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IMPLICATIONS OF PEROXIDE FORMATION IN LOTION AND OINTMENT DOSAGE FORMS CONTAINING POLYETHYLENE GLYCOLS

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ABSTRACT

The influence of various factors on the formation rate of peroxide-like impurities in polyethylene glycols was studied. Conditions of high temperature and agitation increased this rate. Varying formation rates were found with glycols from different manufacturers and this seemed to be related to the initial level of peroxide impurity. Aged samples generated peroxides at a faster rate than glycols recently acquired from a manufacturer. Peroxides were an intermediate in the degradation of glycols to carboxylic acids. It is suggested that an atmosphere of nitrogen be used when solubilizing drugs in glycols at high temperatures. The mixing of polyethylene glycol 1500 at 70° with white petrolatum, resulted in a rapid decrease in peroxide content in the glycol and improved the stability of oxidizable drugs in ointment formulations containing glycol and petrolatum.

INTRODUCTION

The solubilizing properties of polyethylene glycols for hydrophobic drugs are well known and these properties have been utilized in several pharmaceutical formulations. However, like many polyoxyethylene non-ionic surfactants, polyethylene glycols are susceptible to autoxidation. In an earlier report (1), the poor stability of an experimental topical steroid in different samples of polyethylene glycol 300, was related to the levels of peroxide impurity in the glycol sample. Glycols from different manufacturers were found to have varying peroxide impurity levels.

The stability of drugs in polyoxyethylenic vehicles has been the subject of many investigations. Whitworth et al. (2,3) have demonstrated that the instability of aspirin in polyethylene glycol was due in part to a transesterification reaction between the aspirin and the polyethylene glycols. Recently Hamburger and co-workers (4) reported that the degradation of benzocaine hydrochloride in aqueous cetomacrogol solution was due to the development of peroxides. The stability of several antibacterial agents in glycol vehicles has been studied by Coates et al. (5). In this investigation, penicillin and bacitracin were rapidly destroyed in polyethylene glycols. The stability of chloramphenicol (6) and hydrocortisone (7) also declined in glycol vehicles, whereas Boden and Taub (8) suggested polyethylene glycol 400 as a stabilizing solvent in parenteral pentobarbital sodium solutions. The degradation of tripelennamine hydrochloride in polyethylene glycol 300 was reported by Boon and Mace (9) to be dependent on the concentration of ethylene oxide in the vehicle.

Although transesterification and ethylene oxide catalysed degradative mechanisms have been suggested, a survey of the literature

indicated that autoxidation, primarily due to peroxide formation is the most common pathway of drug degradation in formulations containing polyethylene glycols.

This present study was undertaken to investigate the various process factors which influence peroxide formation in polyethylene glycols. In addition, a method is reported which overcomes the instability of oxidizable drugs in polyethylene glycol when incorporated into white petrolatum ointment formulations, without adding antioxidants or chelating agents.

METHODS

Unless otherwise stated, the glycol samples were mechanically stirred in a one liter conical flask immersed in a constant temperature oil bath. The polyethylene stirrer was maintained at a constant depth of 2 cm below the surface of the melted glycol. The levels of peroxide impurity in the glycol were determined by reacting an acidified potassium iodide solution with the glycol for 45 minutes in the dark and titrating the liberated iodine with standard sodium thiosulfate solution. Since the nature of the oxidant (peroxide, N-oxide or peroxide-like material) is unknown, misconception is avoided by expressing the levels of impurity as microequivalents of thiosulfate per gram of sample, as in the following equation (10):

$$P = \frac{T \times N}{PG} \times 10^3$$

where P is the peroxide content expressed as microequivalents of thiosulfate per gram of polyethylene glycol; T is the number of milliliters of thiosulfate for the sample titration minus, the blank titration; N is the normality of the standardized thiosulfate, and PG is the number of grams of polyethylene glycol. Polyethylene glycol 1500 used in the ointment studies was separated from white

petrolatum by allowing the withdrawn sample to settle with no agitation. When the sample was cooled to R.T., the upper petrolatum phase was removed and the lower glycol phase was assayed for peroxide content. All values reported are the average of at least duplicate assays.

RESULTS ND DISCUSSION

The rate of dissolution of steroids and other slowly soluble hydrophobic drugs in polyethylene glycols can be increased by increasing the temperature and agitation conditions. The degradation of glycols via autoxidation has been known for several years (11). Data in Fig. 1 display the breakdown of polyethylene glycols at elevated temperature.

Data in Fig. 2 show peroxide formation from three different lots of polyethylene glycol 400, all from the same manufacturer. It was apparent that the rate of formation of impurity was related to the initial amount of peroxide in the sample. However the rate of peroxide formation in II and III did not increase to that of sample I once the initial levels of I were surpassed. This would suggest that the initial level of peroxide was related to the concentration of some catalyst e.g. metal ions, in the glycol, that is responsible for peroxide formation. This relationship in Fig. 2, however, did not hold when glycol samples from different manufacturers were compared.

The influence of stirring rate on peroxide formation is reported in Fig. 3. As agitation conditions increased, then the levels of impurity also increased. It should be noted that with no agitation, the rate of peroxide formation was decreased. The influence of both heat and oxygen on the degradation of polyethylene glycols is seen in Fig. 4. The rate of formation of peroxide impurities was decreased when air was not stirred into the glycol. Peroxide levels were reduced

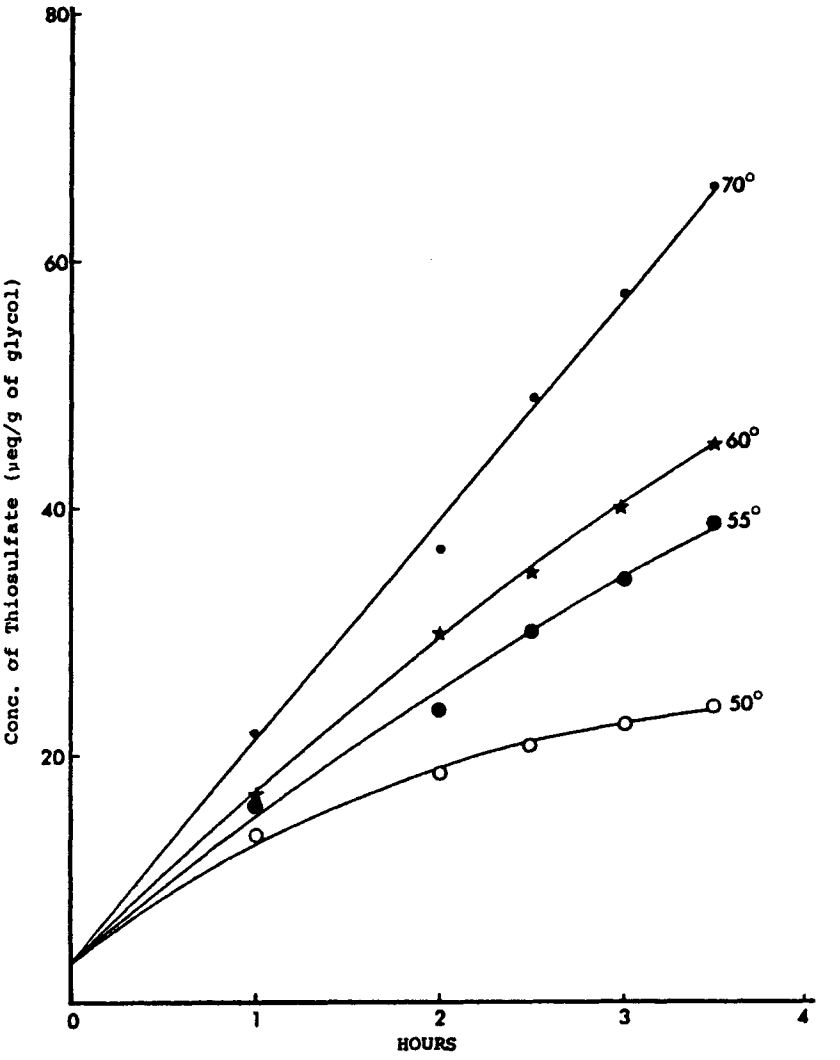


Figure 1

Influence of temperature on peroxide formation in polyethylene glycol 1500 agitated at 250 rpm.

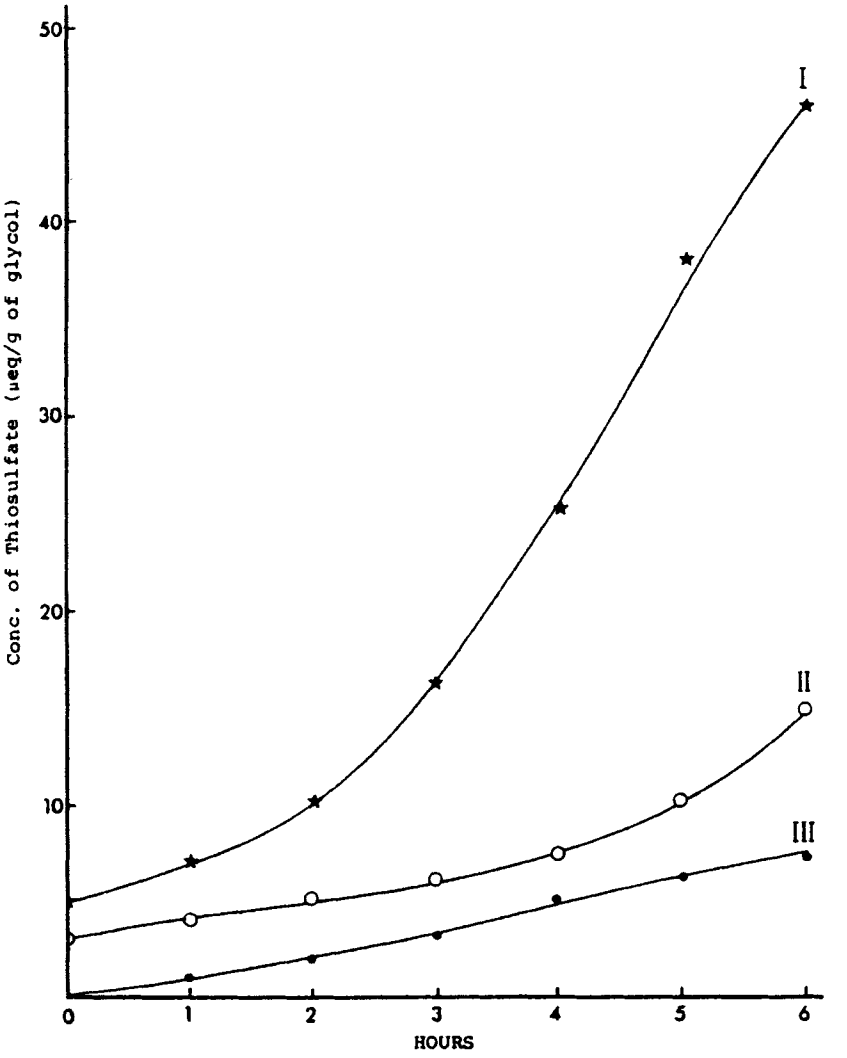


Figure 2

Peroxide formation in three different samples of polyethylene glycol 400, all from the same manufacturer, heated at 60° and agitated at 250 rpm.

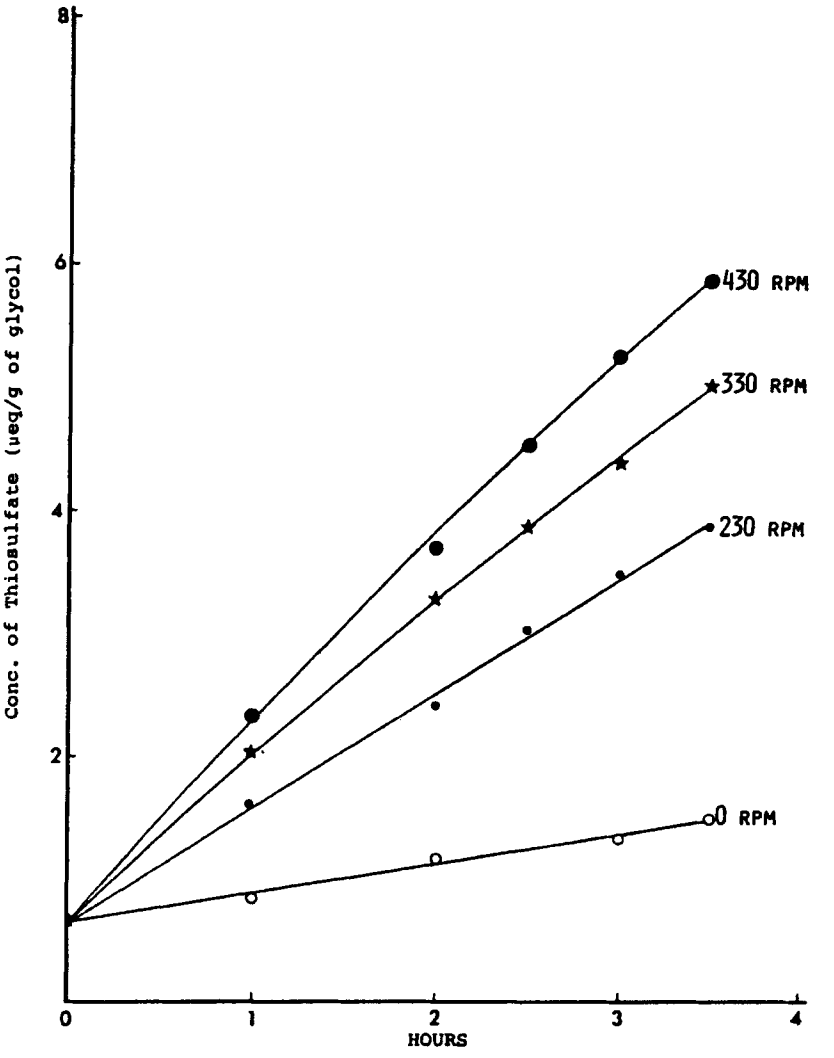


Figure 3

Peroxide formation in polyethylene glycol 1500, heated at 60° under varying agitation conditions.

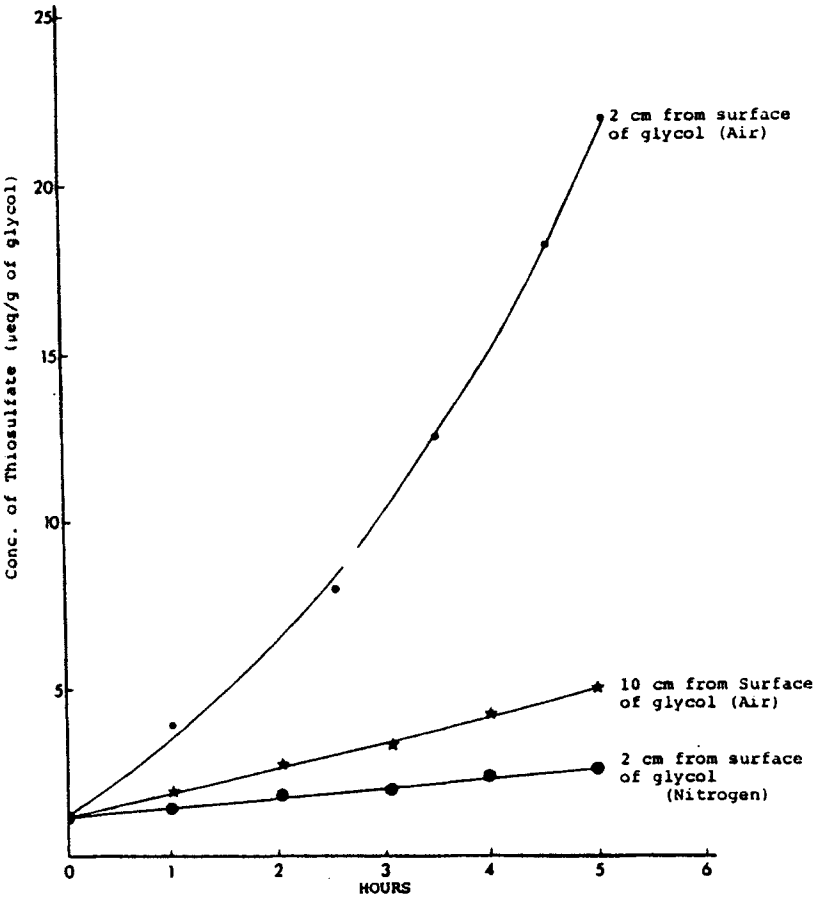


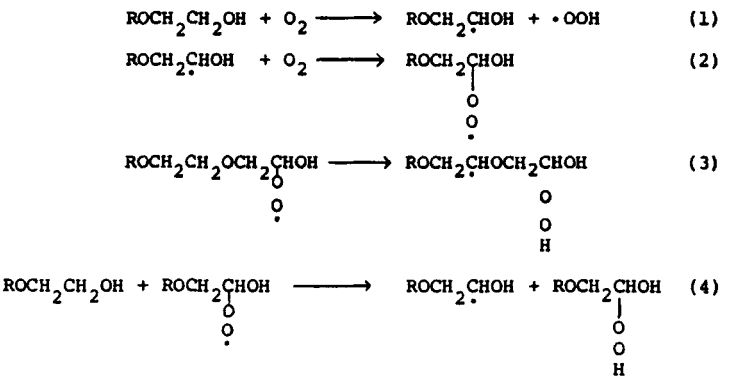
Figure 4
Influence of depth of the stirrer blade on peroxide formation in polyethylene glycol 1500 heated at 60° and agitated at 250 rpm, under an atmosphere of air or nitrogen.

further by purging the medium with nitrogen and maintaining an atmosphere of nitrogen above the glycol. The influence of oxygen was also apparent when several semi-solid polyethylene glycols were

randomly assayed. Glycol samples from the surface contained up to ten times the peroxide levels compared to samples assayed from the bottom of the container. This phenomenom was only evident in aged samples (3 to 8 years) and was not observed in polyethylene glycols recently purchased from the manufacturer. The formation rate of peroxides and initial levels of impurity were lower in fresh samples of glycols, than in aged samples, as seen in Fig. 5. Although it would appear from Fig. 5 that degradation is related to the molecular weight of the glycol this was not the case for glycols from other manufacturers. However this influence of age on the formation rate of peroxide was evident with glycols from all manufacturers. As noted previously by the authors (1), a small quantity of hydrogen peroxide had been added by a manufacturer to its polyethylene glycols to maintain a water clear product. No glycols from that manufacturer were utilized in this present study.

Data in Fig. 6 demonstrate the influence of heat and agitation for an extended period of time. All three samples showed a decline in peroxide levels after a peak was attained. Other samples however, not shown in Fig. 6, plateaued after 3 or 4 days and showed a gradual decline in peroxide after 10 to 15 days.

The following pathway of degradation was reported by McKenzie (12).



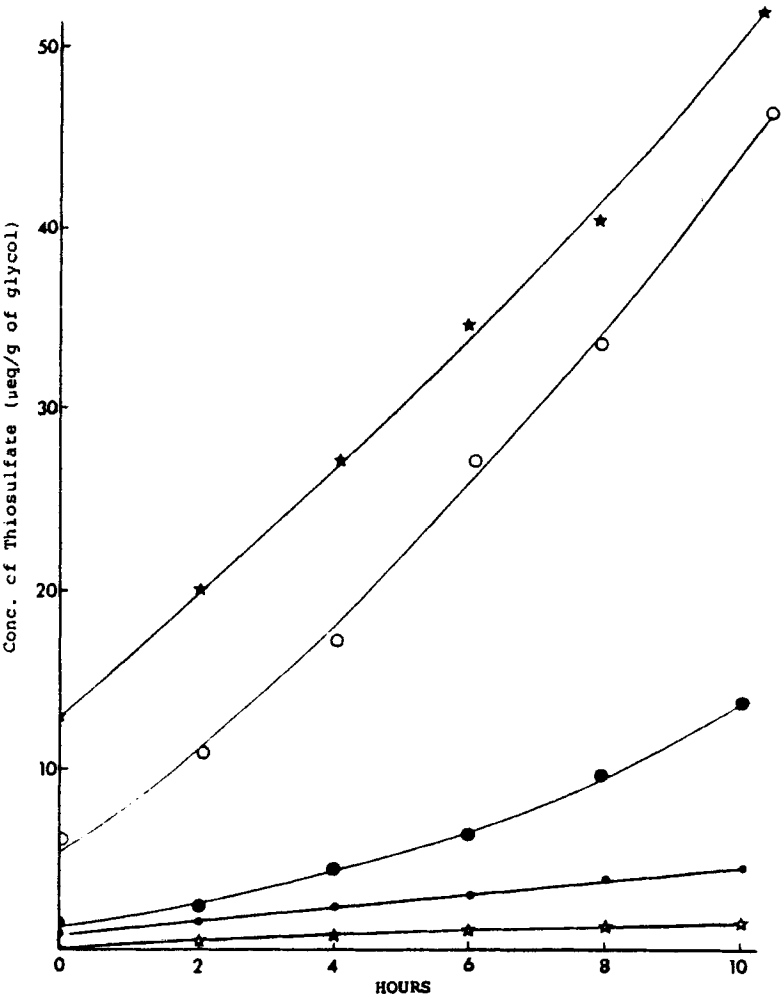


Figure 5

Peroxide formation in new (lower three curves) and aged samples of polyethylene glycols heated at 60° and agitated at 250 rpm.

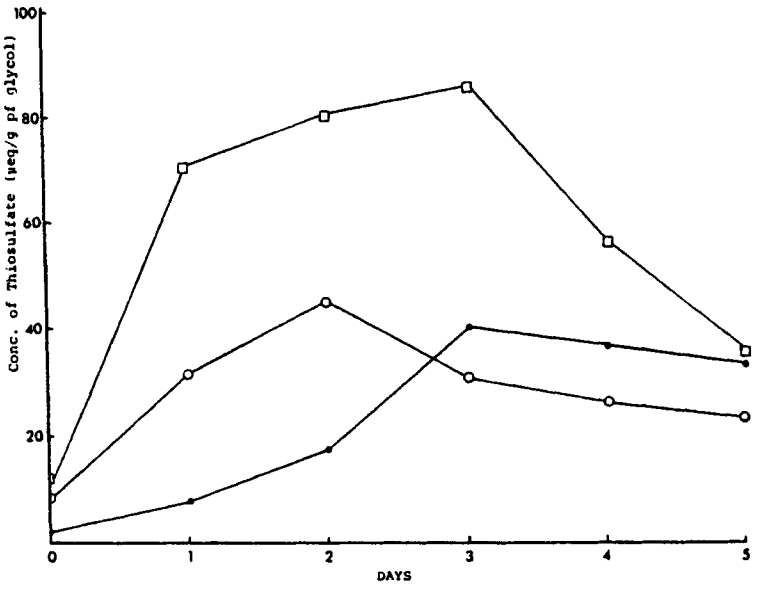


Figure 6

Influence of temperature on three samples of polyethylene glycol 1500 maintained at 60° and agitated at 250 rpm for five days.

This heat instability of peroxides indicated that the peroxide impurities are intermediates in the degradation of glycols to carboxylic acid. Formation of carboxylic acids was followed in the samples in Fig. 6 by titrating the diluted glycol solution with standard sodium hydroxide. In all cases, there was a gradual increase in acidity of the glycol. This suggested that for glycol samples where peroxide formation plateaued for several days, the rate of formation of peroxide approached the rate of degradation of the carboxylic acid. It is obvious then that this gradual decline in pH of the vehicle would have serious implications on the stability of drugs susceptible to acid catalysed hydrolysis.

The problem of autoxidative degradation of steroids in lotion formulations containing polyethylene glycols, was also experienced with ointment formulations. The stability of an experimental topical corticosteroid in polyethylene glycol 1500 - white petrolatum ointment formulations (1:9) has been shown in these laboratories to be influenced by the method of manufacture of the ointment. When the steroid was dissolved in hot polyethylene glycol 1500, cooled to room temperature and mixed with the petrolatum, 30% of the drug degraded after 3 weeks at 40°. On the other hand, when the hot petrolatum (70°) was added to the melted glycol vehicle containing the dissolved steroid and the mixture agitated at 400 rpm to room temperature, then chemical stability was maintained. Less than 2% drug had degraded under the same storage conditions. However after approximately 6 months, the rate of degradation steadily increased. With this latter method, peroxides were believed to be removed by petrolatum via either partitioning or reacting with components of the petrolatum. Using a 1:1 ratio of polyethylene glycol 1500 and white petrolatum, approximately 70-90% of the peroxide impurities were removed from the glycol during the initial 10 min of mixing, as seen in Fig. 7. The increase in peroxide levels following the minima suggests that as more peroxide was formed, the removal process of the petrolatum became saturated as levels in the glycol increased. Preliminary data with other ointments indicate that as the content of petrolatum was increased, the initial partitioning rate of the peroxide increased and subsequent appearance of peroxide in the glycol phase was correspondingly decreased. It should also be mentioned that in the final ointment product the glycol would be dispersed in the petrolatum, and autoxidation under these conditions would be expected to be minimal. These investigations are being continued

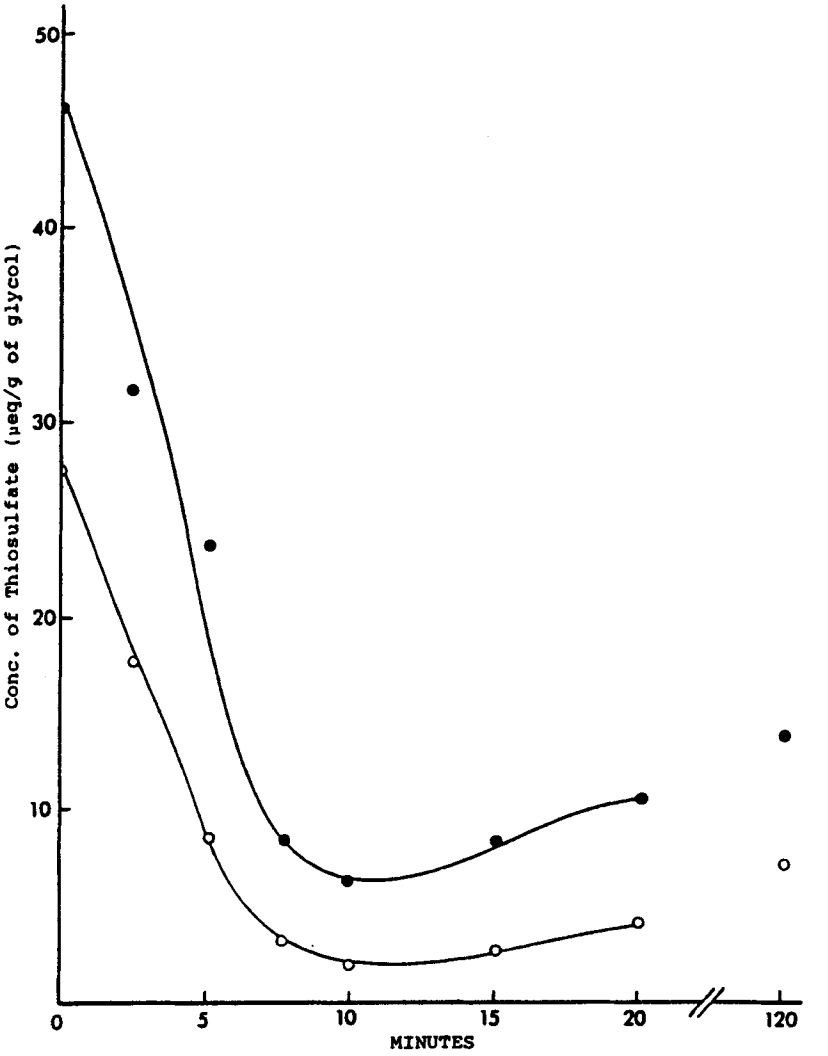


Figure 7

Influence of white petrolatum on peroxide levels in polyethylene glycol 1500 when mixed in a 1:1 ratio at 70° and agitated at 250 rpm.

with white petrolatum from different manufacturers and results will be reported at a later date.

CONCLUSIONS

The breakdown of glycols to peroxides was studied under a variety of experimental conditions. Age, temperatures, oxygen and source of supply of the polyethylene glycols were shown to be influential factors in glycol stability.

The formation of peroxide impurities in liquid and semi-solid formulations containing polyethylene glycol may markedly influence stability of an active ingredient. In order to avoid these problems the authors suggest the formulator to use the highest quality glycols and employ an atmosphere of nitrogen during production. Along with drug stability, monitoring the peroxide and acid levels in the formulation during long term stability studies is recommended.

It has been shown that polyethylene glycols from different suppliers, may produce varying stability data for formulations containing this vehicle. Varying impurity levels of glycols may possibly account for large discrepancies in penicillin stability in glycol mixtures, as reviewed by Coates and coworkers (5).

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Inquiries should be directed to JWM.

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