label claim; this is explained on the basis that there were one-half as many placebos as nitroglycerin tablets and that the placebos were approximately twice the size of the nitroglycerin tablets.

The fact that the placebos intermixed with the nitroglycerin tablets received the most nitroglycerin by migration indicates that soon after volatilization the nitroglycerin must be absorbed by some nearby receptor surface. If this were not so, it would be expected that all of the placebo tablets, regardless of position in the bottle, would reach the same nitroglycerin content. The fact that the placebos both above and below the nitroglycerin tablets received less nitroglycerin than the placebos intermixed with the nitroglycerin tablets is indicative of the small amount of travel that occurs once the nitroglycerin volatilizes. In some respects, this is analogous to the process of molecular distillation.

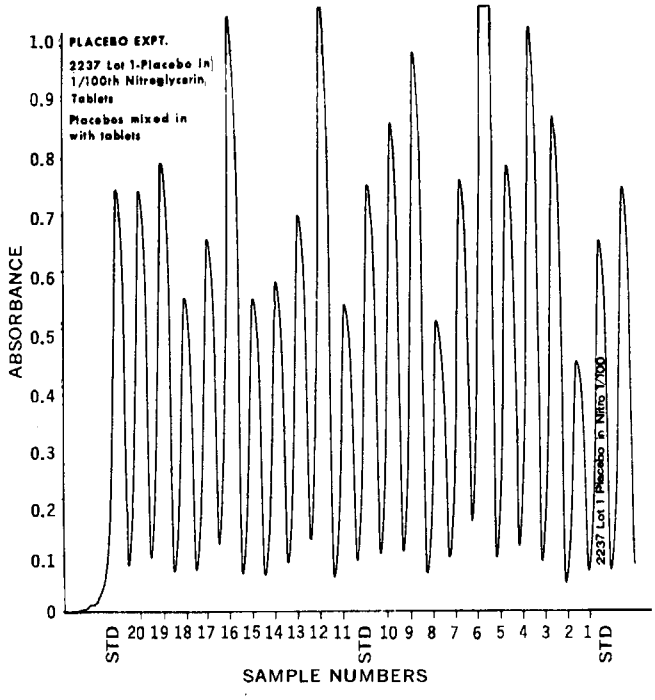

Figure 1—*Curves from automated analysis of placebo tablets intermixed with 600-mcg. (1/100-gr.) nitroglycerin tablets.*

[7] Mylar.
[8] The vapor pressure of nitroglycerin is 0.00026 mm. Hg at 20° (Merck Index).

Table VI—Nitroglycerin Tablets [400 mcg. (1/150 gr.)] with Room Temperature Storage for 1 Month in Commercial Bottles with Excelloseal Liner

Lot Number	Description	Average Assay of 30 Tablets	Range	Standard Deviation	Stuffing Tablet Equivalent
345903	No wax, no rayon	91.0	65.6–115.7	13.0	—
345903	No wax, with rayon[a]	100.6	75.2–126.5	12.2	0.36
345903	With wax, no rayon	91.6	61.4–123.3	16.2	—
345903	With wax, with rayon	96.3	76.9–111.3	9.5	0.22
345904	No wax, no rayon	97.5	67.6–129.4	15.3	—
345904	No wax, with rayon	94.9	69.5–127.3	12.8	0.73
345904	With wax, no rayon	98.2	85.6–118.1	9.3	—
345904	With wax, with rayon	99.2	83.1–120.5	10.9	0.70
345905	No wax, no rayon	94.8	52.5–133.1	19.9	—
345905	No wax, with rayon	96.9	62.2–115.6	13.9	0.76
345905	With wax, no rayon	97.4	64.3–123.2	14.5	—
345905	With wax, with rayon	96.3	61.5–123.9	13.3	0.95
345906	No wax, no rayon	95.3	61.1–124.9	16.4	—
345906	No wax, with rayon	99.7	65.8–138.1	16.6	0.56
345906	With wax, no rayon	97.4	73.8–120.1	11.4	—
345906	With wax, with rayon	97.5	75.8–118.9	10.1	0.55

[a] This is the normal commercial package for the conventional tablets.

It could appear that migration occurred only because of the high concentration gradient that existed between the nitroglycerin and placebo tablets, and that migration would not occur if all tablets in a bottle contained nitroglycerin. However, the evidence presented in Tables II–IV on 60 lots of nitroglycerin tablets demonstrates that the latter premise is untenable. The data show that all lots passed the content uniformity test easily when they were first manufactured, but that the assay range spread considerably as these lots aged. It may be argued that when the lots were first assayed, only 10 tablets were assayed instead of 30, thus lessening the chances of noticing variability. However, since this occurred in about 60 lots, the chances of not seeing this variability should be slim indeed. It is to be noted that the trend is toward higher variability in the reassayed tablets. In spite of a general net loss in potency, the high values are frequently considerably higher than the high values in the starting tablets; the frequency of this occurrence

Table VII—Effect of Stuffing and Cap Liners on Nitroglycerin Tablets [400 mcg. (1/150 gr.)][a] with 1 Month of Storage at 37 and 45°

	37°				45°			
Description	Average Assay of 30 Tablets	Range	Standard Deviation	Stuffing Tablet Equivalent	Average Assay of 30 Tablets	Range	Standard Deviation	Stuffing Tablet Equivalent
No wax, Esterfoil	101.7	89.8–122.1	7.4	—	93.4	77.9–109.7	8.3	—
With wax, Esterfoil	101.5	89.4–119.6	8.2	—	95.3	77.2–116.3	9.8	—
Rayon, Esterfoil	97.9	80.5–113.6	8.5	2.3	101.5	79.5–129.9	11.4	1.8
Tissue, Esterfoil	99.6	80.3–116.2	8.7	2.1	102.0	60.7–126.5	13.9	5.3
Cotton, Esterfoil	98.3	83.7–117.4	8.8	6.8	97.9	59.6–124.8	16.1	12.3
No wax, Tinfoil	101.0	92.0–114.1	6.7	—	101.0	86.8–120.3	7.0	—
With wax, Tinfoil	102.3	90.2–123.6	8.5	—	97.5	82.6–123.5	8.0	—
Rayon, Tinfoil	100.4	64.4–138.4	17.3	3.3	94.4	70.9–112.2	11.4	4.9
Tissue, Tinfoil	103.6	83.5–131.9	10.6	2.8	93.9	39.2–128.7	20.5	4.9
Cotton, Tinfoil	99.0	75.7–126.7	10.6	9.4	90.4	52.1–123.9	15.2	7.6
No wax, wax vinyl	81.6	28.8–104.1	22.0	—	88.8	68.6–107.0	10.9	—
With wax, wax vinyl	102.2	83.4–116.7	7.9	—	87.7	39.6–114.8	19.2	—
Rayon, wax vinyl	93.6	54.6–128.4	17.2	2.8	92.0	72.6–115.3	11.1	3.0
Tissue, wax vinyl	97.1	57.5–142.7	18.9	1.9	94.6	31.5–136.7	24.2	2.5
Cotton, wax vinyl	94.4	65.6–114.7	13.2	10.1	88.2	56.5–109.6	16.1	28.9
No wax, with Mylar[b]	102.1	74.4–117.0	10.5	—	102.3	92.0–123.4	6.5	—
With wax, Mylar	99.9	84.6–115.7	8.7	—	99.8	82.3–110.8	6.9	—
Rayon, Mylar	94.0	64.6–113.0	14.9	2.5	102.0	63.1–134.6	17.2	2.6
Tissue, Mylar	101.6	53.8–146.4	21.1	2.4	97.5	45.1–126.7	19.5	3.6
Cotton, Mylar	—	—	—	—	96.0	50.0–118.0	14.1	10.5
No wax, lubricated vinyl	91.7	58.7–117.1	13.8	—	77.2	29.6–108.7	25.8	—
With wax, lubricated vinyl	90.1	46.5–114.8	17.8	—	72.0	19.9–108.3	25.5	—
Rayon, lubricated vinyl	97.4	51.1–131.3	21.1	1.7	90.2	55.2–132.9	17.9	2.3
Tissue, lubricated vinyl	100.6	48.5–147.4	20.7	1.4	91.6	50.1–118.0	17.9	2.5
Cotton, lubricated vinyl	91.8	55.5–113.0	15.3	2.3	86.0	40.4–134.0	22.5	7.5
No wax, Excelloseal	90.0	50.5–122.9	18.0	—	91.6	40.4–117.6	16.4	—
With wax, Excelloseal	90.0	52.6–129.8	18.5	—	89.6	57.4–116.5	15.7	—
Rayon, Excelloseal	93.9	54.6–132.9	18.0	1.8	104.1	80.5–129.5	14.6	2.8
Tissue, Excelloseal	104.8	74.9–144.1	18.8	2.5	97.7	45.3–140.1	18.8	3.3
Cotton, Excelloseal	96.4	60.2–131.5	15.6	5.9	96.7	61.9–121.6	14.8	11.1
No wax, Aclar[c]	101.0	80.3–116.5	7.9	—	99.2	87.7–115.0	7.7	—
With wax, Aclar	103.2	88.7–119.7	8.2	—	100.9	86.4–117.6	7.7	—
Rayon, Aclar	101.7	68.7–149.3	17.6	18.7	94.7	64.3–126.6	13.9	14.7
Tissue, Aclar	101.8	48.4–129.8	19.4	7.5	97.2	70.7–127.5	15.0	14.1
Cotton, Aclar	104.0	74.3–132.2	16.0	18.7	99.0	68.4–127.0	16.5	33.6

[a] Lot 345906, initial assays: average, 102.7% label claim; range, 92.2–112.7% label claim; and σ, 4.6. [b] Polyethylene terephthalate. [c] Aclar is a fluorohalocarbon. The results above may be weighted too heavily toward failure when stuffing is introduced. The Aclar seals were available only on bottles larger than the bottles used for the other studies so that more stuffing was used in the Aclar sealed bottles.

Table VIII—Comparison at Room Temperature and 4° of Conventional Nitroglycerin Tablets[a]

Release Date	Size of Tablet, mcg. (gr.)	Initial Assay: Average Assay, Percent of Labeled Claim	Initial Assay: Range of Assay, Percent of Labeled Claim	Initial Assay: Standard Deviation, σ	Room Temperature: Average Assay, Percent of Labeled Claim	Room Temperature: Range of Assay, Percent of Labeled Claim	Room Temperature: Standard Deviation, σ	4°: Average Assay, Percent of Labeled Claim	4°: Range of Assay, Percent of Labeled Claim	4°: Standard Deviation, σ
5-67	600 (1/100)	103.2	—[b]	—[b]	100.5	79.0–122.9	11.7	100.9	81.4–125.7	11.4
9-68	600 (1/100)	102.0	—	—	111.5	90.2–145.0	11.5	108.9	90.3–128.3	10.0
1-70	600 (1/100)	99.3	86.1–109.0	6.9	98.3	80.4–118.9	9.2	95.3	65.5–123.7	16.8
2-70	600 (1/100)	101.9	96.9–106.6	3.2	95.6	64.0–118.5	12.5	97.3	74.4–114.5	10.1
6-67	400 (1/150)	103.9	—	—	98.5	76.4–116.5	9.8	106.9	91.5–125.8	8.9
9-68	400 (1/150)	99.7	—	—	99.9	76.7–121.0	10.1	109.1	94.9–143.0	11.0
5-69	400 (1/150)	103.5	—	—	101.1	90.0–123.7	7.7	100.6	84.9–133.7	8.5
12-69	400 (1/150)	97.5	93.0–106.0	4.0	92.6	56.8–130.5	15.2	99.8	64.8–135.0	18.0
1-70	400 (1/150)	100.1	96.0–104.0	2.1	94.6	74.3–120.0	10.3	95.9	77.2–116.7	8.2
9-68	300 (1/200)	101.0	—	—	95.1	72.2–137.1	12.7	104.0	67.7–164.3	19.8
12-69	300 (1/200)	100.0	94.6–104.1	3.0	96.0	66.9–138.1	14.9	97.0	63.2–120.5	13.4
1-70	300 (1/200)	98.1	94.1–102.9	2.8	95.0	63.8–140.3	14.5	100.9	80.3–129.3	12.3

[a] Assays performed 2/17–2/18, 1972. [b] Only average assay is given; individual tablet assays were not being performed until 8-69. However, the ranges shown are typical of our manufacturing capability so that they may be assumed for those lots where ranges are not given. All assays shown that do not indicate assay ranges for individual tablets were done by either the IR or phenoldisulfonic acid procedures of USP XVII and USP XVIII. The automated version of Bell's (6) assay was used for all other samples.

Table IX—Stability of Nitroglycerin Tablets [400 mcg. (1/150 gr.)] in Glass Bottles with Screw Cap and Polyethylene Terephthalate Liner at 25, 37, and 45°

Temperature	Elapsed Time, Months	Lot 1: Average Assay, Percent of Labeled Claim	Lot 1: Range of Assays, Percent of Labeled Claim	Lot 1: Relative Standard Deviation, %	Lot 2: Average Assay, Percent of Labeled Claim	Lot 2: Range of Assays, Percent of Labeled Claim	Lot 2: Relative Standard Deviation, %
25°	0	103.8	94.9–113.5	3.9	104.7	98.5–111.2	3.1
	1	102.0	76.6–122.1	12.7	103.3	64.7–129.8	14.1
	2	102.1	84.9–131.2	10.6	102.2	83.7–119.6	7.9
	3	100.3	74.5–120.7	12.4	102.9	84.9–121.0	9.4
	4	101.2	79.5–128.6	12.6	99.9	80.5–131.0	11.7
	5	101.4	85.9–123.2	10.7	103.1	79.2–127.9	10.7
	6	101.1	81.6–127.0	12.5	104.9	79.7–132.7	14.3
37°	0	103.8	94.9–113.5	3.9	104.7	98.5–111.2	3.1
	1	107.6	72.0–147.2	15.6	101.8	69.5–143.3	17.4
	2	100.0	73.1–130.7	12.9	101.8	86.1–117.0	8.3
	3	99.8	76.7–137.6	13.9	103.7	86.7–113.5	7.2
	4	96.4	76.2–127.6	10.0	99.9	73.5–124.7	12.9
	5	100.1	76.5–142.4	16.7	104.6	73.8–137.1	16.4
45°	0	103.8	74.9–113.5	3.9	104.7	98.5–111.2	3.1
	1	102.3	71.8–142.9	13.9	101.6	74.6–124.3	12.7
	2	97.2	77.5–116.1	10.7	101.8	86.1–117.0	8.3
	3	100.4	76.5–119.4	11.7	97.7	73.7–140.9	12.4
	4	97.3	69.1–120.4	10.4	96.1	62.7–113.9	13.7
	5	98.2	79.0–133.1	10.9	99.7	78.7–119.6	10.0

does not appear to be based on chance. The assays performed on the freshly manufactured lots show one value at 126.5 and all other values (about 800) are below 116.9 (one at 116.9, another at 116.8, and the next high at 115). This finding is in solid contrast with the values obtained after the tablets were manufactured, packaged, and on the market; the high value is 152.6 and there are many tablets assaying greater than 130. Thus, it appears that these higher tablets are picking up nitroglycerin from other tablets.

The absolute age of these tablets is not the sole factor involved in determining whether a product passes or fails content uniformity. The passing tablets ranged in age from 1 to 14 months, whereas some of the tablets that failed were 1–2 months old.

The behavior of the tablets on reassay led to the belief that the problem in this laboratory with nitroglycerin tablets was probably industry wide. Assay of other commercial nitroglycerin tablets revealed that this was indeed true. Analysis of Bell's data (6) on 55 lots of tablets reinforces these observations. These lots encompassed tablets of 600, 400, 300, 250, and 150 mcg. (1/100, 1/150, 1/200, 1/250, and 1/400 gr.) made by four different manufacturers. Bell performed 10 individual tablet assays per lot. Calculation of the percent relative standard deviation for each lot[9] (Table X) gave values that were certainly much higher than the manufacturing process capability. Our manufacturing process usually gives a percent relative standard deviation below 4.5; the values on Bell's samples ranged from 5.4 to 21.8. Forty-one of the 55 values are greater than 7 and 29 are greater than 10. Of the 550 tablets assayed by Bell, 101 fell outside of the USP XVI limits of an average value of 80–112%; 78 of these showed excessive dosage and 23 insufficient nitroglycerin. The high percent relative standard deviations, coupled with the large number of tablets showing excess dosage, give presumptive evidence[10] that migration of nitroglycerin has occurred.

Table V shows the assay results obtained on four newly manufactured lots of nitroglycerin tablets. The close similarity of these lots indicates a pretty uniform manufacturing procedure. Of the

[9] Ten tablets (a small number of tablets for this calculation, but it does give a basis for comparison).

[10] Presumptive only because the range and relative standard deviations of these lots when manufactured were not known. However, since these tablets had to meet weight variation and average potency requirements, it would be unlikely that 78 of 550 tablets would be out of range on the high side.

Table X—Range and Relative Standard Deviation Calculated from Bell's (6) Data

Range of Lot, mg. × 100	Average Assay, mg.	Range of Lot, Percent of Labeled Claim	Average Assay, Percent of Labeled Claim	Relative Standard Deviation, Percent	Range of Lot, mg. × 100	Average Assay, mg.	Range of Lot, Percent of Labeled Claim	Average Assay, Percent of Labeled Claim	Relative Standard Deviation, Percent
600-mcg. (1/100-gr.) Tablets					**300-mcg. (1/200-gr.) Tablets**				
55–80	0.64	85–123	98	11.7	25–40	0.32	78–125	100	13.6
51–75	0.62	78–115	95	12.1	23–36	0.29	72–113	91	13.9
50–70	0.62	77–108	95	11.3	22–39	0.30	69–122	94	20.2
54–76	0.62	83–117	95	11.3	21–41	0.30	66–128	94	21.2
50–69	0.61	77–106	94	12.7	24–48	0.33	75–150	103	21.8
50–75	0.65	77–115	100	11.1	25–29	0.27	78–91	84	5.7
58–86	0.69	89–132	106	12.2	25–29	0.27	78–91	84	5.7
50–87	0.69	77–134	106	14.7	25–30	0.27	78–94	84	6.7
57–78	0.65	88–120	100	10.4	25–31	0.28	78–97	88	5.4
48–73	0.66	74–112	102	11.0	25–30	0.28	78–94	88	5.6
52–74	0.66	80–114	102	9.4	26–39	0.33	81–122	103	12.6
63–78	0.68	97–120	105	7.4	26–41	0.37	81–128	116	11.2
58–71	0.66	89–109	102	6.0	26–41	0.34	81–128	106	17.1
59–71	0.66	91–109	102	5.7	26–39	0.34	81–122	106	11.9
66–75	0.70	102–115	108	5.4	29–41	0.35	91–128	109	13.7
400-mcg. (1/150-gr.) Tablets					**250-mcg. (1/250-gr.) Tablets**				
34–45	0.38	79–105	88	8.5					
38–46	0.41	88–107	95	6.9	21–27	0.24	81–104	92	7.0
31–45	0.39	72–105	91	10.9	21–26	0.24	81–100	92	5.8
35–49	0.42	81–114	98	10.0	21–25	0.24	81–96	92	6.4
32–49	0.39	74–114	91	12.0	22–27	0.24	85–104	92	7.2
38–50	0.45	88–116	105	7.9	21–28	0.24	81–108	92	9.9
35–50	0.43	81–116	100	11.8					
37–47	0.43	86–109	100	8.0					
42–50	0.46	98–116	107	7.4	**150-mcg. (1/400-gr.) Tablets**				
39–47	0.43	91–109	100	7.4					
36–51	0.44	84–119	102	10.4	12–21	0.18	75–131	113	14.5
39–49	0.46	91–114	107	7.2	16–21	0.18	100–131	113	10.9
42–50	0.46	98–117	107	5.8	14–19	0.17	88–119	106	9.5
33–49	0.43	77–114	100	10.5	14–21	0.18	88–131	113	13.6
40–49	0.46	93–114	107	6.0	13–21	0.18	81–131	113	15.7

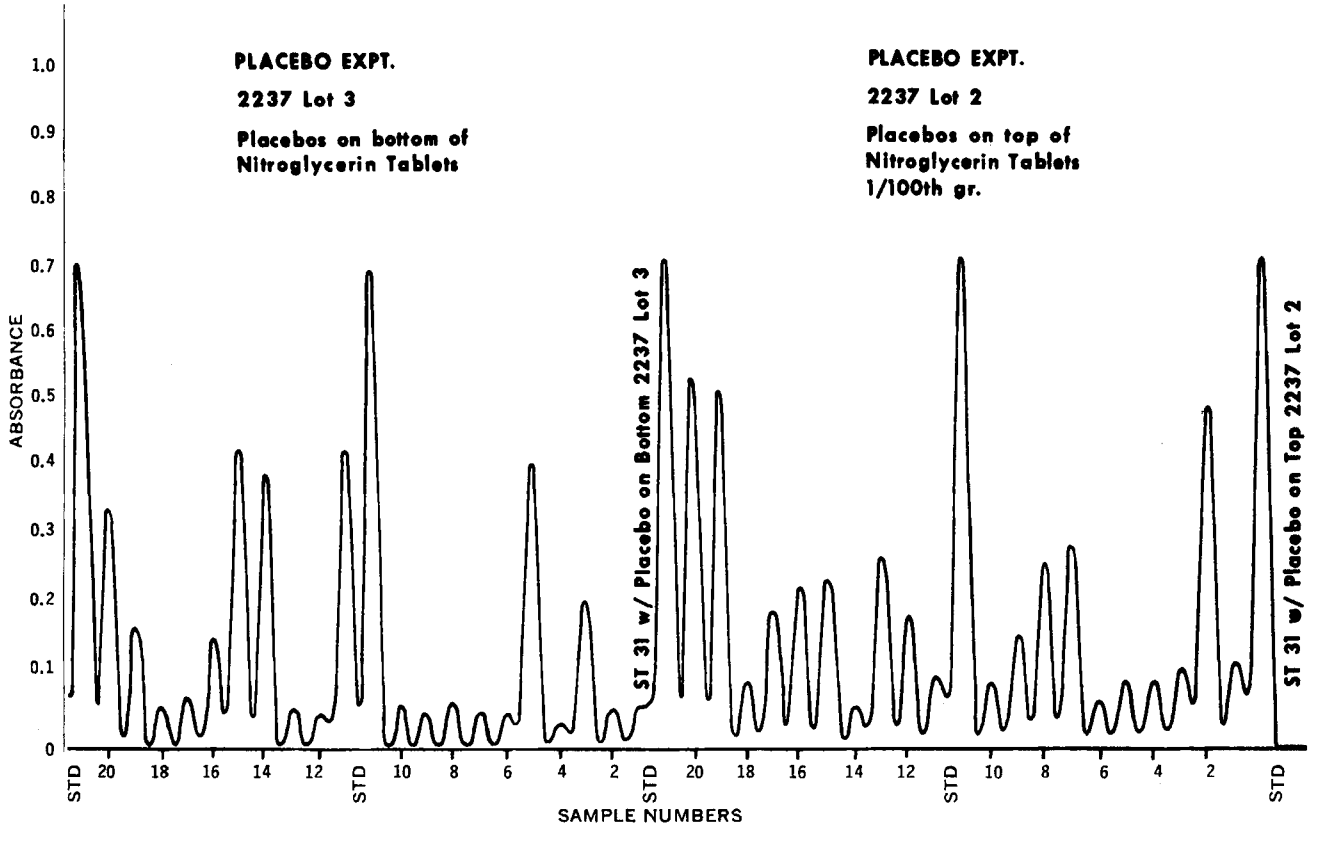

Figure 2—*Curves from automated analysis of placebo tablets. Key: left, placebos on bottom of nitroglycerin tablets; and right, placebos on top of nitroglycerin tablets.*

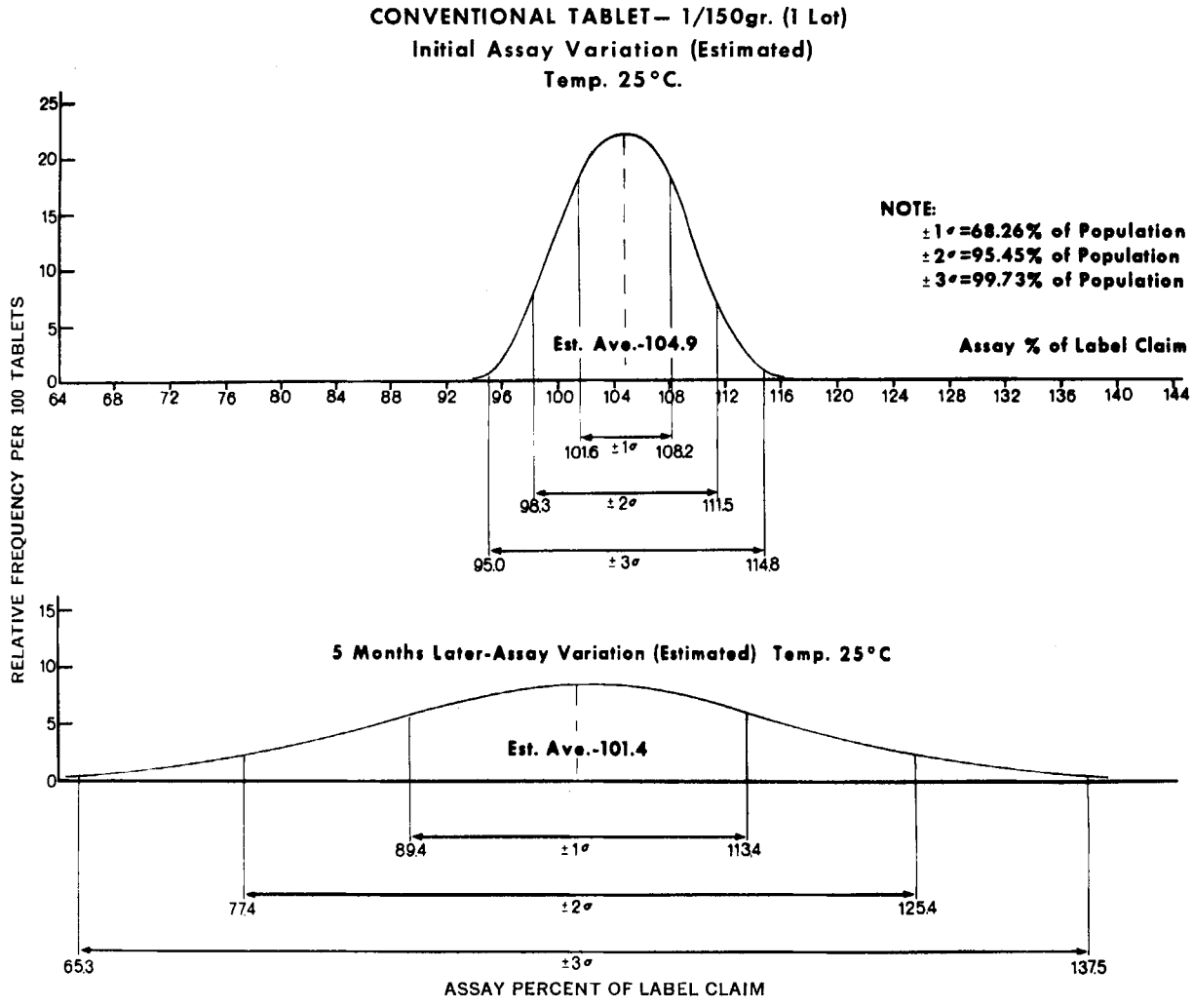

Figure 3—*Distribution curves for conventional sublingual tablets at the time of manufacture and after being packaged for 5–7 months.*

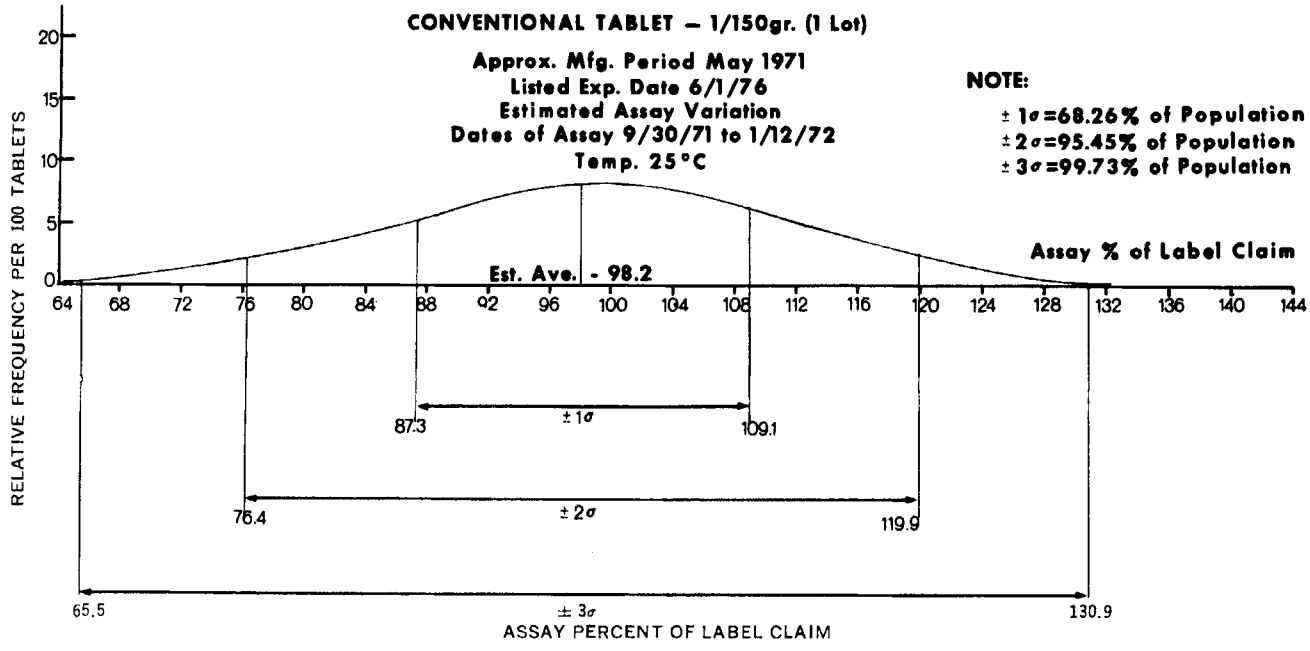

Figure 4—*Distribution curves for conventional sublingual tablets at the time of manufacture and after being packaged for 5–7 months.*

120 tablets tested, no tablet assayed lower than 87.2 nor greater than 114.8% of labeled claim. Since the lots had just been manufactured at the time the tablets (Tables II–IV) were assayed, it was decided to test the effects of certain variables (*e.g.*, time, temperature, stuffing materials, and cap liners) on the stability of nitroglycerin tablets.

Table VI shows the effect of storing these tablets at room temperature for 1 month in commercial bottles[6] using the modifications shown in the table. In all cases, the range of assays for the tablets widened considerably, the lows being lower and the highs being considerably higher in spite of a general net loss in potency. This result can only be explained on the basis that nitroglycerin volatilized and migrated from tablet to tablet. No other explanation is possible based on the average assay, range, and standard deviation of the original tablets.

The effects of using different cap liners and stuffing materials at 37 and 45° for 1 month are shown in Table VII. These accelerated temperature conditions were chosen to screen quickly the effectiveness of cap liners and stuffing materials. Once again, the range of assays widened considerably in spite of a general net loss in potency. The high values are frequently considerably higher than the high value obtained on the initial assay of Lot 345906 or, for that matter, on any of the three other lots made at the same time (Table V). In fact, many of the samples fail content uniformity requirements.

A large amount of nitroglycerin was absorbed by the cotton stuffing. Cotton is still used by pharmacists in repackaging operations; this practice must be discouraged for nitroglycerin tablets. Additionally, it should be noted that of the seven liners evaluated, only four (Esterfoil, tinfoil, polyethylene terephthalate[7], and a fluorohalo-carbon film[11]) offered any protection to the nitroglycerin tablets for even short periods of time. Although these liners are imperfect, they certainly are superior to the wax vinyl, lubricated vinyl, and Excelloseal liners. The latter cap liners seemed to accelerate the instability; it should be emphasized that the stability of no other known drug dosage form seems to be so susceptible to the proper choice of cap liner and stuffing material.

With most unstable drugs, the stability of refrigerated samples is usually better than for samples stored at room or higher temperatures. This is not true with nitroglycerin tablets (Table VIII). The data show that refrigeration does not prevent the development of intertablet variation in conventional sublingual nitroglycerin tablets. This is additional evidence for the complex nature of the instability of sublingual nitroglycerin tablets.

Table IX shows the stability of two additional newly manufactured lots of nitroglycerin tablets at 25, 37, and 45° assayed at monthly intervals. Marked intertablet variability devloped within 1 month after the samples were stored. The loss of content uniformity in these tablets is important, because it means a patient cannot be assured a uniform, predictable dose with this type of tablet unless something can be done to stabilize the nitroglycerin content. Figures 3 and 4 show distribution curves for conventional sublingual tablets at the time of manufacture and after being packaged for 5–7 months. The spread in range of assay results is dramatic when one considers the close range of assay values in the freshly manufactured lots.

The foregoing data and discussion demonstrate that sublingual nitroglycerin tablets are unstable due to volatilization and intertablet migration of nitroglycerin. The inherent low volatility of nitroglycerin and the manufacturing process for making molded sublingual tablets are the predisposing factors leading to instability. During the manufacture of molded sublingual tablets, a 10% nitroglycerin β-lactose adsorbate[12] is blended with a lactose–sucrose mixture. This mixture is then moistened and blended with a mixture of alcohol and water. The resultant tablet mixture is then molded and the tablets so prepared are air dried. While the tablets are air drying, the nitroglycerin is brought to the surface of the tablet by the evaporation of the alcohol and water. This situation is analogous to the development and elution of a solute zone during chromatographic development. Since the tablets are air dried in batches and in contact with each other, it is quite conceivable that the surface concentrations of nitroglycerin are erratic, creating concentration gradients among the tablets. These gradients are in addition to all other stresses inherent in the immediate tablet environment including the stuffing, cap liner, imperfect vapor seal, and temperature.

When the nitroglycerin is brought close to, or at the surface of, the tablet, the stage is set for loss and/or migration, depending on the character of the immediate tablet environment. Once a driving force is present which causes nitroglycerin to volatilize and leave the tablet, the process leading to the development of intertablet dose variation is set in motion. In an attempt to establish an equilibrium condition not only among the tablets but with the stuffing, the cap liner, and an imperfect vapor seal as well, the small amount of volatilized nitroglycerin encounters other tablets. The latter, due to differences in surface concentration of nitroglycerin, porosity, hardness, and proximity to the tablets losing the nitroglycerin, may very well act as partial condensers in the same manner as the packing in a distillation column. Thus, one sees the development of high and low content tablets. Many lots that are uniform when manufactured develop enough intertablet variation within a few months to fail the USP XVIII content uniformity test. This tendency toward failure seems to be an intrinsic property of molded tablets using present manufacturing methods. Our experience with this tablet indicates that stabilization can best be achieved by reformulation.

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[11] Aclar, Allied Chemical Corp.

[12] Supplied by E. I. duPont de Nemours & Co., Inc., Wilmington Del.