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Original Article

Stability of Trinitroglycerin in Polyethylene Glycol 400

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Abstract

In this study, the stability of trinitroglycerin (TNG) in polyethylene (PEG) 400 was investigated according to Arrhenius approach. The reaction rate constant (k) for the thermal disintegration of TNG in PEG 400 at various temperatures was counted based on the percents of remaining TNG at different intervals of time at a specific temperature. The results showed that “k” at 40, 50, 60, 70, 80 and 90 °C were 6.5×10^{-4}, 3.57×10^{-3}, 4.7×10^{-3}, 3×10^{-2}, 6.2×10^{-2} and 6.5×10^{-2}, respectively. By plotting “log k” against temperature (1/T), “k” was obtained at 5 and 20 °C which was 1.47×10^{-5} and 7.94×10^{-5}, respectively. The results showed the time required to attend 90, 80, 70, and 50 percent of the original TNG at 5 °C was 9.76, 20.7, 33, and 64.2 months, respectively. The results assist in the calculation of the expiration time of TNG/PEG 400.

Keywords: PEG 400; Reaction rate constant; Stability; Trinitroglycerin.
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1. Introduction

For over a century, trinitroglycerin (TNG) has been used to prevent or relieve angina pectoris [1]. TNG is available in different pharmaceutical formulations including oral tablets, sustained release capsule or tablets, sublingual pills and alcoholic solution for i.v. administration. TNG is usually formulated with miglyol oil as vehicle in the sublingual pills. Miglyol oil is not miscible with water and is fairly expensive. On the other hand, polyethylene glycol 400 (PEG) is water miscible, not expensive, and readily available in the market. Therefore, this study was undertaken to evaluate the stability of TNG in PEG as a first step for possible substitution of miglyol oil by PEG in the sublingual pills or using TNG in PEG solution directly without special formulation.

It is well known that a number of factors besides concentration may affect the reaction velocity, such as: Temperature, solvent, catalysts, and light. The speed of many reactions increases about 2 to 3 times with each 10 °C rise in temperature. The effect of temperature on reaction rate is given by the following equation, first suggested by Arrhenius:

$$k = Ae^{-Ea/RT}$$

$$\text{or} \quad \log k = \log A - \frac{Ea}{2.303}\frac{1}{RT}$$

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in which “k” is the specific reaction rate, “A” is a constant known as the Arrhenius factor or the frequency factor, “*Ea”* is the energy of activation, “R” is the gas constant, 1.987 calories/deg mole, and “T” is the absolute temperature.

In the past it was a common practice in many drug companies to evaluate the stability of their products by observing them for a year or more. Such a method was time consuming and uneconomical. Accelerated studies at higher temperatures were also used by some companies. For example, some companies used the rule that the storage of liquid at 37 ºC accelerated the decomposition at twice the normal temperature rate, while other manufacturers assumed that it accelerated the breakdown by 20 times of the normal rate [2].

The method of accelerated testing of pharmaceutical products based on the principles of chemical kinetics was demonstrated by Garrett and Carper [3]. According to this technique, the “k” values for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some factors of concentration against time. The logarithms of the specific rates of decomposition are then plotted against the reciprocals of the absolute temperature, and the resulting line is extrapolated to the room temperature or other required temperatures. The k_{20} is used to obtain a measure of the stability of a drug under ordinary shelf conditions. Since TNG products are usually kept in refrigerator, therefore, k_5 was obtained after extrapolation of the resulting line.

2. Materials and methods

2.1. Materials

Glycerin, nitric acid, sulfuric acid, potassium nitrate, phenol, nitroglycerine and ammonia used in this investigation were from Merck Chemical Company.

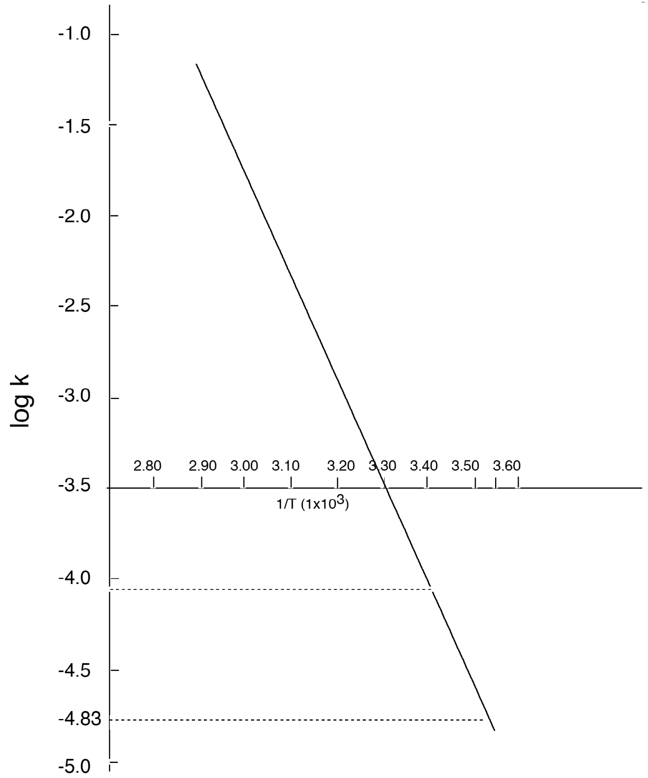

Figure 1. Plot of log k against 1/T for thermal decomposition of TNG in PEG 400 at different temperatures.

Table 1. Stability of TNG in PEG 400 after thermal decomposition at different temperatures for various intervals of time (n = 3).

Time (h)	**The remaining TNG (% ± SD)**					
	40 ºC	50 ºC	60 ºC	70 ºC	80 ºC	90 ºC
0	99.7 ± 0.52	99.7 ± 0.52	99.7 ± 0.52	99.7 ± 0.52	99.7 ± 0.52	99.7 ± 0.52
1	99.5 ± 0.73	99.0 ± 0.70	97.4 ± 0.77	95.7 ± 0.82	93.1 ± 0.73	91.5 ± 0.85
2	99.2 ± 0.83	98.0 ± 0.72	97.9 ± 0.65	94.0 ± 0.75	87.3 ± 0.81	85.1 ± 0.91
3	98.5 ± 0.53	96.1 ± 0.64	95.6 ± 0.72	94.1 ± 0.45	80.4 ± 0.66	76.6 ± 0.83
4	98.2 ± 0.93	95.6 ± 0.74	94.9 ± 0.81	93.1 ± 0.73	78.4 ± 0.78	77.7 ± 0.92
5	98.0 ± 0.92	94.0 ± 0.85	93.5 ± 0.75	86.2 ± 0.93	73.5 ± 0.85	72.3 ± 0.78
16	97.0 ± 0.82	—	—	—	—	—
20	—	93.4 ± 0.92	87.2 ± 1.20	—	—	—

2.2. Phenol disulfonic acid solution

Fifteen grams of colorless phenol was dissolved in 100 ml of concentrated sulfuric acid and heated for 5 h on a water bath. After cooling, it was kept in a closed bottle in the dark.

2.3. Standard KNO_3 solution

Exactly 80 mg of KNO_3 was weighed and transferred to a 100 ml volumetric flask. After dissolving in 1 ml distilled water, the solution was made to volume by glacial acetic acid.

2.4. Standard curve preparation

Different volumes (0.5, 1, 1.5 and 2 ml) of KNO_3 solution were sampled into a 100 ml volumetric flask containing 2 ml phenol disulfonic acid solution. After mixing, it was left for 15 min. at the room temperature. Then, 50 ml distilled water and 10 ml ammonia were added and brought to volume by distilled water. The absorbance of the solution at 410 nm was measured against a blank.

2.5. TNG in PEG 400 solution

TNG (200 mg) was mixed with PEG 400 in a volumetric flask and made to 100 ml with PEG to have a solution of 2 mg TNG/ml PEG.

2.6. General procedure

Two ml of TNG/PEG (2 mg/ml) was transferred into each of 18 test tubes numbered in triplicate by 0, 1, 2, 3, 4 or 5. One set was left at the room temperature and the other set was transferred to an autoclave at 40 ºC. After 1, 2, 3, 4, and 5 h, they were taken out of the autoclave and kept with blanks at the room temperature. The above procedure was repeated exactly at 50, 60, 70, 80 and 90 ºC. After equilibration of the solution temperature with the room temperature, the analysis of the remained TNG in the samples was performed.

2.7. Analytical procedure

Each sample (0.4 ml) was transferred to a 25 ml volumetric flask and phenol disulfonic acid (2 ml) was added and left at the room temperature for 15-30 min. After adding distilled water (10 ml), it was made to volume by ammonia solution. The absorbance of the formed yellow color was measured at 410

Table 2. The reaction rate constant (k) for the thermal decomposition of TNG/PEG at different temperatures.

Temperature (ºC)	**Reaction rate constant (k)**	**log k**
5	1.47 x 10-5	- 4.83
20	7.94 x 10-5	- 4.18
40	6.50 x 10-4	- 3.18
50	3.57 x 10-3	- 2.45
60	4.70 x 10-3	- 2.33
70	3.00 x 10-2	- 1.52
80	6.20 x 10-2	- 1.21
90	6.50 x 10-2	- 1.18

nm with a Bausch and Lomb spectrophotometer.

3. Results and discussion

The most significant property of the nitrate esters is violent detonation on slight shock. More than enough oxygen is present to convert the carbon and hydrogen into the corresponding oxides, with liberation of elemental nitrogen [4]. None of the decomposition products such as N_2, CO_2 and H_2O interfere with TNG analysis by spectrophotometry. TNG is decomposed at 50-60 ºC, appreciably volatile at 100 ºC, evolves nitrous yellow vapors at 135 ºC, and explodes at 218 ºC [5]. In a previous study, the predicted stability for a PEG 400 solution of TNG in term of its 10% decomposition (90% remaining) at 25 ºC was approximately 7 days [6], but the stability at 5 ºC was not investigated. Various analytical procedures for the determination of TNG were reported such as spectrophotometry and high performance liquid chromatography [6-8].

To measure the stability of TNG in PEG at the room temperature and at 5 ºC, the reaction rate constant (k) at the required temperatures is necessary. For this purpose, primarily the percentage of TNG/PEG 400 remained at various temperatures (40-90 ºC) for different periods of times was measured (Table 1) by using the phenol disulfonic acid method [8]. Then, the reaction rate constant (k) of TNG/PEG 400 was calculated for different temperatures (40–90 ºC) (Table 2). The following equation was applied to calculate k at different temperatures:

$$k = \frac{2.303}{t} \log Co/C \quad \text{equation 1}$$

in which "t" is the time interval between the original concentration (Co) of TNG and the remaining concentration (C) at some time later. By plotting log k against 1/T, the constant "k" at 20 ºC and 5 ºC was measured (1.47×10^{-5} and 7.94×10^{-5}, respectively) by extrapolating the straight line such as shown in Figure 1. Because TNG is usually kept in the cold (refrigerator) during marketing, therefore, its expiration date should be calculated on the basis of decomposition at 5 ºC. In this respect and by substituting "k" in equation 1, the time necessary for the remaining percentage of TNG at a specified temperature was obtained (Table 3). From this study, the expiration time for TNG/PEG 400 is estimated to be about 33 months.

Table 3. Comparison of the stability of TNG in PEG 400 at 5 ºC and 20 ºC.

Temperature (ºC)	Period of time (months) for remaining TNG/PEG (%)			
	90 %	**80 %**	**70 %**	**50 %**
20	1.82	3.85	ND	11.96
5	9.76	20.7	33.0	64.2

ND: not detected

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