Table III—Diflorasone Diacetate (I) Assay Results for Cream and Ointment Formulations Using Peak Area Ratio Response

Formulation[a]	I Found, mg/g[b]	Percent of Label, %
Cream		
A	0.494–0.505	98.8–101.0
B	0.483 0.510	96.6–102.0
Ointment		
C	0.488–0.498	97.6–99.6
D	0.451–0.485	90.2–97.0

[a] Product (A and C) and experimental (B and D) formulations. [b] Range of assay results obtained after assaying four lots per formulation.

Quantitation of III–VII was examined to determine if the responses of these structurally related compounds were linear over the 0.1–1.0% (w/w) range. These data were obtained to test the applicability of the method for potential impurities. The individual slopes for the calibration curves using peak area percent for III–VII were all 0.96–1.00 and the y-intercepts were not significantly different from zero. The coefficients of correlation, r, for plots of related compounds added *versus* amount found were all >0.999.

DISCUSSION

Presented in Table III are the range of results obtained using the procedure for cream and ointment product formulations A and C and cream and ointment experimental formulations B and D. The precision of the method was determined by replicate analyses of lots from each formulation. The day-to-day assay precision, expressed as *RSD*, was ~1.8% for cream formulations A and B and ~1.3% for ointment formulations C and D.

In addition to the determination of I in cream and ointment formulations, three lots of bulk drug were assayed for purity on the "as is" basis (Table IV). The *RSD* for the purity determination of I was ~1.0% using peak area ratio response.

The chromatographic method described is an accurate and precise method for the determination of diflorasone diacetate (I) in creams, ointments, and bulk drug. The method was found to be reproducible as well as rugged, making it suitable for use as a routine assay. The ability of the method to separate structurally related compounds makes the method useful for monitoring bulk drug and product stability.

Table IV—Diflorasone Diacetate Assay Results for Bulk Drug Using Peak Area Ratio Response

Lot	Assay[a] %	RSD, %
I1	99.3	1.1
I2	99.2	0.9
I3	99.7	0.7

[a] Calculated on the "as is" basis; the results are averages of six determinations over 2 d.

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Effect of Nitroglycerin-Soluble Additives on the Stability of Molded Nitroglycerin Tablets

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Abstract □ Nitroglycerin vapor pressures at 25°C were determined for additive–nitroglycerin systems over the additive–nitroglycerin weight ratio range of 0.5 to 3.0 for 16 additives exhibiting solubility in nitroglycerin. The effects of the additives on nitroglycerin chemical stability at 25°C and 50°C were also studied. Tablet stability characteristics, *i.e.*, content uniformity, open-dish stability, and chemical decomposition were evaluated for selected tablet formulations. Most additives lowered the vapor pressure of nitroglycerin sufficiently to stabilize content uniformity when used at additive–nitroglycerin weight ratios near 1. Higher additive levels are needed for significant potency stabilization in open-dish stability tests, but these levels normally decrease the chemical stability of nitroglycerin. However, stabilization of content uniformity, a twofold reduction of potency loss in an open-dish stability test, and chemical stability are possible with at least three of the additives studied.

Keyphrases □ Nitroglycerin—vapor pressure in sublingual molded tablets, intertablet migration, effect of additives □ Tablet stability—nitroglycerin sublingual molded tablets, vapor pressure, intertablet migration, effect of additives

A number of workers have emphasized both the physical instability of molded nitroglycerin tablets arising from vaporization, and subsequent migration of nitroglycerin, and the improvement in stability obtained by incorporating a nitroglycerin-soluble additive in the formulation (1–7). The additive lowers the vapor pressure of nitroglycerin which results in: (*a*) a reduction of the evaporation rate of nitroglycerin from tablets exposed to ambient air currents (1); (*b*) a marked decrease in losses due to absorption in packaging material (7); (*c*) stabilized content uniformity, in that most of the intertablet nitroglycerin migration which occurs in conventional (unstabilized) tablets is thermodynamically impossible in a closed system of stabilized tablets (4). A modest vapor pressure reduction is sufficient to stabilize the content uniformity within a sample of tablets (4). However, both evaporation rate and package absorption are least for the formulation of lowest vapor pressure.

Although there have been several reports of chemical instability in nitroglycerin tablets (8, 9), chemical decomposition is normally not a problem in conventional nitroglycerin tablets. However, the agent employed to stabilize content uniformity may have an adverse effect on chemical stability. Several studies (7, 8, 10) suggest that both povidone (7) and polyeth-

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Table I—Reduction of Nitroglycerin Vapor Pressure at 25°C by Additives[a]

Additive	Density	Mol. Wt.	Eq. 1 Parameters			P/P_0		$(\partial \ln P/\partial \ln N)_A$	
			χ_0	n	b	R = 1.0	R = 2.0	R = 1.0	R = 2.0
I Povidone	1.10	35,000	+0.174	4	−12.5	0.46	0.07	1.6	3.8
II Polyethylene glycol 400	1.11	400	+3.89	1	−6.77	0.56	0.22	1.0	1.7
III Polyethylene glycol 4000	1.11	4,000	+0.50	2	−3.56	0.62[b]	0.62	0[b]	0[b]
IV Polyethylene glycol 20,000	1.10	20,000	+0.343	4	−14.7	0.58[b]	0.58	0[b]	0[b]
V Polyoxyl 40 stearate	1.08	2,060	−0.082	2	−1.216	0.58	0.33	0.65	1.0
VI Polyoxyethylene(23) lauryl ether	1.06	1,200	+0.885	2	−2.438	0.67	0.36	0.65	1.1
VII Octoxynol	1.065	692	+0.576	2	−1.192	0.67	0.42	0.49	0.82
VIII Polysorbate 20	1.08	1,226	−0.24	2	−0.580	0.58	0.35	0.57	0.83
IX Polysorbate 60	1.06	1,310	+0.528	4	−3.14	0.71	0.37	0.59	1.3
X Polysorbate 80	1.06	1,308	+0.242	4	−2.07	0.67	0.38	0.56	1.1
XI Ethylenediamine tetra [polyoxyethylene (52) polyoxypropylene (12)]	1.08	12,000	−0.166	2	−1.213	0.59	0.33	0.66	1.0
XII Ethylenediamine tetra [polyoxyethylene (132) polyoxypropylene (16)]	1.08	27,000	+0.019	2	−2.43	0.63[c]	0.63	0[c]	0[c]
XIII Polaxamer 188	1.08	8,350	−0.888	2	−0.233	0.51	0.47[d]	0.66	0.0[d]
XIV 50% Acetylated monoglycerides	0.94	400	—	—	—	0.94[e]	0.85	≃0.09	—
XV 100% Acetylated monoglycerides	0.99	440	1.253	2	−1.105	0.79	0.56	0.34	0.65
XVI Bis(2-ethylhexyl)phthalate	0.980	390	1.568	4	−1.263	0.96	0.74	0.17	0.58

[a] At selected R values (R is additive-nitroglycerin weight ratio). [b] Equilibrium solubility is R = 0.9. [c] Equilibrium solubility is R = 0.8. [d] Equilibrium solubility is R = 1.1. [e] Incomplete solubility even at R = 0.5. A small fraction of the sample appears to be essentially insoluble in nitroglycerin.

ylene glycol (8, 10) may accelerate the hydrolysis of nitroglycerin to a point where, at high temperature, decomposition becomes a significant factor in tablet stability. This study was initiated to investigate the effects of selected nitroglycerin-soluble materials on nitroglycerin vapor pressure and on tablet stability as part of an effort to develop tablet formulations which would stabilize content uniformity without adversely affecting chemical stability.

EXPERIMENTAL SECTION

Materials and Assay Procedure—The nitroglycerin and povidone were described previously (4). The other additives were obtained from commercial sources[1] and were used as supplied except for vacuum drying to remove volatiles. Nitroglycerin-additive samples were prepared as previously described (4). Samples denoted "powder" are nitroglycerin-additive-β-lactose systems in powder form containing ~1.5% nitroglycerin.

Nitroglycerin was assayed as described previously (7) while dinitroglycerin and mononitroglycerin were assayed semiquantitatively by TLC (11) and quantitatively by HPLC. The HPLC method[2] employed a partisil ODS column[3] and a 230 nm UV detector[3]. The solvent was 70:30 (v/v) water-acetonitrile at a flow rate of 3 mL/min. Four peaks were observed with partially decomposed nitroglycerin with retention times (1–5 min) in the following order: nitric acid with glycerol, mononitroglycerin (both isomers), dinitroglycerin (both isomers), and nitroglycerin. High levels of povidone yielded a small peak at the dinitroglycerin retention time, making a small povidone correction necessary. This peak appeared to be due to unreacted monomer. Variation in the solvent composition between the sample and the elution medium resulted in small positive or negative peaks at the mononitroglycerin retention time. Probably because of this interference, the mononitroglycerin assay data are much less precise than the corresponding data for the di- and tri-esters.

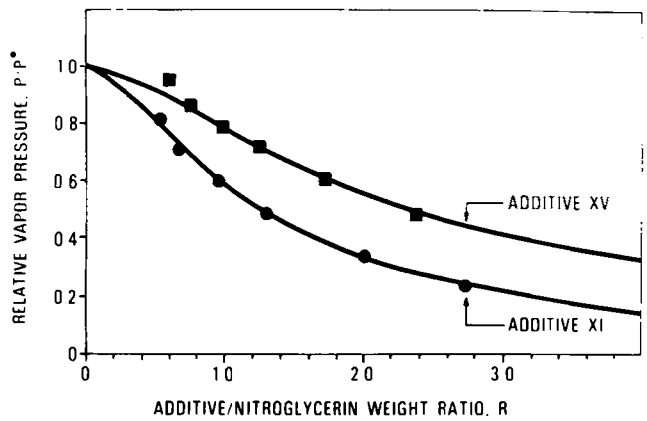

Figure 1—*Vapor pressure of nitroglycerin at 25°C in solutions of nitroglycerin and additive XV (■) and additive XI (●). The lines represent* P/P_0 *calculated from Eq. 1.*

Vapor-Pressure Measurements—Vapor pressures were measured by the modified Knudsen effusion method (4, 12). Powder systems of nominal additive-nitroglycerin weight ratios of 0.5, 1.0, and 2.0 were studied. Differential measurements (4, 12) were made on each sample. Continuous measurements of vapor pressure were made (4) on samples of additive-nitroglycerin weight ratios of 0.5. Replicate measurements were carried out (4).

RESULTS

Vapor-Pressure Reduction—Vapor-pressure results are summarized in Table I. Density data are either measured in this laboratory or were given by the supplier of the additive. The additive molecular weight was calculated from the average chemical formula or was taken directly from information provided by the supplier.

Vapor pressure raw data were found to be well represented by the equation (13):

$$\ln P/P_0 = \ln(1-\phi_2) + \left(1 - \frac{V_1}{V_2}\right)\phi_2 + \chi\phi_2 \qquad \text{(Eq. 1)}$$

where P is the vapor pressure of the additive-nitroglycerin solution, P_0 is the vapor pressure of pure nitroglycerin, ϕ_2 is volume fraction of additive in the

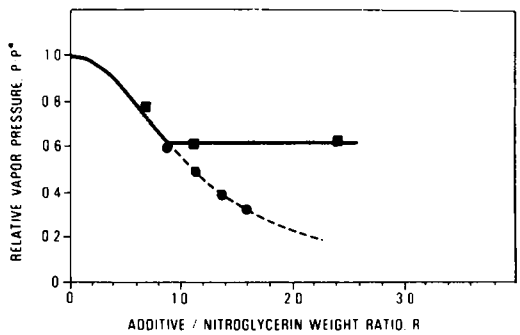

Figure 2—*Vapor pressure of nitroglycerin at 25°C in a nitroglycerin-additive system exhibiting incomplete miscibility (polyethylene glycol 400). Key: (■) equilibrium (time zero) data; (●) dynamic (real time) data in a supersaturated system.*

[1] The sources of the additives (Table I) were: II, III, IV, Baker Chemical Co.; V (Myrj 52), VI (Brig 35), VIII (Tween 20), IX (Tween 60), X (Tween 80), ICI, Atlas Chemical Co.; XI (Tetronic 707), XII (Tetronic 904), XIII (Pluronic F68), BASF Wyandote Chemical Co.; XIV (Myvacet 5-07), XV (Myvacet 9-40).

[2] J. W. Becker and J. A. Sefranka, unpublished results.

[3] Waters Associates, Milford, Mass.

Table II—Water Absorption and Chemical Stability of Additive–Nitroglycerin Powder Systems

	Additive	R	Water Content of Powder, % (w/w) at 87% Rel. Humidity[a]	Decomposition, % after 2 months at 50°C (Dinitroglycerin Content)[b]	
				Dried	87% Rel. Humidity
	None	0	1.3	1 (N)	0 (N)
I	Povidone	1	2.1	38 (M)	33 (M)
		2	3.1	—	45 (M)
II	Polyethylene glycol 400	1	2.7	10 (T)	15 (M)
		2	3.8	—	13 (T)
V	Polyoxyl 40 stearate	1	1.5	0 (N)	7 (M)
		2	2.4	—	15 (M)
VI	Polyoxyethylene (23) lauryl ether	1	1.6	4 (T)	6 (T)
		2	2.2	—	15 (M)
VII	Octoxynol	1	1.4	0 (N)	1 (N)
		2	1.6	—	1 (N)
VIII	Polysorbate 20	1	1.7	5 (T)	7 (T)
		2	2.1	—	15 (M)
IX	Polysorbate 60	1	1.6	2 (T)	6 (M)
		2	2.1	—	12 (M)
X	Polysorbate 80	1	1.4	14 (M)	10 (M)
		2	1.8	—	— (M)
XI	Ethylenediamine tetra [polyoxyethylene(52)polyoxypropylene (12)]	1	1.4	3 (T)	11 (M)
		2	2.1	—	22 (M)
XV	100% Acetylated monoglycerides	1	1.2	0 (N)	2 (N)
		2	1.4	—	3 (N)

[a] The water contents of the dried powders were all in the range 0.45–0.58% (w/w). [b] Storage in closed glass bottles. Dinitroglycerin content determined by TLC; N = none detected; T = trace observed (~2–5%); M = moderate level observed.

nitroglycerin phase, V_1 and V_2 are the molar volumes of nitroglycerin and additive, respectively, and χ is the interaction parameter which was arbitrarily assumed to have the form:

$$\chi = \chi_0 + b\phi_2^n \qquad \text{(Eq. 2)}$$

where χ_0, b, and n are constants evaluated from the data. An integer value of n was chosen to give the best linear least-squares fit of χ as a function of ϕ_2^n. Additivity of volume was assumed so ϕ_2 may be calculated from the additive-to-nitroglycerin weight ratio, R, according to:

$$\phi_2 = \frac{R}{R + \rho_2/\rho_1} \qquad \text{(Eq. 3)}$$

where ρ_2 and ρ_1 are the densities of additive (Table I) and nitroglycerin (14), respectively.

Data representative of systems exhibiting complete miscibility of nitroglycerin and additive over the composition range studied are shown in Fig. 1. The solid line represents P/P_0 calculated from Eq. 1 while the squares and circles are experimental points obtained by averaging at least four independent measurements. With some additives (III, IV, XII, XIII), miscibility is observed only at lower R values. Consequently, the vapor pressure of these systems at equilibrium is independent of composition at R values larger than the solubility limit (Fig. 2, square symbols). However, during the vapor pressure measurement, R increases as effusion proceeds and normally a supersaturated solution of additive in nitroglycerin is formed. The data represented by circles (Fig. 2) were obtained from supersaturated solutions formed during the effusion measurement.

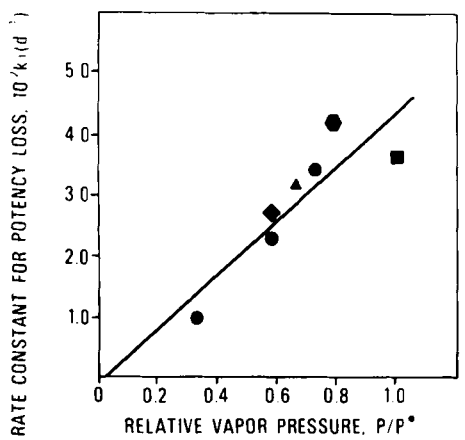

Figure 3—*Correlation between potency losses in open-dish stability tests and nitroglycerin vapor pressures. Key: (■) no additive; (●) additive V; (▲) additive VII; (◆) additive VIII; (●) additive XV.*

Smoothed values of relative vapor pressures, P/P_0, and values of the partial derivative $(\partial \ln P/\partial \ln N)_A$, were calculated from Eq. 1 (Table I). Here, A and N are the masses of additive and nitroglycerin, respectively. A large value of this derivative indicates that evaporation of a small amount of nitroglycerin from the sample produces a large reduction in vapor pressure.

Stability—*Chemical Stability of Powders*—The chemical stability of nitroglycerin in additive–nitroglycerin phases was studied for both dried powders[4] and for powders equilibrated with 87% relative humidity prior to storage (Table II). The systems studied were ~98% lactose powder with the additive–nitroglycerin phase coated on the lactose crystals.

Tablet Stability in Closed Bottles—The effects of selected additives on chemical stability and content uniformity stability were investigated for tablet samples sealed in glass bottles (Table III). As an index of chemical stability at ambient temperature, dinitroglycerin content (HPLC assay) after 2 years storage at 25°C are listed.

Potency losses after 2 years at 25°C averaged 12% for the tablets containing povidone (with no apparent correlation with level of povidone), ~9% for tablet Lot N, an average of 6% for the tablets without an additive, and 2–5% for other tablets. As a measure of chemical stability at high temperature, potency losses after 6 months at 50°C were determined for selected tablet lots (Table III). Potency loss data are uncertain within ~±3%, so except for the greater potency losses shown by lot K, lot N, and the povidone containing lots, all lots are essentially equivalent. Content uniformity (Table III) is expressed as the relative standard deviation for single tablet nitroglycerin assay (weight nitroglycerin per unit tablet weight) of thirty tablets.

Tablet Stability in an Open-Dish Test—Tablets were stored at 25°C in open petri dishes exposed to ambient air currents. Thirty tablet samples were taken for single tablet assay at day six and day twelve. The observed changes in potency and content uniformity are tabulated (Table IV).

DISCUSSION

Vapor Pressure and Open-Dish Stability—The loss in tablet potency during open-dish storage is undoubtedly due to evaporation of nitroglycerin, and therefore the rate of loss should correlate with the nitroglycerin vapor pressure. To provide rate data suitable for correlation with the tablet vapor pressure, effective first-order rate constants for potency loss were determined from the data in Table IV[5]. The resulting rate constants are plotted as a function of relative vapor pressure of nitroglycerin (from Table I) in Fig. 3. The line is the linear regression line ($r = 0.88$). Considering the difficulty in obtaining

[4] The dried samples were air dried in a forced-air oven at 43°C. Relative humidity decreases in ambient air (25°C; relative humidity, ~55%) ~three-fold when heated to 43°C by the drying oven. Thus, the dried samples were equilibrated with ~18% relative humidity at 43°C.

[5] The data were consistent with first-order loss of nitroglycerin, *i.e.*, linear semilogarithmic plots of potency *versus* time. However, insufficient data were available to reveal subtle variations from first-order behavior.

Table III—Stability of 0.3-mg Nitroglycerin Tablets in Closed Bottles

Tablet Lot[a]	Additive	R	Chemical Stability: Dinitroglycerin, % (2 years at 25°C)	Chemical Stability: Potency Loss, % (6 months at 50°C)	Content Uniformity, σ (w/w)[b]: Initial	6 months at 25°C	2 years at 25°C
A	None	0	1.0	4	5	9	10
B	None	0	0.4	—	7	—	13
C	None	0	0.7	—	4	—	16
D	I	1	7.6	—	3	—	3
E	I	1	8.2	92	2	—	4
F	I	1	8.6	—	2	—	5
G	I	2	4.3	—	1	—	2
H	I	3	1.5	—	1	—	2
I	V	0.6	1.5	5	4	4	5
J	V	1	1.8	6	2	4	4
K	V	2	4.4	40	3	6	6
L	VII	1	1.2	6	3	3	4
M	VIII	1	2.1	6	2	3	5
N	X	1	6.8	29	3	—	7
O	XV	1	1[c]	8	5	5	5

[a] All lots were experimental lots prepared for this study. [b] *RSD* for assay of 30 tablets in weight of nitroglycerin per unit weight of tablet. [c] Semi-quantitative TLC result.

Table IV—Stability of Nitroglycerin Tablets Exposed to Ambient Air (Open-Dish Evaporation Test)

Tablet Lot	Additive	R	Potency, μg/Tablet: Initial	6 d	12 d	Content Uniformity, σ (w/w): Initial	6 d	12 d
A	None	0	344	292	222	5	9	15
I	Polyoxyl 40 stearate	0.66	351	295	233	4	2	1
J	Polyoxyl 40 stearate	1.0	361	316	275	2	2	2
K	Polyoxyl 40 stearate	2.0	352	327	314	3	3	3
L	Octoxynol	1.0	364	308	249	3	3	3
M	Polysorbate 20	1.0	368	308	266	2	3	2
O	100% Acetylated monoglycerides	1.0	351	296	212	5	4	2

reproducible potency loss data on samples stored in an open dish[6], the correlation is very good. The rate of potency loss is essentially proportional to the initial vapor pressure of nitroglycerin in the tablet formulation.

Content Uniformity of Tablets—Poor content uniformity at the time of manufacture may arise from causes unrelated to the volatility of nitroglycerin, *i.e.*, poor mixing, solution migration during drying and subsequent tablet surface erosion, *etc.* However, a decrease in content uniformity on aging in closed bottles is due to migration of nitroglycerin, largely intertablet migration (2-4).

An additive will be effective in preventing intertablet nitroglycerin migration if two criteria are met (4): (*a*) the additive lowers the vapor pressure of nitroglycerin by more than ~15%; (*b*) Evaporation of nitroglycerin from the additive-nitroglycerin phase results in significant further reduction of vapor pressure [*i.e.*, the quantity $(\partial \ln P/\partial \ln N)_A$ (Table I) should be large[7]].

If criterion *a* is met, condensation of nitroglycerin in empty tablet pores is prevented, while meeting criterion *b* minimizes condensation in tablet pores that are partially filled with nitroglycerin-additive phase (4). Thus, the relative importance of criteria *a* and *b* depends on whether the small pores (condensation sites) in fresh tablets are empty or are partially filled with nitroglycerin-additive phase. This detailed information is not available. However, if both criteria are met, the additive should be effective in preventing significant intertablet transfer of nitroglycerin.

On this basis, all additives studied, with the exception of additive XIV, should stabilize content uniformity if used at the proper level. Additives III, IV, XII, and XIII are soluble in nitroglycerin only at lower R values, and therefore to meet criterion *b*, these additives must be used at levels below the solubility limit. However, in each of these cases, a value of R may be chosen to give both large $(\partial \ln P/\partial \ln N)_A$ and $P/P_0 < 0.85$.

The lower effective limit for $(\partial \ln P/\partial \ln N)_A$ in a formulation is not known. However, content uniformity data (Tables III and IV) suggest that $(\partial \ln P/\partial \ln N)_A > 0.3$ is sufficient. The formulation for tablet lot O (additive XV at R = 1) yields a stabilized tablet with respect to content uniformity with $P/P_0 = 0.79$ and $(\partial \ln P/\partial \ln N)_A = 0.34$. All other tablet formulations with additives produced greater reductions of vapor pressure and larger values $(\partial \ln P/\partial \ln N)_A$ without any obvious improvement in content uniformity stability.

Chemical Decomposition—Except for XV and VII, the additives accelerate the decomposition of nitroglycerin. In general, the effect of the additive on stability is minimal at R = 1 but becomes significant at R = 2. A particularly good example of this behavior is shown by tablets (Table III) and dried powders (Table II) containing additive V. Samples at R = 0.66 and R = 1.0 are essentially stable, while samples at R = 2 are unstable.

Samples containing I, II and X (Tables II and III) appear to be unstable at 50°C, even at R = 1, but at least for I and II, the high temperature stability is not particularly sensitive to additive levels above R = 1. Potency loss data (*Results* section) suggest the same conclusion at 25°C for I, although the dinitroglycerin content decreases as R increases (Table III). However, at 25°C the stability of nitroglycerin is sensitive to the level of soluble polyethylene glycol[8]. Samples with R = 1 apparently are stable, but the 25°C-stability of nitroglycerin in a phase containing a high level of polyethylene glycol (R = 2) is poor[8].

Since hydrolysis is a major reaction pathway for decomposition of nitroglycerin in tablets, water content and alkalinity of the nitroglycerin phase should be important variables. Although the water content of the nitroglycerin phase could not be measured (15), the water content of the powder system as a whole was determined (Table II). The water content of all dried samples was 0.45-0.58% (w/w). As expected, the data generally show greater decomposition for the sample equilibrated at high humidity (I and X are exceptions) than for the corresponding dried sample.

The alkalinity was characterized by measuring the pH of a 10% aqueous solution (or dispersion) of the additive in water[9]. The hydrolysis rate would be expected to be at a minimum in a weak acid (16, 17). The exact relationship between pH of a 10% aqueous solution of additive and acid- or base-catalysis in a nitroglycerin-additive phase is not clear. However, if acidic or basic impurities in the additives used were the dominant factor in stability, one would expect a good correlation (nonlinear) between pH and stability; good correlation was not observed[9].

Disintegration Time—While a detailed discussion of disintegration time is beyond the scope of this study, the effect of the additive on disintegration time merits comment. An additive may function as an additional binder re-

[6] Variations in air currents with storage location and presence of materials which may absorb nitroglycerin near the storage location limit reproducibility of open-dish stability data.

[7] Lilly 0.6-mg tablets are stabilized with Povidone at R = 0.6 which results in $(\partial \ln P/\partial \ln N)_A = 0.59$. Other established stabilized formulations (Lilly 0.3- and 0.4-mg tablets and Parke Davis Nitrostat) yield larger values of this derivative.

[8] Dried powders (lactose-nitroglycerin-additive) were aged 2 years at 25°C. Polyethylene glycol 400 and polyethylene glycol 1000 systems at R = 0.62 showed only trace levels of dinitroglycerin, but at R = 2.2, the ratio of dinitroglycerin species to trinitroglycerin was ~0.6. Potency loss for the polyethylene glycol 400 sample was 52%. Polyethylene glycol 4000 at R = 2.2, which is soluble only to R = 0.9, showed only trace levels of dinitroglycerin. Even at R = 2, potency losses and dinitroglycerin contents (as percentage of total nitroglycerin compounds) were only several percent for additives V, VII, and XV and were <15% for other additives studied (VI, VIII, IX, X, and XI).

[9] The measured pH values for the indicated additives were: I (3.5), II (6.0), V (4.6), VI (2.4), VII (3.5), VIII (3.9), IX (3.9), X (3.8), XI (7.8), and XV (5.8). These additives were all vacuum dried before use.

sulting in an increase in disintegration time, the effect increasing as the additive content of the tablet increases. For example, conventional tablets (Table III) typically disintegrate within ~10 s, but tablets with additives present at 1% of the tablet weight require 20–30 s for all additives except povidone. Tablets formulated with 2% of either additive V or additive VIII require ~100 s for disintegration. These times refer to tablets aged 2 years at 25°C. While 100 s is near the UPS limit for 2 min, a reduction in tablet density will significantly reduce the disintegration time. The data quoted above refer to a fixed tablet density (1.16 g/mL). Thus, it may be possible to reduce the tablet density by using less lactose, thereby reducing the disintegration time to a more acceptable level.

With the exception of tablets containing additive I (povidone), the disintegration times for fresh tablets are essentially the same as for aged tablets. Fresh tablets containing 1% povidone typically disintegrate within 20 s, but after prolonged aging (more than 2 years at 25°C) they may require 1–2 min for disintegration. Evidently the povidone cross-links to some extent which retards disintegration. When these tablets are left undisturbed in water for some time, a "ghost" of insoluble material in the shape of the tablet remains. Thus, with the exception of severely aged povidone-containing tablets, excessive disintegration time is not a problem for the tablet systems studied (Table III), at least for ≤1% additive.

CONCLUSIONS

A number of nitroglycerin-soluble additives sufficiently lower the vapor pressure of nitroglycerin to stabilize the content uniformity of molded nitroglycerin tablets. In general, an additive–nitroglycerin weight ratio, R, of 1 is adequate for this purpose. Tablet potency losses in open-dish evaporation tests are roughly proportional to the vapor pressure of nitroglycerin in the tablet, and higher levels of additive (R = 2) are normally needed to achieve a significant improvement in open-dish stability. However, with few exceptions (VII and XV) high additive levels lead to reduced chemical stability, particularly at high temperature, and a compromise must be made between chemical stability and open-dish stability. For packaging in sealed glass bottles, open-dish potency loss is of little importance, and a compromise of chemical stability is not necessary. For example, additives VII and XV stabilize content uniformity with no measurable loss of chemical stability and several other additives (V in particular) do not seriously affect chemical stability when used at R = 1[10].

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[10] Only two stabilized nitroglycerin tablet products are available in the U.S. market. Parke-Davis' formulation uses polyethylene glycol 4000 as the additive while the Lilly formulation currently uses povidone.

γ-Aminobutyric Acid Uptake Inhibition and Anticonvulsant Activity of Nipecotic Acid Esters

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Abstract □ *n*-Alkyl esters of nipecotic acid were prepared by Fischer esterification, and the esters were evaluated against bicuculline-induced seizures in mice. Evaluation of the alkyl esters for inhibition of γ-aminobutyric acid uptake into mouse whole brain mini-slices revealed that the order of potency was proportional to chain length. The octyl ester inhibited γ-aminobutyric acid and β-alanine uptakes by apparently nonspecific mechanisms. A variety of phenyl esters of nipecotic acid were also synthesized utilizing either dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole as the condensing agent. Most of the phenyl esters were potent inhibitors of γ-aminobutyric acid uptake. The uptake inhibition appeared to involve specific and nonspecific (detergent-like) mechanisms. The *m*-nitrophenyl and *p*-nitrophenyl esters were particularly potent against bicuculline-induced seizures in mice.

Keyphrases □ Nipecotic acid esters—synthesis, anticonvulsant activity □ Anticonvulsant agents—potential, nipecotic acid esters, synthesis

γ-Aminobutyric acid appears to act as a major inhibitory neurotransmitter in the central nervous system (1–3). Impairment in γ-aminobutyric acid neurotransmission may contribute to the symptoms of Huntington's disease, Parkinsonism, and epilepsy (4). Thus, compounds that potentiate γ-aminobutyric acid neurotransmission have considerable therapeutic potential.

(±)-Nipecotic acid (I) has been found to be a potent inhibitor of γ-aminobutyric acid uptake into rat cerebral cortex (5) and mouse whole brain mini-slices (6). The *R*-(−) enantiomer of nipecotic acid (I) has approximately five times greater affinity for the γ-aminobutyric acid uptake carrier than the *S*-(+) enantiomer (7).

As with several other compounds (8) having the potential of interacting with the γ-aminobutyric acid system, (±)-nipecotic acid (I) does not readily penetrate the blood–brain barrier (9). However, prodrug esters of nipecotic acid (I) that pass into the central nervous system have been evaluated for anticonvulsant activity (10–13) and γ-aminobutyric acid uptake inhibition (13, 14).

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