Rapid Determination of Nitroglycerin Volatility Using Thermogravimetric Analysis

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Abstract □ The effect of selected tablet components on the volatility of nitroglycerin from compressed sublingual tablets was studied by thermogravimetric analysis. The results, confirmed by chemical analyses, showed that nitroglycerin volatility is significantly reduced by the use of povidone USP and microcrystalline cellulose NF in tablet formulations. In general, the stabilizing effect of these materials was dependent on the presence and the concentration of each other. These studies demonstrated the utility of thermogravimetric analysis as a rapid and reliable means of screening nitroglycerin formulations for stability purposes.

Keyphrases □ Nitroglycerin—volatility, effect of various tablet components, thermogravimetric determination □ Volatility—nitroglycerin, effect of various tablet components, thermogravimetric determination □ Thermogravimetry—determination, effect of various tablet components on nitroglycerin volatility □ Tablets—nitroglycerin, effect of various tablet components on volatility, thermogravimetric determination □ Vasodilators, coronary—nitroglycerin, volatility, effect of various tablet components, thermogravimetric determination

In recent years considerable attention has been focused on nitroglycerin stability. Several investigators have conducted extensive research to improve the volatility and, thus, content uniformity of nitroglycerin tablets (1–9). It is now well established that nitroglycerin stability can best be improved by reformulation of conventional molded tablets rather than by modifications in packaging materials. One approach toward this end has been the inclusion of various macromolecular substances in tablet formulations (3–7, 9).

From the experimental standpoint, the dependency of nitroglycerin stability in tablet formulations has been studied using extreme conditions of storage, *i.e.*, completely exposing the tablets to air or to high vacuum, followed by chemical analysis of individual tablets. While studies of this type are of fundamental value in development work, they are generally time consuming when a large number of formulations is investigated.

Therefore, as an alternative procedure, thermogravimetric analysis was explored for its utility in screening various nitroglycerin formulations. It was found that thermogravimetric analysis affords a rapid and reliable means of evaluating the influence of various tablet components on the volatility of nitroglycerin. This report describes preliminary studies which ultimately led to the development of a stabilized compressed nitroglycerin tablet (9).

EXPERIMENTAL

Tablet Preparation—Nitroglycerin tablets, containing 0.6 mg of drug in each 30-mg tablet, were prepared using nitroglycerin spirit (9.1% w/v), alcohol USP, lactose (anhydrous) USP, starch USP, microcrystalline cellulose[1] NF, and calcium stearate NF. The diluent mixture was granulated with a solution or dispersion of a binder in nitroglycerin spirit and alcohol USP. When necessary, a small amount of water was employed to aid dispersion of the binder.

Ethylcellulose[2], povidone USP[3], hydroxypropyl methylcellulose[4], and gelatin USP were used as binders and were added to each formulation at a ratio of 1:2 with respect to nitroglycerin. The amount of starch was maintained constant (25%) while, in later experiments, microcrystalline cellulose and povidone were included at various levels to determine the stabilizing effects of these materials. The wet granulated product after drying at 30–35° was mixed with the lubricant and compressed into 0.40-cm tablets.

Thermogravimetric Studies—The volatility of nitroglycerin from tablets was studied by following the change in sample weight as a function of time under isothermal conditions. Two tablets representing each formulation were placed into the pan of the thermogravimetric analyzer[5] previously equilibrated at the desired temperature. The instrument was operated at a sensitivity of 0.2 mg/2.54 cm (1 in.). A stream of nitrogen gas was passed through the furnace containing the sample at a constant flow rate of 20 ml/min to remove the gaseous products evolved during the experiment.

Generally, after 1.5 hr of treatment at 80°, sufficient weight loss was observed for comparison of relative stability. However, in later experiments, it was necessary to extend the tests over 4 hr to permit adequate opportunity for volatilization of nitroglycerin.

Nitroglycerin Assay—To compare and confirm the volatility of nitroglycerin by thermogravimetric analysis, samples of each formulation were subjected to individual tablet assay before and after the thermogravimetric analysis treatment using the spectrophotometric method of Bell (10).

RESULTS AND DISCUSSION

The results of nitroglycerin volatility from various tablet formulations are summarized in Fig. 1 and Table I. Figure 1 depicts typical thermograms, which are of two general types. The first type, represented by curves A and B, shows linearity over the entire thermogram. These linear thermograms correspond to formulations prepared from anhydrous materials, so the weight loss observed can be totally attributed to the volatility of nitroglycerin.

The second type (curves C–G and placebo) is characterized by a sudden change in sample weight during the initial stage of the experiment but later exhibits the same general linearity as the first type. These thermograms are associated with tablets prepared from excipients containing water, *e.g.*, starch. It can be seen from Fig. 1 that the placebo tablets containing lactose and starch exhibited a similar pattern of weight loss in the first 10 min of the thermogravimetric analysis.

In duplicate determinations, the initial portions of the thermograms exhibited slight variations in the amount of weight loss, apparently due to minor differences in the water content of different samples, but reproducibility was excellent for the remaining linear portions of the curves. From these results, it can be assumed that the initial weight loss is almost entirely due to the evaporation of water and, for practical purposes, can be omitted from consideration. Therefore, the volatility of nitroglycerin is taken as the loss in sample weight after the first 10 min of the thermogravimetric analysis.

From the data in Table I, it can be seen that nitroglycerin volatility in different formulations as determined by thermogravimetric analysis showed an acceptable level of agreement with chemical assay results. Table I also shows that tablets containing povidone had a significant reduction in the loss of nitroglycerin. Formulations containing gelatin, on the other hand, exhibited similar stability as the tablets containing no binder. The addition of hydroxypropyl methylcellulose or ethylcellulose caused some improvement in tablet stability but not to a significant extent.

[1] Avicel PH-102, American Viscous Division of FMC Corp.

[2] Ethocel, 100 cps, Hercules Inc.
[3] Plasdone K 29-32, General Aniline and Film Corp.
[4] Methocel, 60 HG 50 cps, Dow Chemical Co.
[5] DuPont model 950 analyzer with model 900 console.

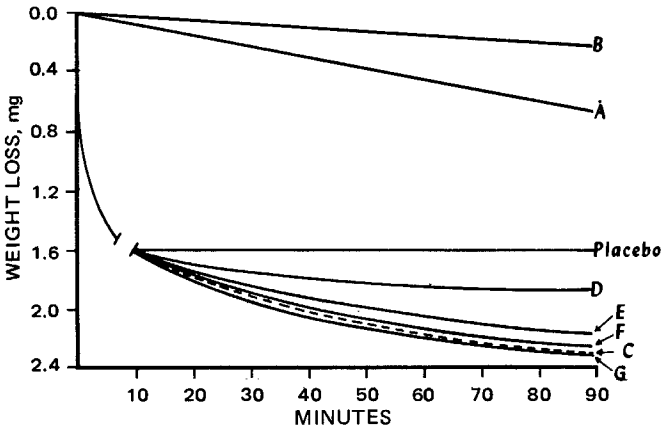

Figure 1—*Typical thermograms of nitroglycerin tablets containing various binders. See Table I for details.*

These preliminary experiments prompted the use of povidone as a stabilizing agent in the formulation of a compressed sublingual nitroglycerin tablet. Additional stability screening experiments were then designed to examine further the effect of various concentration ratios of povidone along with an additional stabilizer, *i.e.*, microcrystalline cellulose (11).

Figure 2 summarizes the volatility of nitroglycerin tablets prepared with three different concentrations of microcrystalline cellulose and povidone at various ratios with respect to nitroglycerin. The samples were subjected to thermogravimetric analysis at 80° for 4 hr. This figure illustrates the stabilizing effect of povidone and shows that better nitroglycerin stability was achieved as the level of povidone was increased in each formulation. This result can best be seen with formulations containing no microcrystalline cellulose, where addition of povidone at a 1:4 ratio resulted in a retention of 86% of the original potency during the test period as compared to 10% for tablets without povidone. The retention of nitroglycerin content in formulations prepared with 50% microcrystalline cellulose was also increased from 81 to 92% by inclusion of povidone at a 1:4 ratio.

Figure 2 also demonstrates the effect of microcrystalline cellulose in reducing the volatility of nitroglycerin. Since this material possesses

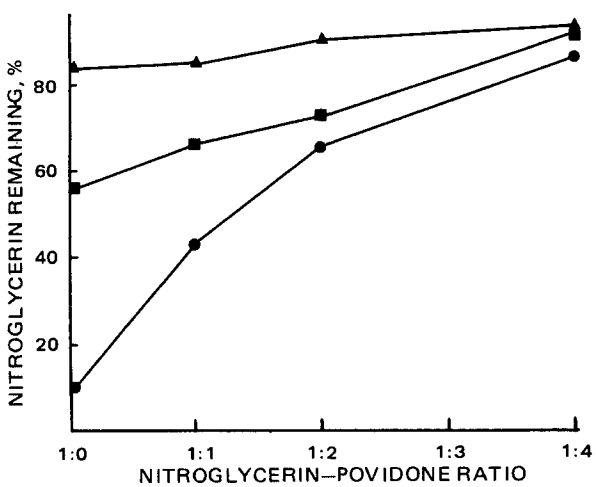

Figure 2—*Volatility of nitroglycerin tablets as a function of the nitroglycerin–povidone ratio. These tablets were prepared with different concentrations of microcrystalline cellulose. Key: ●, 0%; ■, 25%; and ▲, 50%.*

Table I—Comparison of Thermogravimetric and Chemical Analyses for the Volatility of Nitroglycerin Tablets

Formulation		Nitroglycerin Remaining, %	
Designation	Composition[a]	Thermogravimetric Method	Chemical Method
A	Lactose	54	51
B	Lactose, povidone	84	83
C	Lactose, starch	25	23
D	Lactose, starch, povidone	84	82
E	Lactose, starch, hydroxypropyl methylcellulose	45	42
F	Lactose, starch, ethylcellulose	34	30
G	Lactose, starch, gelatin	25	22

[a] Each tablet also contained 0.6 mg of nitroglycerin.

excellent compression characteristics, judicious selection of its concentration along with that of povidone allows the formulation of compressed nitroglycerin tablets with optimum stability as well as disintegration and bioavailability properties (9).

The studies reported here clearly show the utility of thermogravimetric analysis as a simple, rapid, and reliable means to investigate the volatility of nitroglycerin formulations. This method also permits the selection of accelerated test conditions which can be controlled precisely. The volatility of nitroglycerin can be studied from one or two tablets, thereby eliminating the migration of the drug from tablet to tablet during accelerated stability studies. By the use of thermogravimetric analysis, potentially stable formulations can be selected in a short period; and, finally, by the use of thermogravimetric analysis at various temperatures, the kinetics of nitroglycerin volatility from tablets may be studied.

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