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# The influence of Azone, propylene glycol and polyethylene glycol on in vitro skin penetration of trifluorothymidine

Nitin V. Sheth [1,2], Donna J. Freeman [1], William I. Higuchi [2] and Spotswood L. Spruance [1]

[1] *Center for Infectious Diseases, Diagnostic Microbiology and Immunology and the Division of Infectious Diseases, Department of Medicine, School of Medicine; and* [2] *Department of Pharmaceutics, College of Pharmacy, University of Utah, Salt Lake City, UT 84132 (U.S.A.)*

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## Summary

Topical formulations of the antiviral compound trifluorothymidine (TFT) were prepared with different proportions of Azone, propylene glycol (PG), polyethylene glycol (PEG-300) and/or water and evaluated by measuring in vitro diffusion of TFT through excised guinea pig skin. Azone dramatically increased drug flux. With 5% Azone in the vehicle, TFT flux values increased 3–4-fold as the ratio of PG : PEG-300 in the vehicle went from 0 : 100 to 100 : 0. In experiments without Azone, the TFT penetration rate in PG was 4-fold greater compared to water and 17-fold greater compared to PEG-300. In summary, Azone and PG both enhanced membrane permeability relative to water and acted synergistically on the penetration of the antiviral compound, while PEG-300 appeared to be less efficient than water as a vehicle.

## Introduction

5-Trifluoromethyl-2′-deoxyuridine (trifluorothymidine, trifluridine; TFT) is a structural analogue of the natural deoxyribonucleoside, thymidine, and a potent inhibitor of herpes simplex virus (HSV) (Heidelberger and King, 1979). The major therapeutic use of TFT has been in the topical treatment of HSV keratitis as a 1% ophthalmic solution (Viroptic, Burroughs-Wellcome) (Carmine et al., 1982). Success with TFT in the treatment of HSV corneal disease suggests that this drug may be useful as a topical therapeutic agent for other HSV infections of the epithelium such as herpes labialis and genitalis.

In previous studies, a marked enhancement of the penetration of TFT through excised guinea pig and human skin has been demonstrated in the presence of 1-dodecylazacycloheptan-2-one (Laurocapram, Azone) (Spruance et al., 1984). Azone is an agent which enhances the percutaneous absorption of a number of different chemicals such as antibiotics, glucocorticoids and fluorouracil (Stoughton, 1982; Stoughton and McClure, 1983). The optimum concentration of Azone varies with both the drug and the formulation being examined, however, concentrations of 2–10% appear to be appropriate for most formulations (Stoughton and McClure, 1983). The structural formulae for TFT and Azone are shown in Fig. 1.

*Correspondence*: S.L. Spruance, Division of Infectious Diseases, University of Utah, Salt Lake City, UT 84132, U.S.A.

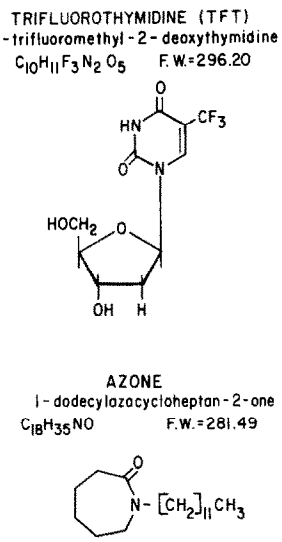


Fig. 1. Structural formulae of TFT and Azone.

Our prior studies were performed with formulations containing various percentages of TFT and Azone in a mixed vehicle of propylene glycol (PG) and polyethylene glycol (PEG). We also observed that enhanced penetration of TFT was associated with high concentrations of PG in the presence of a fixed percentage of Azone. This interesting finding suggested an interaction between Azone and PG.

The purpose of the present study was to examine the nature and extent of the possible interaction of PG and Azone on the barrier properties of skin. We considered that PG might have a direct effect on the stratum corneum or it might affect the penetration of TFT by altering the solubility of Azone or TFT in the formulation. A series of vehicles containing different proportions of PG and PEG-300 was prepared. The solubility of TFT in these vehicles was then determined and the penetration of TFT from these vehicles through excised guinea pig skin was examined with Franz single-chambered glass diffusion cells.

## Materials and Methods

*Skin*

Hartley strain, outbred, female albino guinea pigs, 200–250 g each, were obtained from Charles River Breeding Labs, Wilmington, MA. The animals were sacrificed with ether and close-shaved with electric clippers. Two to four 3 × 3 cm specimens of full-thickness skin were removed from the back by dissection. The skin was clamped into glass diffusion cells and used in an hour as described below.

*Drug formulations*

TFT and Azone were obtained from Allergan Pharmaceuticals, Irvine, CA. PG and PEG-300 were obtained from Sigma Chemicals, St. Louis, MO. [$^3$H]TFT was supplied by Moravek Biochemicals, Brea, CA. The specific activity was 15 Ci/mmol and the concentration was 15 mCi/ml. The radiolabeled compound was > 98% pure as determined by thin-layer chromatography (TLC) (Spruance et al., 1984). Radiolabeled formulations of TFT were prepared by stirring 5 μl of [$^3$H]TFT with 2 ml of each of the liquid test formulations. The subsequent activity of the formulations was 20–40 cpm/μg TFT.

*Solubility determinations*

The solubility of TFT in different solutions was determined utilizing [$^3$H]TFT. Labeled TFT was prepared by dissolving 3 g of unlabeled TFT in 10 ml of methanol, adding 5 μl of [$^3$H]TFT and stirring the solution for 3 h to ensure uniform mixing. This solution was then allowed to evaporate slowly to a powder at 37°C over a period of 2 days. An aliquot was examined in a Beckman liquid scintillation counter to determine the specific activity. In selected experiments, [$^3$H]TFT for solubility studies was prepared by recrystallization. Six grams of TFT and 5 μl of [$^3$H]TFT were dissolved in 25 ml of methanol at 45°C. Ten ml of cold water was added slowly and crystals allowed to form overnight at room temperature. The crystals thus obtained were filtered through Whatman filter paper No. 1 (American Scientific Products, McGaw Park, IL) and washed 3 times with 10 ml of chilled water to remove impurities. The crystals were then dried at room temperature for 24 h and excess moisture removed by heating at 110°C for half an hour. Recrystallized TFT was examined by TLC and found to be 99.7% pure.

The solubility of TFT in different vehicles was determined by mixing 200–500 mg of solid [$^3$H]TFT of known specific activity in a stoppered test tube with 2 g of vehicle. The solution was mixed by vortexing for 5 min and then agitated with a mechanical shaker for 5 days at 37°C in a water bath until equilibrium was attained. Samples were then withdrawn and clarified by passage through a Millipore filter with an average pore size of 0.22 μm (Millipore, Bedford, MA). Radioactivity in the filtrate of each sample was then measured with the liquid scintillation counter.

*In vitro drug diffusion experiments*

Franz single-chamber glass diffusion cells (Crown Glass, Somerville, NJ) were used in this study. The receiver chamber has a volume of 7 ml and was filled with 0.15 M NaCl, 0.01% thimerosal (Sigma Chemicals, St. Louis, MO). Guinea pig skin was clamped across a 1.6 cm diameter opening at the top of the cell with the stratum corneum facing upwards. The receiver chamber was kept at 37°C by circulating water through an external jacket. There is a single port for withdrawal of samples from the receiver chamber, and stirring was achieved with an elongated magnetic stir bar constructed to our specifications by the Division of Artificial Organs, University of Utah. The exposed skin surface was enclosed on the sides by a small upper chamber. One-hundred μl of drug solution was applied onto the stratum corneum at time zero and the upper chamber was then sealed with parafilm. Two-hundred μl samples were withdrawn from the receiver chamber at intervals and replaced with 200 μl of fresh receiver solution. The samples were then assayed for radioactivity in the scintillation counter.

In selected experiments, excised guinea pig skin was pretreated with Azone before exposure to TFT. One-hundred μl of undiluted Azone was applied to the stratum corneum. After 6 h, the excess Azone was wiped off with tissue paper and the antiviral formulation applied thereafter.

*Computations and statistics*

The specific activity of each formulation (cpm/μg TFT) was determined from the radioactivity of each formulation and the proportion of TFT. The activity of samples from the receiver chamber of the diffusion apparatus was converted from cpm/ml to μg/ml. The penetration of TFT through skin was then described by a plot of μg TFT/ml vs time in hours. The slope of the curve and the intercept on the x-axis (lag time) were determined by linear regression. Drug flux (μg TFT/cm$^2$ · h) was calculated from the slope (μg TFT/ml · h), the volume of the receiver chamber (ml), and the area of the skin surface through which diffusion was taking place (cm$^2$). Comparisons were made with Student's *t*-test. All probabilities were two-tailed and $P \leq 0.05$ was considered significant.

## Results

*Solubility determinations*

The solubility of TFT at 37°C in different proportions of PG and PEG-300 with and without 5% Azone is reported in Table 1. The solubility of TFT was essentially the same for these solutions. Solubility studies of TFT in a PG : water vehicle system were performed with recrystallized TFT (Table 2). For the solutions of PG and water, the solubility of TFT increased with increasing proportions of PG in the vehicle. The solubility of TFT in PG and PEG-300 was two-fold greater than the solubility in water (Tables 1 and 2).

*In vitro studies of TFT diffusion through excised guinea pig skin*

The penetration of 5% TFT through excised

TABLE 1
SOLUBILITY OF TFT IN DIFFERENT PROPORTIONS OF PG AND PEG-300 WITH AND WITHOUT AZONE

| Proportions of vehicle constituents (PG : PEG-300) (PG : PEG-300) | Solubility of TFT without Azone (% w/w) | Solubility of TFT with 5% Azone (% w/w) |
|---|---|---|
| 0 : 100 | 11.1 ± 1.8 [a] | 12.4 + 2.7 |
| 10 : 90 | 12.2 ± 1.8 | 13.0 ± 2.8 |
| 35 : 65 | 14.2 ± 0.5 | 13.4 ± 1.4 |
| 60 : 40 | 15.4 ± 1.4 | 14.0 ± 1.5 |
| 85 : 15 | 13.3 ± 1.2 | 13.3 ± 0.9 |
| 100 : 0 | 12.1 ± 0.7 | 12.2 ± 0.4 |

[a] Means ± S.D., n = 3–6, at 37°C.

TABLE 2
SOLUBILITY OF TFT IN DIFFERENT PROPORTIONS OF PG AND WATER

| Proportions of vehicle constituents (PG : water) | Solubility of TFT (% w/w) |
|---|---|
| 0:100 | 6.5 ± 0.4 [a] |
| 20:80 | 6.8 ± 0.1 |
| 40:60 | 8.9 ± 0.3 |
| 60:40 | 11.9 ± 0.4 |
| 80:20 | 13.7 ± 0.4 |
| 100:0 | 13.0 ± 0.3 |

[a] Means ± S.D., n = 3–6, at 37°C.

guinea pig skin from different vehicle systems was studied in Franz single-chamber glass diffusion cells at 37°C by measuring the concentration of TFT in the receiver chamber as a function of time. The effects on TFT penetration of changing proportions of PG and PEG-300 with 5% Azone in the formulation are shown in Fig. 2. The plot indicates that the data are linear over all but a few of the last points and significant depletion of the drug reservoirs did not occur. We assumed that the system was functioning as if the drug dose was infinite and applied Fick's law to analysis and interpretation of the data (Franz, 1983). The lag period and flux for each of the different vehicles are shown in Table 3. TFT flux increased 3-fold as the proportion of PG in the vehicle went from zero to 100%. The lag period was inversely related to flux and went from a high of 25.9 h in the absence of PG to 6.8 h with 100% PG. After 24 h, experiments with a vehicle containing 100% PG had a 22-fold greater concentration of TFT in the receiver chamber than when the vehicle contained 100% PEG-300 (438.8 vs 19.7 μg TFT/ml, $P < 0.001$).

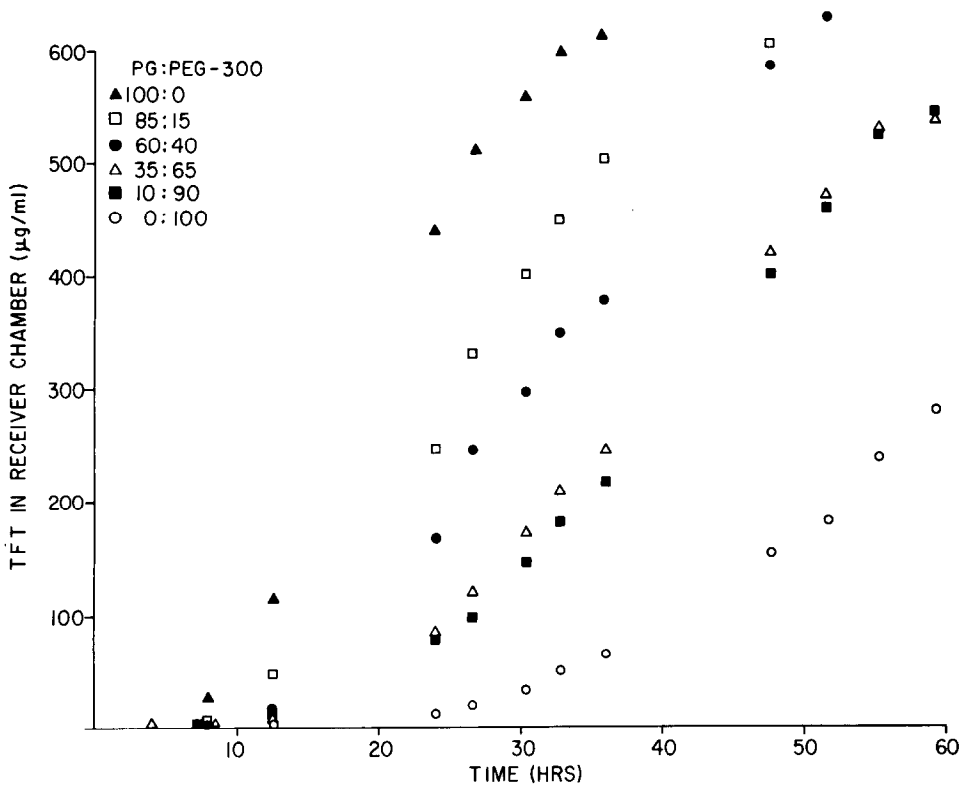


Fig. 2. Penetration of TFT through guinea pig skin *in vitro* from vehicles containing 5% Azone and different proportions of PG : PEG-300. 100 : 0 (▲), 85 : 15 (□), 60 : 40 (●), 35 : 65 (△), 10 : 90 (■), zero : 100 (○). Each point represents the mean of 3 experiments.

TABLE 3
PENETRATION OF 5% TFT (w/w) THROUGH GUINEA PIG SKIN IN VITRO IN VEHICLES CONTAINING 5-AZONE AND DIFFERENT PROPORTIONS OF PG AND PEG-300

| Proportions of vehicle constituents (PG : PEG-300) | Lag period (h) | Flux of TFT ($\mu g/cm^2 \cdot h$) |
|---|---|---|
| 0:100 | 25.9 ± 3.0 [a] | 29.9 ± 13.1 |
| 10:90 | 19.8 ± 0.8 | 44.1 ± 7.5 |
| 35:65 | 17.4 ± 1.4 | 47.1 ± 4.0 |
| 60:40 | 12.0 ± 1.0 | 55.6 ± 3.3 |
| 85:15 | 9.3 ± 2.1 | 72.1 ± 10.2 |
| 100:0 | 6.8 ± 0.7 | 91.0 ± 12.1 |

[a] Means ± S.D., n = 3, at 37°C.

Changes in the drug vehicle might alter the solubility of Azone, influence the delivery of Azone to the stratum corneum, and bring about the observed variations in the flux of TFT. To examine this possibility and to study aqueous vehicle systems in which Azone is insoluble, experiments were performed in which excised guinea pig skin was pretreated with undiluted Azone for 6 h prior to use in diffusion studies. Table 4 shows the results of studies with Azone-pretreated skin examining the flux of TFT from a 5% formulation in three different vehicle systems: PG : PEG-300, PG : water and water : PEG-300. For the PG : PEG-300 vehicles, the TFT flux values were 50–100% greater than for the same vehicles when Azone was in the formulation (Table 3), indicating that petreatment results in a greater Azone effect. Additionally, the lag times with Azone pretreatment were only 1–2 h (data not shown) compared with 6.8–25.9 h (Table 3), suggesting that the effect of Azone on the stratum corneum requires a period of time to become established. Increasing proportions of PG and less PEG-300 resulted in a 3.7-fold increase in TFT flux similar to that noted in the previous experiments when Azone was in the formulation, indicating that variable Azone solubility in the vehicle could not be an explanation for the effect.

Experiments with TFT in PG : water and water : PEG-300 systems (Table 4) were performed to demonstrate the individual contributions of PG and PEG-300 to TFT flux. In the PG : water system, flux rose by 30–40% as the concentration of PG was increased from zero to 100%. In the water: PEG–300 vehicle system, a 3-fold decrease in flux occurred as the concentration of PEG-300 went from zero to 100%.

To further examine the effect of PG and PEG-300 on drug flux, TFT was formulated in 100% PG, PEG-300 or water without pre-treatment of skin with Azone or Azone in the formulation. The flux of TFT through guinea pig skin in these three vehicles is reported in Table 5. TFT flux from PG was 4-fold higher than from water and 17-fold greater compared to PEG-300. Flux is propor-

TABLE 4
PENETRATION OF 5% TFT (w/w) THROUGH GUINEA PIG SKIN IN VITRO IN DIFFERENT VEHICLE SYSTEMS AFTER PRETREATMENT OF SKIN WITH AZONE

| Proportions of vehicle constituents | Flux of TFT ($\mu g/cm^2 \cdot h$) | | |
|---|---|---|---|
| | PG: PEG-300 | PG: Water | Water: PEG-300 |
| 0:100 | 48.3 ± 11.7 [a] | 141.2 ± 21.2 | 48.3 ± 11.7 |
| 10:90 | 50.0 ± 9.2 | 146.2 ± 6.4 | 59.1 ± 9.3 |
| 35:65 | 98.5 ± 23.5 | 147.1 ± 33.3 | 114.5 ± 8.4 |
| 60:40 | 102.4 ± 0.6 | 183.5 ± 91.0 | 112.0 ± 13.0 |
| 85:15 | 133.0 ± 0.9 | 198.0 ± 8.2 | 134.0 ± 28.1 |
| 100:0 | 180.9 ± 9.0 | 180.9 ± 9.0 | 141.2 ± 21.2 |

[a] Means ± S.D., n = 2–4, at 37°C.

TABLE 5
PENETRATION OF 5% TFT (w/w) THROUGH GUINEA PIG SKIN IN DIFFERENT VEHICLES WITHOUT AZONE

| Vehicle | Flux of TFT ($\mu g/cm^2 \cdot h$) | Thermodynamic activity of TFT [a] | Calculated maximum flux [b] ($\mu g/cm^2 \cdot h$) | Statistical probability ($p$) |
|---|---|---|---|---|
| PG | 2.54 ± 1.72 [c] | 0.42 | 6.36 ± 4.31 | 0.002 |
| Water | 0.63 ± 0.51 | 0.76 | 0.83 ± 0.68 | 0.09 |
| PEG-300 | 0.15 ± 0.08 | 0.45 | 0.34 ± 0.16 | |

[a] $C_0/C_s$, where $C_0$ is the TFT concentration in the vehicle (5%) and $C_s$ is the saturation solubility of TFT in the corresponding vehicle (Tables 1 and 2).
[b] Observed flux/thermodynamic activity.
[c] Means ± S.D., n = 7–11, at 37°C.

TABLE 6
PENETRATION OF 5% TFT (w/w) THROUGH GUINEA PIG SKIN IN VITRO IN VEHICLES CONTAINING 5% AZONE AT 25°C AND 37°C

| Proportions of vehicle constituents (PG: PEG-300) | Flux of TFT ($\mu g/cm^2 \cdot h$) | |
|---|---|---|
| | At 25°C | At 37°C |
| 10:90 | 7.7 ± 1.9 [a] | 44.1 ± 7.5 |
| 85:15 | 21.1 ± 4.9 | 72.1 ± 10.2 |

[a] Means ± S.D., n = 3.

tional to the thermodynamic activity of the drug in the vehicle (Higuchi, 1960), which may be approximated by the ratio of solute concentration to its saturation solubility in the vehicle (Coldman et al., 1969). The thermodynamic activity of TFT in water is higher than in PG or PEG-300 (Table 5). Maximum flux (observed flux/thermodynamic activity) has been used to describe the intrinsic permeability of a membrane to a specific penetrant (Michaels et al., 1975). Making the assumption that TFT flux would be proportional to the TFT concentration in the vehicle up to saturation, we calculated maximum flux for TFT in PG, PEG-300 and water (Table 5). Maximum TFT flux from PG was 8-fold greater than that from water and 19-fold greater than from PEG-300. Calculated maximum flux of TFT in water was two-fold higher than when PEG-300 was the vehicle, but this difference was of borderline statistical significance ($P = 0.09$).

To study the degree to which vehicle phenomena were affected by temperature, TFT in two different proportions of PG: PEG-300 with 5% Azone were studied at 25 and 37°C. The flux values are shown in Table 6. TFT flux values were 3–6-fold lower at 25°C than at 37°C. The temperature effect was more pronounced in the vehicle containing the higher percentage of PEG-300 (PG: PEG-300, 10 : 90).

## Discussion

We have investigated the effect of 5% Azone on the transcutaneous flux of TFT in different vehicle formulations. Solutions studied contained 5% Azone and 5% TFT in different proportions of PG, PEG-300 and/or water. The penetration-enhancing effect of Azone was augmented 3–4-fold in formulations containing 100% PG compared to 100% PEG-300.

Solubility studies and in vitro diffusion experiments with multiple combinations of vehicle constituents were performed to investigate the basis of the vehicle effect. TFT was soluble to a similar extent in different proportions of PG and PEG-300, making it most unlikely that a change in thermodynamic activity plays a role. High concentrations of PG were associated with increased drug flux whether skin was pretreated with Azone or Azone was in the formulation, excluding differential solubility of Azone as a cause. Studies of PG and PEG-300 separately were performed with and without Azone using water as the second vehicle constituent. Use of 100% PG was associated with a distinct increase in flux compared to water with and without Azone, and adjustment of flux for thermodynamic activity of the solutions only augmented the difference. These data indicate that PG directly alters the permeability of the stratum corneum to TFT. The effect of PG with Azone was 20-fold greater than without Azone in comparison with water (increase of 40 vs 1.9 $\mu g$ $TFT/cm^2 \cdot h$, Tables 4 and 5), indicating a synergistic rather than a simple additive interaction between the two penetration-enhancing agents. Conversely, the flux of TFT from PEG-300 was consistently less than from aqueous solution, and the difference was of considerable magnitude in the presence of Azone (Table 4). While much of the difference between TFT in water and PEG-300 may be attributed to the difference in thermodynamic activity (Table 5), the remaining discrepancy suggests a differential effect between water and PEG-300 on membrane permeability. In summary, augmentation of TFT flux in a vehicle system containing Azone, PG and PEG-300 is due to a synergistic action on stratum corneum permeability by Azone and PG. The effect of PG is dramatized by the comparison with PEG-300, a solvent which may be less efficient than water as a vehicle for the antiviral compound.

Previous studies with ointment formulations containing 5% Azone, 1% TFT at 25°C identified

that a PG : PEG proportion of 85 : 15 resulted in a 20-fold greater TFT flux than an ointment containing PG : PEG in a proportion of 10 : 90. The difference in flux was clinically significant in an animal model of HSV infection (Spruance et al., 1984). In the present studies, a difference in TFT flux between these vehicles were again observed at 25°C but was less marked (Table 6). The more marked vehicle effect in our previous study may be related to the use of ointments containing higher molecular weight PEG. A study by Davis et al. (1981) of different molecular weight PEG showed that high molecular weight PEG retarded the penetration of methyl salicylate. Another study by Maak and Zesch (1984) identified that liquid, low molecular weight PEG penetrated human skin better than solid, high molecular weight PEG.

A number of reports have described PG as a penetration enhancer for the transport of various corticosteroids (Barret et al., 1965; Busse et al., 1969; Christie and Moore-Robinson, 1970; Pepler et al., 1971; Polano and Pone, 1976; Portney, 1965). In these studies, a small quantity of PG was used to partially or completely solubilize the drug. Poulsen et al. (1968) showed that the maximum release rate of 0.025% fluocinolone acetonide or fluocinolone acetonide acetate was obtained from a vehicle containing a sufficient amount of PG to solubilize the steroid completely: 20% PG for fluocinolone acetonide and 75% PG for its ester. Concentrations of PG higher than that required to solubilize each drug decreased the drug release. Similar findings were obtained with hydrocortisone (Shahi and Zatz, 1978; Feldmann and Maibach, 1966). The present study has documented that the skin penetration rate of TFT is maximal in 100% PG. Mollgaard and Hoelgaard (1983) showed that 100% PG enhanced the penetration of estradiol and metronidazole and Feldmann and Maibach (1966) demonstrated that undiluted PG enhanced the penetration of testosterone.

The varied action of PG on the penetration of different drugs may be due to differences in drug solubility. A low drug concentration with high drug solubility in PG and resultant adverse partitioning of the drug is presumably the factor responsible for decreasing the release rate of corticosteroids from vehicles containing a high concentration of PG (Ostrenga et al., 1971; Poulsen et al., 1968; Shahi and Zatz, 1978; Feldmann and Maibach, 1966). In the present study, the increased penetration rate of drug at high concentrations of PG is likely due to an increase in the permeability coefficient of the skin while a high concentration of TFT relative to solubility prevented a decrease in penetration from adverse partitioning. Various theories have been proposed for the mechanism of action of PG on skin permeability. Since PG penetrates into the layers of the skin, a 'carrier' mechanism has been postulated in which PG carries the drug through the barrier layer (Busse et al., 1969; Mollgaard and Hoelgaard, 1983; Polano and Ponec, 1976). Others have hypothesized that PG alters the barrier properties of stratum corneum (Idson, 1975, 1983; Sarkany and Hadgraft, 1969; Shelly and Melton, 1949).

In contrast to PG, polyethylene glycol (PEG) has been uniformly reported to be a relatively poor vehicle for the penetration of salicylic acid (Stolar et al., 1960), methyl nicotinate (Barret et al., 1964), various corticosteroids (Barret et al., 1965; Brode, 1968; Pepler et al., 1971; Sarkany et al., 1965; Tissot and Osmundsen, 1966), dithranol and triacetyl derivative (Kammerau et al., 1975), various polar and non-polar alcohols (Blank, 1964) and phenols (Schutz, 1957). Furthermore, an increase in the molecular weight of PEG resulted in a lower penetration rate for methyl salicylate (Davis et al., 1981), and the penetration of PEG into skin was reported to be inversely proportional to molecular weight (Maak and Zesch, 1984). The effect of PEG on skin penetration has been postulated to be due to a 'drug–vehicle interaction' resulting in a lower thermodynamic activity of the drug (Davies et al., 1981; Hadgraft, 1983; Higuchi, 1960; Shelly and Melton, 1959; Stolar et al., 1960). Others have suggested that the effect of PEG is due to a change in the microviscosity of the vehicle (Davis et al., 1981; Hadgraft, 1983) and also to its inability to hydrate the stratum corneum or to its osmotic effect which tend to dehydrate the stratum corneum (Barrett et al., 1964).

These investigations have confirmed that constituents of the drug vehicle in addition to Azone can strongly influence drug diffusion. Further

studies of the mechanism of action of PG and PEG-300 are in progress.

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