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Nitroglycerin Stability in Polyethylene Glycol 400 and Povidone Solutions

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Abstract □ The stability of solutions of nitroglycerin in several common pharmaceutical solvents and compounds used as tablet excipients was investigated using a UV spectrophotometric assay. Included in the study were povidone (I), polyethylene glycol 400 (II), and solvents such as absolute alcohol, propylene glycol, and glycerol. At the elevated temperatures of the accelerated stability studies, only II demonstrated a considerable adverse effect on the stability of the nitroglycerin solution. It is postulated that a "reaction compound" was formed between nitroglycerin and II which regenerated nitroglycerin depending on hydrolysis conditions. Based on the Arrhenius equation and with initial rates of up to 6 hr of degradation, the predicted stability for a II solution of nitroglycerin in terms of its 10% decomposition at 25° was approximately 7 days.

Keyphrases □ Nitroglycerin—stability in polyethylene glycol 400 and povidone solutions □ Stability—nitroglycerin in polyethylene glycol 400 and povidone solutions □ Polyethylene glycol 400—nitroglycerin solutions, stability □ Povidone—nitroglycerin solutions, stability □ Vasodilators, coronary—nitroglycerin, stability in polyethylene glycol 400 and povidone solutions

The problems encountered with nitroglycerin tablet stability, contributing to a loss of content uniformity (1) and possible potency variation, were the direct result of a measurable vapor pressure of nitroglycerin at room temperature (2). Attempts to overcome these difficulties included changes in the material of the nitroglycerin dosage form container and its cap liner (2). However, nitroglycerin volatilization still was not controlled effectively (3).

Reformulation of the tablet by incorporating "fixatives" (4–7) and changing the manufacturing process from molding to direct compression (8) were other attempts to control this physical problem. These steps were demonstrated to reduce successfully nitroglycerin volatility. For instance, polyethylene glycol 400 (II) (4) and povidone (I) (5, 6) have been employed as fixatives or stabilizing agents in nitroglycerin tablets to reduce volatility and thus maintain content uniformity and potency. A combination of I and microcrystalline cellulose (7), used as stabilizers, was demonstrated to be even more effective (3). The evaluation of these reformulated tablets was based on content uniformity and various physical tests, such as hardness, disintegration, and volatility, as well as exposure to several extreme conditions.

The current study was conducted to investigate the possible chemical interactions between nitroglycerin in solution and I and II since no such data were reported previously. If I or II exerted a detrimental effect, further studies would be conducted to predict nitroglycerin stability in the particular solvent.

EXPERIMENTAL

Nitroglycerin Stock Solution—*Preparation*—A 5-g portion of nitroglycerin mixture powder[1] in lactose was weighed and placed in a suitable separator. Chloroform[2], 10 ml, and 50 ml of deionized distilled water were added and the mixture was shaken gently for about 5 min to extract the nitroglycerin. The lower chloroform layer containing the extracted nitroglycerin was filtered[3].

The chloroform solvent was evaporated by blowing nitrogen gas on the surface until a constant weight of the pale-yellow viscous liquid of nitroglycerin was obtained. A sufficient volume of absolute alcohol was added to the weighed residue to obtain a nitroglycerin stock solution of approximately 1.0 mg/100 μl.

Standardization—This step was based on the USP method (9) with slight modifications. A standard solution of potassium nitrate was prepared by dissolving about 80 mg of potassium nitrate pellets[4], accurately weighed, with 1 ml of deionized distilled water in a 100-ml volumetric flask. Sufficient acetic acid[5] was then added to volume and mixed. A 100-μl volume of nitroglycerin solution to be standardized was withdrawn accurately and placed in a 100-ml volumetric flask containing 1 ml of acetic acid.

After the addition of 2 ml of phenoldisulfonic acid reagent, the mixture was shaken vigorously on a mechanical shaker for 3 min and allowed to stand at room temperature for another 15 min. Approximately 25 ml of deionized distilled water was added to dilute the reaction mixture before the addition of 10 ml of strong ammonia solution[5] and its final dilution to volume with deionized distilled water. Concurrently, 1 ml of the previously prepared standard potassium nitrate solution was pipetted into a 100-ml volumetric flask and treated similarly for the analysis as in the sample.

The absorbances at 410 and 600 nm of both solutions were determined simultaneously against a reagent blank. The strength of the nitroglycerin stock solution was then calculated from the equation:

$$\text{mg}/100\ \mu\text{l} = 0.749C[(A_{410} - A_{600})_U/(A_{410} - A_{600})_S] \quad \text{(Eq. 1)}$$

where 0.749 is a factor for relating the nitrate content of potassium nitrate to that of nitroglycerin, C is the potassium nitrate concentration in milligrams per milliliter in the potassium nitrate standard solution, and the subscripts U and S refer to the nitroglycerin sample and the potassium nitrate standard, respectively.

[1] S.D.M. No. 17, ICI America Inc., Wilmington, Del.
[2] ACS grade, Allied Chemical Corp., Morristown, N.J.
[3] Whatman filter paper No. 2.
[4] NF XI, Matheson, Coleman & Bell, Norwood, Ohio.
[5] ACS grade, Fisher Scientific Co., Fair Lawn, N.J.

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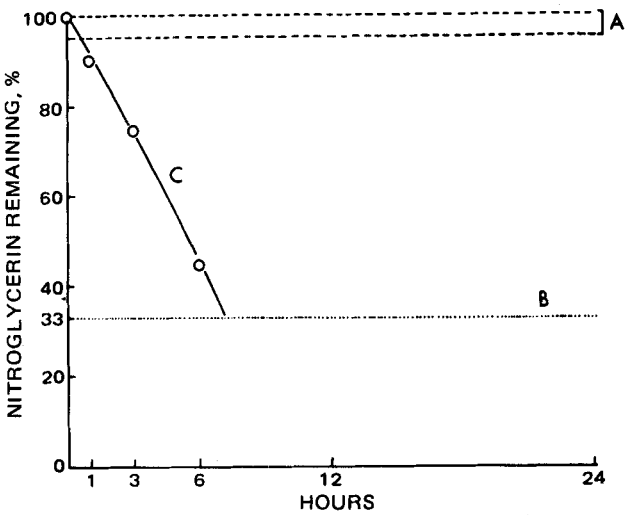

Figure 1—*Percentage of nitroglycerin remaining as a function of time in various solvent solutions at 80 ± 0.5° determined by UV spectrophotometry. Key: A, percentage range of nitroglycerin remaining in absolute alcohol, alcohol–water, glycerin, propylene glycol, and povidone; B, lower limit for the assay; and C, curve for percent nitroglycerin remaining in polyethylene glycol 400 solution.*

Analytical Method—The UV kinetic assay developed by Fung *et al.* (10) was employed in most determinations for nitroglycerin in aqueous solutions. A 1-ml volume of aqueous nitroglycerin solution was mixed with 3 ml of 0.05 *M* NaOH in methanol in a 1-cm cell. The determinations were made on a spectrophotometer[6] at the maximum at 336 nm. From these values, the amount of nitroglycerin was determined subsequently from calibration graphs made with nitroglycerin in the corresponding solvents.

In studies with I and II, the analysis was repeated using 0.1 *M* NaOH and the maximum absorbance readings obtained at 328 nm (11). This slightly modified procedure was based on a later report (11). However, no significant differences in the results were observed. In addition, a colorimetric method, involving an alkaline hydrolysis of nitroglycerin and subsequent diazotization and coupling of the nitrites formed with *N*-(1-naphthyl)ethylenediamine dihydrochloride (12), was performed on these test samples. Only I and II were analyzed by both the modified UV procedure and the Bell method since they represented those compounds that previously showed either an adverse effect or no effect on nitroglycerin stability in solution.

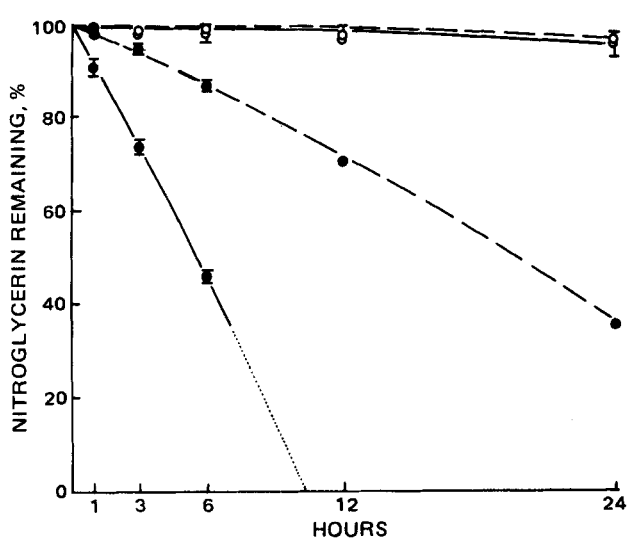

Figure 2—*Percentage of nitroglycerin remaining in povidone (○) and polyethylene glycol 400 (●) solutions as a function of time at 80 ± 0.5° compared using the spectrophotometric (—) and colorimetric (– –) methods.*

[6] Cary model 118, Varian Instruments Division, Palo Alto, Calif.

Table I—Percentage of Nitroglycerin Remaining in Polyethylene Glycol 400 and Povidone Solutions as a Function of Time at 80 ± 0.5°

Solvent	Method[a]	Hours 1	3	6	12	24
Polyethylene glycol 400	A	90.05	74.53	44.63	<33.00	<33.00
	B	99.73	95.62	88.03	69.92	34.96
Povidone	A	99.01	97.86	97.81	96.72	95.08
	B	99.57	98.81	98.03	97.37	96.55

[a] A = UV kinetic assay (10). B = colorimetric method (12).

Stability of Nitroglycerin Solutions—Samples containing the equivalent amount of 3 mg of nitroglycerin, as accurately transferred from the alcoholic stock solution, and 0.4 ml of the various solvents were subjected to a water bath temperature of 80 ± 0.5°. The solvents included absolute alcohol[7], water, glycerin[2], propylene glycol[8], polyethylene glycol 400[9], and alcohol–water (1:1) containing 10% (w/v) povidone[10]. All were used without further purification. At the end of 0, 1, 3, 6, 12, and 24 hr, flasks containing these mixtures were withdrawn from the water bath and adjusted to 10 ml with deionized distilled water. The percent nitroglycerin remaining in the different solvents was calculated and plotted as a function of time.

Nitroglycerin Degradation Kinetics in II—Replicate volumes containing the same quantities of nitroglycerin and II as used in the previous experiment were placed in 10-ml volumetric flasks. These flasks were subjected to both ambient room temperature and water bath temperatures of 40, 50, 60, and 70 ± 0.5°. Flasks were removed at 0, 1, 3, 6, 12, and 24 hr and subsequently diluted to volume with deionized distilled water.

Graphs of the percent nitroglycerin remaining as plotted against time for the various temperatures were obtained. Straight lines were drawn through the initial linear plots corresponding up to 6 hr of study. The slopes, representing the estimates of specific rates or rate constants, k, obtained within this initial period of nitroglycerin degradation were employed to construct the Arrhenius plot.

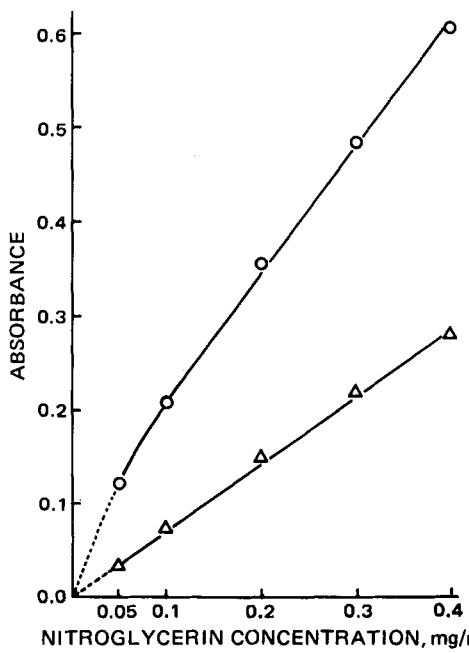

Figure 3—*Plot of absorbances as a function of nitroglycerin concentration in polyethylene glycol 400 solution. Key: ○, maximum absorbance determined at 336 nm by the spectrophotometric assay; and △, absorbance at 550 nm obtained by the colorimetric method.*

[7] U.S.I. absolute pure ethyl alcohol USP–NF reagent.
[8] Laboratory grade, Fisher Scientific Co., Fair Lawn, N.J.
[9] USP grade, Ruger Chemical Co., Irvington-On-Hudson, N.Y.
[10] Plasdone C-15, GAF Corp., New York, N.Y.

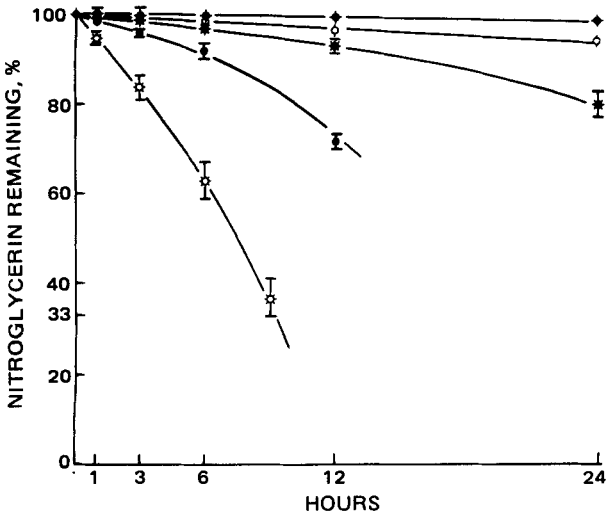

Figure 4—*Percentage of nitroglycerin remaining as a function of time in polyethylene glycol 400 solution at different temperatures as determined by the spectrophotometric method. Key: ◆, room temperature (~25°); ○, 40°; ✱, 50°; ●, 60°; and ☼, 70 ± 0.5°.*

RESULTS AND DISCUSSION

Nitroglycerin stability in the presence of various solvents as determined by the Fung UV kinetic assay (10, 11) is represented schematically in Fig. 1. Absolute alcohol, alcohol-water (1:1), glycerin, propylene glycol, and 10% (w/v) povidone exerted no deleterious effects on nitroglycerin stability. Not less than 95% of the original nitroglycerin remained after 24 hr under conditions of the specified accelerated stability studies with these solvents. However, under identical conditions and in a solution of II, the amount of nitroglycerin decreased considerably with time.

It is postulated that a "reaction compound" was formed between nitroglycerin and II which increased in amount with time. This reaction could result in a reduced amount of free nitroglycerin molecules determinable by the Fung method. The assay of nitroglycerin in this solvent by the Bell method (12), employing sodium hydroxide in place of strontium hydroxide as the hydrolyzing agent, confirmed the marked reduction of assayable nitroglycerin occurring with II (Table I and Fig. 2). However, the amount of nitroglycerin remaining in II after exposure to heat when determined by the Fung method was comparatively lower than that obtained by the Bell colorimetric method. This difference could be attributed partly to the more drastic hydrolysis procedure employed in the Bell method, which resulted in a relatively greater breakdown of the reaction compound, releasing more free nitroglycerin, and, consequently, a higher recovery for the analysis.

Based on the calibration plot obtained by the Fung method in contrast to that obtained by the Bell method, the absorbance below 0.2 (Fig. 3), corresponding to approximately 0.1 mg of nitroglycerin/ml (in this case, 33% nitroglycerin) remaining could not be validly correlated with concentration. Consequently, no plots were included in the graphs (Figs. 1 and 2) representing determinations at 12 and 24 hr for the nitroglycerin solution in II since they showed absorbance readings of 0.1334 and 0.0952, respectively.

The stability of a nitroglycerin solution in II represented in terms of percent nitroglycerin remaining as a function of time for up to 24 hr is shown in Fig. 4. Decomposition is presumed to be complex because of the nonlinear curves becoming especially noticeable after 6 hr. Thus, for each temperature studied, straight lines were drawn through only the initial parts of the plots to derive the specific rates, k. An Arrhenius plot (Fig. 5) then was obtained using these values and gave a linear correlation coefficient of 0.994.

The calculated $t_{90\%}$, which corresponds to the time for 10% nitroglycerin decomposition, was estimated to be 7.4 days based on $k_{40°}$ and $k_{50°}$ values of 0.250 and 0.625%/hr, respectively. This value agrees favorably with that obtained for nitroglycerin samples of similar composition when subjected to actual ambient room temperature conditions. The observed $t_{90\%}$ value for nitroglycerin where temperature varied between 20 and 24° was approximately 10 days.

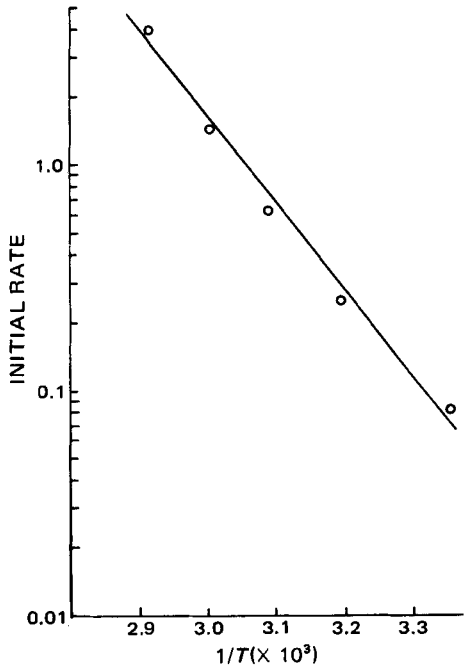

Figure 5—*Arrhenius plot for initial degradation rates of nitroglycerin in polyethylene glycol 400 solution as a function of temperature.*

In conclusion, on the basis of these experimental data obtained for a simple solution of nitroglycerin in II, extra care should be observed when formulating liquid pharmaceutical dosage forms of similar compositions. A tablet dosage form of nitroglycerin, formulated with markedly lower proportions of either II or polyethylene glycol 4000 and subjected to 37° and at 85% relative humidity for up to 39 months, was reported to exhibit good stability (13).

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