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# Effect of Tocopheryl Polyethylene Glycol Succinate on the Percutaneous Penetration of Minoxidil from Water/Ethanol/Polyethylene Glycol 400 Solutions

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**ABSTRACT** We described to achieve the local retention of minoxidil which has penetrated the skin with minimization of its absorption into the general circulation and elimination of local irritation induced by propylene glycol. The effect of tocopheryl polyethylene glycol succinate (TPGS) on the penetration flux of minoxidil and its retention in the skin from topical minoxidil formulations consisting of water, alcohol, and polyethylene glycol 400 was characterized by an experimental design of ten solvent formulations in this study. Results show that the addition of TPGS was only able to improve the solubility of minoxidil in those solvent systems containing higher proportions of water and PEG 400, and the extent of improvement was also more profound with the addition of TPGS at concentrations higher than 5%. For those solvent systems containing a higher fraction of alcohol, an insignificant change in minoxidil solubility with increasing added amounts of TPGS was noted even with the tendency to decrease the solubility of minoxidil with higher amounts of TPGS. Increasing the amount of TPGS added gradually increased the flux and the corrected flux from solvent formulations with a lower solubility parameter, but decreased those from solvent systems with a higher solubility parameter. With the addition of TPGS, solvent formulation F6 (alcohol:PEG 400 of 50:50) was demonstrated to be the optimal choice by having an improved local effect and a reduced systemic effect compared to the reference of 2% Regaine®. Tocopheryl polyethylene glycol succinate (TPGS) was mainly retained locally in the stratum corneum, and the amount was proportional to the increase in the amount of TPGS added to these ten solvent formulations.

**KEYWORDS** Minoxidil, TPGS, Penetration, Solubility, Regaine®

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## INTRODUCTION

Minoxidil is a pyrimidine derivative (2,4-diamino-6-piperidinopyrimidine-3- oxide) initially developed as a potent antihypertensive agent. It has attracted

dermatological attention because it produces hypertrichosis as a side effect in most patients who take the drug orally. However, patients who receive the systemic administration of minoxidil can experience side effects including pigmentation and coarsening of facial features, fluid retention, tachycardia, nausea, fatigue, dyspnea, and gynecomastia (Mehta et al., 1975; Burton & Marshall, 1979; Zappacosta, 1980). Topical application of minoxidil should eliminate those side effects. As part of an overall assessment of the safety of this drug for topical application, the amount absorbed through the skin and into the body must be considered (Franz, 1985). Therefore, it is necessary with the percutaneous delivery of minoxidil to focus on providing a means of limiting the efficacy of hypertrichosis on the local site and avoiding an excess of minoxidil entering the blood circulation to which would produce side effects, including its systemic hypotensive effects.

For the purpose of achieving therapeutic effectiveness by topical application, the commercial minoxidil product is formulated with a vehicle comprised of 60% ethanol, 20% water, and 20% propylene glycol in order to improve the solubility of minoxidil, thus leading to its effective penetration for therapy (Tata et al., 1995). Among these three co-solvents, ethanol and propylene glycol are both claimed to be penetration enhancers. Results of a study conducted by Tata and coworkers who applied 50 uL/cm$^2$ of a 2% solution containing ethanol and propylene glycol as co-solvents indicated that the penetration of minoxidil into and through the skin increased as the ethanol fraction of the binary solvent vehicle increased (Tata et al., 1995). A report by Ferry et al. revealed that the thermodynamic activity of minoxidil in solution is likely to be modified by the kinetics of propylene glycol (Tsai et al., 1992).

Regarding side effects, both irritant and allergic contact reactions to topical minoxidil or the vehicle ingredients have been reported (Whitmore, 1992; Fiedler-Waiss, 1987; Tosti et al., 1985; Scheman et al., 2000). Some of these are due to the relatively high concentrations of propylene glycol used as a solvent in commercially available minoxidil formulations. Propylene glycol dermatitis is a well-recognized phenomenon which can occur from exposure to many topical medications (Rietschal & Fowler, 1995). An alternative formulation for patients with contact reactions to topical 2% or 5% minoxidil vehicle ingredients was reported by Scheman et al. (2000). That study showed that a PEG 400 mixture may be a useful alternative vehicle for patients with intolerance to propylene glycol, or those with vehicle-dependent contact allergy to minoxidil in either propylene or hexylene glycol. It seems more appropriate to optimize the components of topical formulations for minoxidil with enhancing effects on penetration but not to such an extent as to experience profound dermatological side effects or systemic effects.

Tocopheryl polyethylene glycol succinate (TPGS) is a water-soluble derivative of a natural source of vitamin E and functions as a surfactant with an hydrophilic lipophilic balance (HLB) value of 13.2. Previously, the effect on the enhancement of the solubility and percutaneous penetration of estradiol with the use of TPGS in a binary cosolvent system containing water and ethanol was characterized (Sheu et al., 2003). Results showed that the solubility of estradiol improved in the presence of TPGS through micellar solubilization. Permeability values ($P_{eff}$), which describe the overall effects ($DK/H$) on the stratum corneum (SC), decreased with increasing TPGS concentrations for media containing 0%, 40%, 60%, and 80% alcohol, whereas they increased then decreased with increasing TPGS concentrations for media containing 10% and 20% alcohol. These results further delineate that interfacial coverage of TPGS with increasing TPGS concentrations and hindrance of the partitioning of estradiol by the increasing alcohol content might play a role in influencing the permeability of estradiol. It was thought that this effect of TPGS on the permeability of estradiol could be applied in the topical delivery of minoxidil by enhancing the local retention in the skin leading to improved therapeutic effects but with minimization of the systemic side effects.

In this study, the penetration flux of minoxidil and its retention in the skin were characterized from topical minoxidil solutions with the addition of TPGS in various compositions of co-solvent systems consisting of water, alcohol, and polyethylene glycol 400 (for replacing propylene glycol).

## MATERIALS AND METHODS

Minoxidil was obtained from Fabbrica Lombarda Ammino Acdi (Milan, Italy). Regaine® topical solutions (2% and 5%) were purchased from a local market sold by Pharmacia (Taby, Sweden). Polyethylene glycol 400

**TABLE 1** Solvent Formulations of Topical Minoxidil Solutions Designed Using Design Expert

| Formulations | Water (%) | Alcohol (%) | PEG 400 (%) |
|---|---|---|---|
| F1 | 100 | 0 | 0 |
| F2 | 0 | 100 | 0 |
| F3 | 0 | 0 | 100 |
| F4 | 50 | 50 | 0 |
| F5 | 50 | 0 | 50 |
| F6 | 0 | 50 | 50 |
| F7 | 66.67 | 16.67 | 16.67 |
| F8 | 16.67 | 66.67 | 16.67 |
| F9 | 16.67 | 16.67 | 66.67 |
| F10 | 33.33 | 33.33 | 33.33 |

was supplied by Fluka (Buchs, Switzerland). Alcohol was obtained from Taiwan Tobacco and Liquor Co. (Taipei, Taiwan). D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) was supplied by Eastman Chemical (Kingsport, TN, USA).

## Formulation Designs

According to the mixture design, ten solvent formulations (F1–F10) containing three solvents (water, alcohol, and PEG 400) at different ratios were designed using Design Expert (V 5.0, Stat-Ease, Minneapolis, MN, USA). One of these was the center point of the mixture design. A detailed formulation is listed in Table 1. Since some patients demonstrate the phenomena of vehicle-dependent allergic contact dermatitis (ACD) to the propylene glycol present in Regaine®, it was replaced with PEG 400 in this study to eliminate the ACD syndrome patients.

## Solubility Study

The effect of TPGS on the solubility of minoxidil in these ten solvent formulations was compared. An excess of minoxidil was added to the test vehicle containing 0%–20% w/w TPGS and agitated at 37°C for more than 24 h. The supernatants were sampled and diluted. The concentration of minoxidil was then determined by the UV absorbance measurement at $\lambda_{max}$ of 286 nm with reference to a calibration curve.

The numerical data obtained were analyzed using DESIGN-EXPERT® software. The best-fitting mathematical model (linear, quadratic, or special cubic model) was selected based on the comparisons of several statistical parameters including the coefficient of variation (C.V.), the multiple correlation coefficient ($R^2$), adjusted multiple correlation coefficient (adjusted $R^2$), and the predicted residual sum of the squares (PRESS), provided by the DESIGN-EXPERT software. Among them, PRESS indicates how well the model fits the data, and for the chosen model, it should be small relative to the other models under consideration.

## Percutaneous Penetration Studies

Nude mice (strain BALB/nu), aged 6–8 weeks and weighing approximately 20 g, were obtained from the Laboratory Animal Center of National Taiwan University, Taipei, Taiwan, ROC. The mice were killed by spinal dislocation. Fresh skin was excised from the abdominal region, and was washed with 0.9% NaCl (saline) before being placed on a Franz-type diffusion cell (membrane surface area of 2.8 $cm^2$ and a cell volume of 6.4 mL). A 2% (w/v) minoxidil solvent formulation containing 0%–20% w/v TPGS was placed on the donor side, and a saline pH 7.4 phosphate-buffered solution containing 0.02% sodium azide was used as the receptor medium; this was maintained at 37°C with a stirring rate of 500 rpm. At predetermined time intervals, 200-uL aliquots were withdrawn from the receptor compartment and replaced with an equal volume of fresh medium. The concentration of minoxidil was determined by validated High Performance Liquid Chromatography (HPLC) analysis described below. The amounts of minoxidil retained in the donor ($M_d$) and receptor compartments ($M_r$) after the penetration studies were also measured by the same HPLC method.

## HPLC Analysis of Minoxidil

Minoxidil concentrations were analyzed using an HPLC method with a reverse-phase ODS-2 column. Measurements were taken with UV detection at a wavelength of 286 nm. The mobile phase consisted of methanol/$H_2O$/glacial acetic acid (750/250/10, v/v/v, pH 3.0) at a delivery rate of 1 mL/min. This method was validated in the linear concentration range of from 0.1 to 100 μg/mL. Precision and accuracy for the intraday and interday measurements were within acceptable ranges.

## HPLC Analysis of TPGS

Tocopheryl polyethylene glycol succinate (TPGS) was determined with an HPLC method reported by Traber et al. (Traber et al., 1988) after saponification to form vitamin E using a reverse-phase C8 column (Lichrospher 250–4, 5 um, Merck, Germany). Measurements were taken with UV detection at a wavelength of 284 nm. The mobile phase consisted of methanol/10 mM phosphoric acid (95/5, v/v) at a delivery rate of 1 mL/min. Vitamin E acetate was used as the internal standard. This method was validated in the linear concentration range of from 2 to 100 μg/mL. Precision and accuracy for the intraday and interday measurements were within acceptable ranges.

## Theoretical Considerations

Besides the general definition based on Fick's Law, the steady state flux ($J_{ss}$) across the skin at time *t* also parallels the rate of change in the penetrant's concentration in the receiver side of the cell as expressed by Eq. 1:

$$J_{ss} = Dk/h \cdot (C_{vs} - C_t) = V/A \cdot dC_t/dt; \quad (1)$$

where D is the diffusion coefficient in the stratum corneum, k is the partition coefficient between the stratum corneum and the vehicle, h is the thickness of the stratum corneum, $C_{vs}$ is the drug concentration in the vehicle, $C_t$ is the penetrant's concentration in the receiver side of the cell, V is the volume of the receiver compartment, A is the area available for penetration, and $dC_t/dt$ is the rate of change of the penetrant's concentration in the receiver side of the cell. At steady state, the flux ($J_{ss}$) through the skin membrane is a function of both $K_p$ and the solute concentration ($C_{vs}$) or solubility ($C_s$) in the case of suspensions in the donor side and is expressed by Eq. 2 as follows:

$$J_{ss} = D \cdot k \cdot (C_{vs} - C_t)/h = K_p \cdot (C_{vs} - C_t)$$

or

$$J_{ss} = D \cdot k \cdot (C_s - C_t)/h = K_p \cdot (C_s - C_t), \quad (2)$$

$$J_{ss} = D \cdot k \cdot C_{vs}/h = K_p \cdot C_{vs}$$

or

$$J_{ss} = D \cdot k \cdot C_s/h = K_p \cdot C_s \quad (3)$$

where $K_p$ (= D · k/h) is defined as the permeability coefficient. If sink conditions are assumed to be maintained throughout the study, the concentration gradient is considered equal to $C_{vs}/h$ or $C_s/h$. Then $K_p$ can be calculated based on Eq. 3 for both cases. Furthermore, k is the ratio of the drug solubility in the SC ($C_{sc}$) to that in the vehicle ($C_s$) by definition so that

$$\begin{aligned} J_{ss} &= (D/h \cdot C_{sc}/C_s) \cdot C_{vs}, \\ J_{ss} &= (D/h \cdot C_{sc}) \cdot (C_{vs}/C_s); \end{aligned} \quad (4)$$

where $C_{vs}/C_s$ is defined as the extent of saturation of drug in the vehicle, and (D/h · $C_{sc}$) describes the overall effects of the vehicle system (co-solvent and enhancer) on the skin. According to Eq. 4, the enhancing effect of the vehicle system on the penetration of drug can be solely attributed to its effects on the skin by normalization with respect to the extent of drug saturation in the vehicle. If $C_{vs}$ is constant, which is equal to $C_s$, then Eq. 4 can be further simplified to become Eq. 5:

$$J_{ss} = (D/h \cdot C_{sc}). \quad (5)$$

Under this specific condition, therefore, the flux obtained from the linear portion at steady state directly describes the overall effects of the co-solvent system on the skin. However, the extents of saturation of the drug ($C_{vs}/C_s$) for those ten solvent formulations differed. The corrected flux ($J_{corrected}$), as defined by ($J_{corrected} = J_{ss}/C_{vs} \cdot C_s = D/h \cdot C_{sc}$) with respect to the saturated concentration for the corresponding vehicle, was also used to transform Eq. 4 to Eq. 5 which is used to describe the overall effects of the vehicle on the skin. $C_s$ and $C_{sc}$ are designated the saturated concentrations of the drug in the corresponding vehicle and SC, respectively.

The amount of minoxidil (R, μg) retained in the skin was calculated by $R = M_0 - (M_d + M_r)$, where $M_0$ is the total amount of minoxidil used in the penetration

studies. $M_d$, and $M_r$ are the respective amounts of minoxidil retained in the donor and receptor compartments after the penetration studies.

## RESULTS AND DISCUSSION

Ten solvent formulations (Table 1) consisting of water, alcohol, and PEG 400 in different ratios with the addition of different amounts of TPGS (0%–20%) were designed to examine their influence on both the flux and the amount of minoxidil retained in the skin using hairless mouse skin as the barrier with reference to their influence on the solubility of minoxidil. Based on Fick's law as shown by Eq. 3, the influence of TPGS added at various concentrations in different solvent mixtures on the flux ($J_{ss}$) should be dependent on the sum of the individual effects on $K_p$ (D*k/h) and $C_{vs}$. Tocopheryl polyethylene glycol succinate (TPGS) is able to improve the penetration flux by increasing drug solubility as a result of micellar solubilization and is able to modify the solubilization potential of the resulting solvent mixture, both of which lead to an increase in the effective concentration ($C_{vs}$). Tocopheryl polyethylene glycol succinate (TPGS) as the surfactant can also effectively improve or enhance the drug flux by its ability to decrease the interfacial tension to produce a favorable partitioning of the drug into the skin and to modify the interfacial barrier function of the SC, both of which decrease the resistance to drug permeation (k, partition coefficient). Permeation of TPGS with the solvent mixture dissolved into the skin altered the resistance of the diffusion pathway (D, diffusion coefficient) and thickness of barrier (h) to interactively modify the flux of the drug.

The solubility of minoxidil in these ten vehicle formulations with the addition of various amounts of TPGS was determined, and the results are shown in Fig. 1. It indicates that the addition of TPGS is only able to improve the solubility of minoxidil in those solvent systems containing higher proportions of water and PEG 400, and the extent of improvement was also more profound with the addition of TPGS at concentrations higher than 5%. However, the solubility of minoxidil in most of those formulations was lower than 2%. It further reveals that TPGS was the most efficient at improving the solubility of minoxidil in solvent systems that contained 100% water. For those solvent systems containing higher fractions of alcohol, an insignificant change in minoxidil's solubility with the increasing amount of TPGS added was noted, even with the tendency for decreasing solubility of minoxidil with higher amounts of TPGS. Nevertheless, the solubilities of minoxidil in those formulations were all greater than 2%, and were close to 5% for formulations containing 100% alcohol.

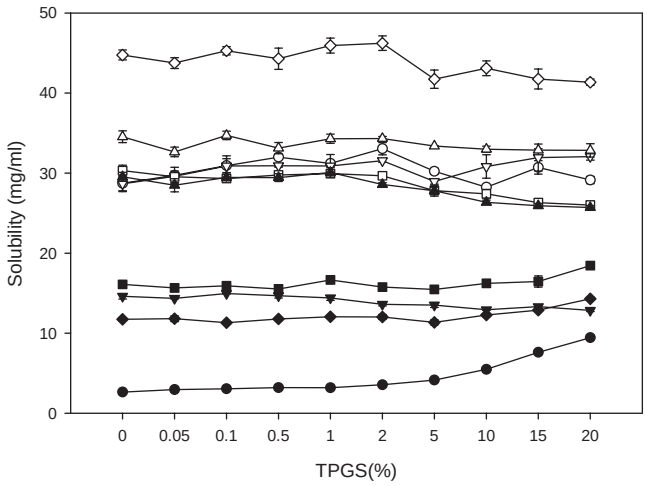


**FIGURE 1** **Effect of TPGS on the Solubility of Minoxidil in Ten Solvent Formulations (Key: F1, ●; F2, ○; F3, ▼; F4, ▽; F5, ; F6, □; F7, ♦; F8, ◇; F9, ▲; F10, Δ).**

In theory, there are two possible mechanisms responsible for influencing drug solubility for a surfactant like TPGS: one is the solubilization of micelles formed in the solvent system when the concentration of TPGS is higher than the critical micelle concentration (CMC) in the corresponding solvent system; and the other is modification of the solubilization potential of the resulting solvent mixture containing solubilized TPGS which influences the free drug concentration which is not incorporated into the micelles. The critical micelle concentration (CMC) of TPGS in various solvent systems and the significance of the modification of solubilization potential of the resulting solvent system are regarded as two determinant factors on the extent of the improvement in drug solubility. For those added concentrations of TPGS higher than the CMC in the corresponding solvent systems, the extent of improvement is expected to depend on both how much of the drug is incorporated into the micelles and what the free drug concentration in the resulting solvent system is with increasing added amounts of TPGS. However, it should be attributed to modification of the solubilization potential of the solvent mixture with the addition

of various amounts of TPGS as might be indicated by the resulting solubility parameter for the corresponding vehicle system which in turn determines the drug solubility when the amount of TPGS added is below that of the CMC. It would be reasonable to use the difference in the solubility parameter between the solvent system and the drug as an indicator to rationalize the influence of TPGS in the solvent formulations on the free amount of minoxidil in the corresponding solvent mixture. The closer the solubility parameters between the solvent mixture and drug are, the higher the solubility will be (Martin et al., 1983).

As reported (Sokol et al., 1993; Yu et al., 1999), the CMC of TPGS in water is around 0.2 mg/mL (~0.02%), which is lower than the lowest added amount of TPGS (0.1%) used in this study. The HLB value of TPGS is 13.2, and one would rationally expect it to be freely soluble in those solvent systems containing a higher fraction of alcohol. Because of that, the CMC of TPGS in those solvent systems containing higher proportions of water (i.e., F1, F3, F5, and F7) should be lower, and the added amount of TPGS could be higher than the respective CMC which would lead to an increase in minoxidil's solubility by micellar solubilization with increasing amounts of TPGS added. On the other hand, the amount of TPGS added to those solvent systems containing a larger fraction of alcohol (i.e., F2, F4, F6, F8, and F10) was expected to be lower than the respective CMC which only resulted in modification of the solubility parameter of the solvent mixture with increasing amounts of TPGS added to a less-favorable level for solubilization which led to a decrease in the solubility of minoxidil. This is consistent with the results demonstrated for those formulations.

Quantification of the effect of each solvent on the solubility of minoxidil at each concentration of TPGS was evaluated based on a mixture design. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters such as CV (coefficient of variation), $R^2$, adjusted $R^2$, PRESS, etc. provided by the software, DESIGN EXPERT. The results of model selection demonstrated that the quadratic model, which has no interaction term for the three factors, was the most statistically appropriate model for describing the overall effect of these three solvents on the solubility of minoxidil at TPGS concentrations of 0%–20%. Table 2 lists the coefficients of the model fitting for the effect of TPGS on the solubility of minoxidil. The influencing potential as indicated by the coefficients of the corresponding term for the same TPGS content was in the order of alcohol > PEG 400 > water. However, the coefficients with an increasing amount of TPGS added significantly increased with respect to water, insignificantly changed with respect to alcohol, but slightly decreased with respect to PEG 400. The interactive effect on the solubility of minoxidil was the greatest for water and alcohol, followed by water and PEG 400, and was the least for alcohol and PEG 400. Nevertheless, the interactive effect of water and either alcohol or PEG 400 significantly decreased with an increasing amount of TPGS added, whereas that for alcohol and PEG 400 changed insignificantly. It was concluded that water is the determinant factor in the interaction with TPGS in influencing the solubility of minoxidil in these solvent systems through the effects on both the CMC of TPGS in these solvent systems and the difference between their corresponding solubility parameters as described above.

**TABLE 2** Coefficients of Model Fitting for the Effect of TPGS on the Solubility of Minoxidil

| TPGS (%w/v) | A | B | C | AB | AC | BC |
|---|---|---|---|---|---|---|
| 0 | 0.90 | 3.38 | 2.71 | 4.83 | 3.88 | 1.81 |
| 0.05 | 1.02 | 3.42 | 2.70 | 4.61 | 3.54 | 1.63 |
| 0.1 | 1.03 | 3.46 | 2.74 | 4.66 | 3.48 | 1.51 |
| 0.5 | 1.09 | 3.49 | 2.73 | 4.47 | 3.32 | 1.50 |
| 1 | 1.08 | 3.47 | 2.71 | 4.53 | 3.63 | 1.62 |
| 2 | 1.18 | 3.52 | 2.65 | 4.31 | 3.34 | 1.61 |
| 5 | 1.32 | 3.43 | 2.65 | 3.87 | 3.01 | 1.62 |
| 10 | 1.60 | 3.38 | 2.60 | 3.65 | 2.64 | 1.75 |
| 15 | 1.91 | 3.46 | 2.63 | 2.99 | 2.02 | 1.41 |
| 20 | 2.13 | 3.42 | 2.59 | 2.65 | 2.06 | 1.50 |

A = Water; B = Alcohol; and C = PEG 400.

Figure 2 depicts the semi-logarithmic relationship between the solubility of minoxidil and the solubility parameter of these ten solvent formulations with the addition of various amounts of TPGS. Results revealed that a second- order relationship exists between the logarithmic solubility of minoxidil and the solubility parameter of these ten solvent formulations. The solubility is maximized for the solvent mixture with a solubility parameter of around 15, which is close to the value for minoxidil (15.45) calculated based on Fedor's method (James, 1989). With the

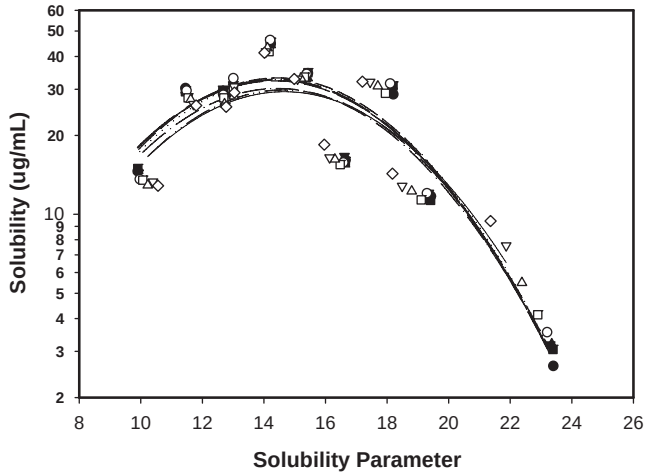


**FIGURE 2** **The Semi-logarithmic Relationship Between the Solubility of Minoxidil and the Solubility Parameter of Solvent Formulations with the Addition of Various Amounts of TPGS (% w/v) (Key: 0%, –●–; 0.1%, —‖—; 0.5%, —▲—; 1.0%, ——▼——; 2.0%, …○…; 5.0%, —…□—…; 10.0%, —…Δ—…; 15.0%, —◇—; 20.0%, ··♦··).**

addition of TPGS, the relationship apparently remains the same. This indicates that the influence of increasing the amount of TPGS added on the solubility of minoxidil in the corresponding solvent mixture might possibly be mainly attributed to alteration in the difference in the solubility parameter between minoxidil and the solvent mixture to which TPGS is added.

The fluxes of minoxidil from Regaine (2% and 5%) and these ten solvent formulations containing various amounts of TPGS were further evaluated using nude mouse skin as the barrier, and the results are illustrated in Figs. 3 and 4 (Fig. 4 showing formulation F6

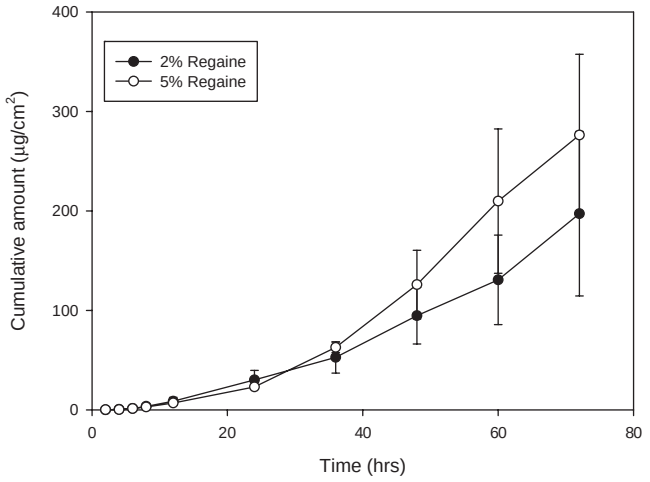


**FIGURE 3** **Penetration Profiles of 2% and 5% Regaine Solutions Through Nude Mouse Skin.**

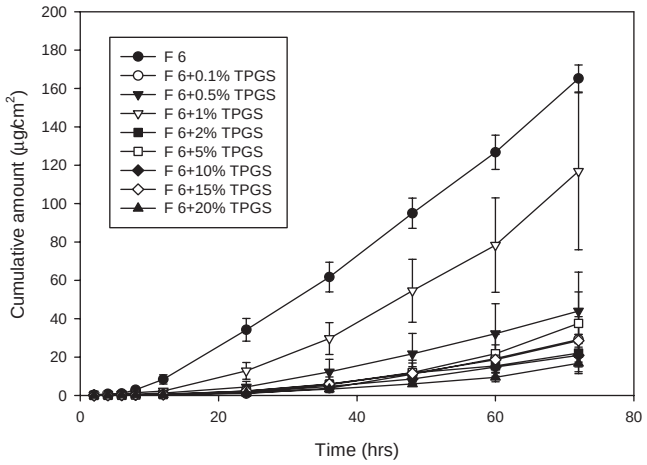


**FIGURE 4** **Cumulative Amounts of Minoxidil Penetrating vs. Time Through Nude Mouse Skin with the Addition of Various Amounts of TPGS. (Formulation 6 as a Typical Example.)**

containing various amounts of TPGS as a typical example), respectively. Fluxes for Regaine and minoxidil from these ten solvent formulations containing various amounts of TPGS were obtained from the linear portion of the penetration profiles at steady state. The fluxes for 2% and 5% Regaine were 3.44 ± 1.81 and 5.45 ± 2.22 ug/cm$^2$/h, respectively, and those for the ten solvent formulations with different amounts of TPGS are listed in Table 3. The permeability coefficients ($K_p$) as defined in the theoretical section by Eq. 3 were calculated with the assumption of a constant concentration of minoxidil in the donor compartment ($C_{vs}$), and the results are presented in Table 4. Both the flux and the permeability coefficients of minoxidil through mouse skin were initially enhanced to a maximum and then decreased with the increasing amount of TPGS added as noted for formulations F2, F3, F4, F5, F8, and F9. In contrast, both were gradually reduced when TPGS incorporated into the formulations F1, F6, F7, and F10 was increased correspondingly.

In comparison, the fluxes for F1, F2, and F4 were greater than that for 2% Regaine, and the fluxes changed with the addition of TPGS and were also all higher than that for 2% Regaine. However, the fluxes for F5 and F6 supplemented with different amounts of TPGS were all lower than that for 2% Regaine. The fluxes for F7 and F8 were close to that for 2% Regaine and changed insignificantly with the addition of TPGS. The flux for F3 without TPGS was profoundly lower than that for 2% Regaine, but the addition of TPGS in a lower range (<2%) enhanced the flux to the extent that it was higher than that for 2% Regaine. It

**TABLE 3** The Flux (μg/cm$^2$/h) and the Amount of Drug Retained in Skin for Minoxidil from Ten Solvent Formulations in the Presence of TPGS

| TPGS %, w/v | F1 | | F2 | | F3 | | F4 | | F5 | | F6 | | F7 | | F8 | | F9 | | F10 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | J[a] | R[b] | J | R | J | R | J | R | J | R | J | R | J | R | J | R | J | R | J | R |
| 0 | 7.98 ± 0.60 | 9893 ± 371 | 11.00 ± 2.52 | 2852 ± 1135 | 0.07 ± 0.10 | 1560 ± 1364 | 8.13 ± 0.38 | 13687 ± 247 | 0.89 ± 0.29 | 2134 ± 147 | 2.61 ± 0.08 | 1935 ± 251 | 3.93 ± 1.39 | 2842 ± 641 | 2.34 ± 0.37 | 1716 ± 446 | 0.31 ± 0.19 | 2449 ± 86 | 9.96 ± 0.76 | 666 ± 365 |
| 0.1 | 6.26 ± 0.18 | 8533 ± 476 | 14.63 ± 2.39 | 5087 ± 1249 | 5.00 ± 2.39 | 1253 ± 336 | 8.34 ± 0.38 | 3340 ± 215 | 0.96 ± 0.12 | 2643 ± 210 | 0.60 ± 0.26 | 4365 ± 1181 | 2.22 ± 0.41 | 6629 ± 57 | 4.32 ± 1.13 | 3169 ± 490 | 2.52 ± 0.22 | 2266 ± 426 | 1.62 ± 0.13 | 645 ± 60 |
| 0.5 | 4.61 ± 0.31 | 7706 ± 766 | 15.57 ± 0.94 | 5440 ± 1851 | 3.61 ± 2.46 | 1510 ± 350 | 10.12 ± 0.44 | 3678 ± 1148 | 0.92 ± 0.19 | 2357 ± 64 | 0.83 ± 0.36 | 4260 ± 446 | 3.87 ± 0.64 | 6666 ± 181 | 4.59 ± 0.08 | 3620 ± 160 | 0.34 ± 0.13 | 2664 ± 807 | 1.33 ± 0.21 | 474 ± 40 |
| 1 | 4.83 ± 0.76 | 8183 ± 487 | 15.87 ± 2.14 | 10141 ± 122 | 3.68 ± 1.53 | 995 ± 289 | 6.28 ± 0.10 | 4094 ± 1209 | 1.44 ± 0.81 | 2428 ± 661 | 1.89 ± 0.64 | 3653 ± 80 | 2.54 ± 0.03 | 4991 ± 138 | 4.05 ± 0.09 | 3173 ± 185 | 1.71 ± 0.43 | 2882 ± 404 | 3.15 ± 0.85 | 189 ± 143 |
| 2 | 3.17 ± 1.47 | 7717 ± 1698 | 9.08 ± 2.08 | 6785 ± 1693 | 4.77 ± 2.65 | 1175 ± 136 | 6.60 ± 0.84 | 6095 ± 1494 | 1.19 ± 0.56 | 3129 ± 875 | 0.37 ± 0.16 | 6960 ± 321 | 2.24 ± 0.33 | 3355 ± 117 | 5.42 ± 1.71 | 3252 ± 1896 | 2.41 ± 0.92 | 2764 ± 247 | 3.46 ± 1.31 | 346 ± 91 |
| 5 | 3.87 ± 2.85 | 6319 ± 124 | 8.44 ± 0.35 | 3446 ± 483 | 2.83 ± 0.68 | 2000 ± 1012 | 10.00 ± 0.79 | 4306 ± 1233 | 1.22 ± 1.12 | 2578 ± 408 | 0.87 ± 0.39 | 7259 ± 1342 | 2.51 ± 0.32 | 2873 ± 314 | 2.84 ± 0.33 | 6852 ± 1187 | 2.38 ± 0.11 | 2494 ± 218 | 2.11 ± 0.80 | 524 ± 317 |
| 10 | 4.39 ± 0.07 | 7166 ± 639 | 5.30 ± 0.71 | 3864 ± 1130 | 1.55 ± 0.44 | 2908 ± 276 | 7.53 ± 1.27 | 3779 ± 2146 | 1.34 ± 0.34 | 1919 ± 46 | 0.42 ± 0.10 | 4381 ± 998 | 2.28 ± 0.35 | 2395 ± 516 | 3.36 ± 0.83 | 9443 ± 3552 | 8.89 ± 2.88 | 1857 ± 596 | 1.71 ± 0.32 | 207 ± 79 |
| 15 | 3.60 ± 0.81 | 5830 ± 1105 | 8.050 ± 0.449 | 7461 ± 814 | 2.97 ± 0.48 | 2221 ± 204 | 7.32 ± 0.58 | 4360 ± 1547 | 0.39 ± 0.52 | 1856 ± 944 | 0.54 ± 0.06 | 4400 ± 498 | 2.86 ± 0.30 | 1932 ± 456 | 2.87 ± 0.24 | 14969 ± 326 | 1.32 ± 0.10 | 1304 ± 235 | 1.64 ± 0.47 | 1561 ± 595 |
| 20 | 6.14 ± 0.25 | 5140 ± 665 | 4.81 ± 0.72 | 3850 ± 565 | 0.98 ± 0.24 | 1963 ± 352 | 10.99 ± 2.52 | 1380 ± 595 | 0.74 ± 0.39 | 3212 ± 1069 | 0.37 ± 0.13 | 3916 ± 523 | 2.37 ± 0.44 | 335 ± 53 | 3.04 ± 0.92 | 2180 ± 277 | 4.25 ± 0.72 | 917 ± 313 | 1.15 ± 0.08 | 1447 ± 771 |

[a] J = Flux (μg/cm$^2$/h).
[b] R = Retention (μg).

**TABLE 4** Permeability Coefficients ($\times 10^3$, cm/h), Corrected Flux ($\mu g/cm^2/h$), and the Relative Ratio of R/F for Minoxidil from Ten Solvent Formulations in the Presence of Various Amounts of TPGS

| | | TPGS (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Formulation | Parameters | 0 | 0.1 | 0.5 | 1 | 2 | 5 | 10 | 15 | 20 |
| | Permeability | 3.028 | 2.049 | 1.442 | 1.518 | 0.893 | 0.937 | 0.801 | 0.473 | 0.650 |
| F1 | Corrected flux | 7.982 | 6.257 | 4.606 | 4.828 | 3.166 | 3.873 | 4.390 | 3.598 | 6.135 |
| | R/F | 0.64 | 0.71 | 0.87 | 0.88 | 1.27 | 0.85 | 0.85 | 0.84 | 0.43 |
| | Permeability | 0.546 | 0.731 | 0.778 | 0.793 | 0.454 | 0.422 | 0.265 | 0.403 | 0.240 |
| F2 | Corrected flux | 15.673 | 22.617 | 24.899 | 24.761 | 14.995 | 12.755 | 7.483 | 12.360 | 7.002 |
| | R/F | 0.14 | 0.18 | 0.18 | 0.33 | 0.39 | 0.21 | 0.38 | 0.48 | 0.41 |
| | Permeability | 0.004 | 0.335 | 0.246 | 0.256 | 0.351 | 0.210 | 0.120 | 0.223 | 0.077 |
| F3 | Corrected flux | 0.065 | 5.003 | 3.605 | 3.680 | 4.769 | 2.831 | 1.553 | 2.972 | 0.983 |
| | R/F | 11.54 | 0.13 | 0.22 | 0.14 | 0.13 | 0.37 | 0.97 | 0.39 | 1.04 |
| | Permeability | 0.407 | 0.417 | 0.506 | 0.314 | 0.330 | 0.500 | 0.376 | 0.366 | 0.550 |
| F4 | Corrected flux | 11.656 | 12.882 | 15.647 | 9.692 | 10.413 | 14.476 | 11.598 | 11.694 | 17.622 |
| | R/F | 0.87 | 0.21 | 0.19 | 0.34 | 0.48 | 0.22 | 0.26 | 0.31 | 0.07 |
| | Permeability | 0.055 | 0.060 | 0.059 | 0.087 | 0.075 | 0.079 | 0.083 | 0.024 | 0.040 |
| F5 | Corrected flux | 0.884 | 0.956 | 0.922 | 1.444 | 1.185 | 1.224 | 1.340 | 0.392 | 0.744 |
| | R/F | 1.26 | 1.43 | 1.33 | 0.87 | 1.36 | 1.09 | 0.74 | 2.47 | 2.25 |
| | Permeability | 0.130 | 0.030 | 0.041 | 0.094 | 0.019 | 0.044 | 0.021 | 0.027 | 0.018 |
| F6 | Corrected flux | 3.950 | 0.878 | 1.228 | 2.826 | 0.549 | 1.215 | 0.570 | 0.713 | 0.476 |
| | R/F | 0.38 | 3.77 | 2.66 | 1.00 | 9.74 | 4.32 | 5.40 | 4.22 | 5.48 |
| | Permeability | 0.335 | 0.197 | 0.329 | 0.211 | 0.186 | 0.221 | 0.186 | 0.223 | 0.166 |
| F7 | Corrected flux | 3.925 | 2.224 | 3.869 | 2.543 | 2.238 | 2.510 | 2.282 | 2.857 | 2.367 |
| | R/F | 0.37 | 1.55 | 0.89 | 1.02 | 0.78 | 0.59 | 0.54 | 0.35 | 0.07 |
| | Permeability | 0.117 | 0.216 | 0.230 | 0.203 | 0.271 | 0.142 | 0.168 | 0.144 | 0.152 |
| F8 | Corrected flux | 5.232 | 9.783 | 10.164 | 9.306 | 12.518 | 5.924 | 7.236 | 5.995 | 6.288 |
| | R/F | 0.38 | 0.38 | 0.41 | 0.41 | 0.31 | 1.25 | 1.46 | 2.70 | 0.37 |
| | Permeability | 0.015 | 0.126 | 0.017 | 0.086 | 0.121 | 0.119 | 0.445 | 0.066 | 0.213 |
| F9 | Corrected flux | 0.456 | 3.705 | 0.499 | 2.574 | 3.447 | 3.308 | 11.719 | 1.712 | 5.466 |
| | R/F | 4.09 | 0.47 | 4.06 | 0.87 | 0.59 | 0.54 | 0.11 | 0.51 | 0.11 |
| | Permeability | 0.498 | 0.081 | 0.067 | 0.158 | 0.173 | 0.105 | 0.086 | 0.082 | 0.058 |
| F10 | Corrected flux | 17.193 | 2.811 | 2.203 | 5.406 | 5.932 | 3.513 | 2.820 | 2.668 | 1.894 |
| | R/F | 0.03 | 0.21 | 0.18 | 0.03 | 0.05 | 0.13 | 0.06 | 0.46 | 0.65 |

R = retained amount.
F = Flux.

became lower than that of 2% Regaine with further increases in the amount of TPGS added. The flux for F9 was lower than that for 2% Regaine, but the addition of a higher amount TPGS produced a flux greater than that for 2% Regaine. Finally, the flux for F10 was higher than that for 2% Regaine and the addition of TPGS led to most of the fluxes being lower than that for 2% Regaine.

As described above by Eq. 3, the influence of TPGS added at various concentrations in different solvent formulations on the flux ($J_{ss}$) is apparently dependent on the sum of the individual effects on $C_{vs}$ and $K_p$. More precisely, the flux at steady state was proportional to the thermodynamic activity of minoxidil on the donor side (drug activity for penetration), and to the enhancing effects of TPGS with the solvent formulation it dissolved on these three parameters (D, k, and h) on which $K_p$ depends. For a fixed concentration of 2% minoxidil employed in this study, the thermodynamic activity of minoxidil on the donor side would differ. It is predicted to increase with increases in both the free drug concentration (that which is not incorporated into the micelles of TPGS) on the donor side which is available for penetration and the extent of saturation of minoxidil in the solvent formulations which is dependent on whether the added TPGS forms micelles in the solvent formulations or all of it is solubilized. $K_p$ calculated based on Eq. 3 using the

same $C_{vs}$ as for 2% resulted in a discrepancy of being either over- or under-estimated for those solvent mixtures with TPGS which solubilities that were either higher or lower than 2%, respectively.

In this regard, the corrected fluxes ($J_{corrected}$) as theoretically expressed in Eq. 5 and which more appropriately describe the overall effects of the addition of TPGS interacting with solvent formulations dissolved on the skin were calculated and are listed in Table 4. Quantification of the individual effects of the three solvents on the corrected flux of minoxidil at different added amounts of TPGS was evaluated based on the mixture design; their coefficients of model fitting are listed in Table 5. Results demonstrate that the overall effects on minoxidil penetration of each individual solvent on the skin decreases with increasing TPGS content in the range of from 0% to 5% for water, whereas it increased and then correspondingly decreased in the same range of TPGS content for alcohol and PEG 400. At larger amounts of TPGS (10%–20%), the influence of the three solvents on the corrected fluxes of minoxidil showed a tendency to increase again. Further, the positive influence of alcohol on the corrected flux was the most profound among the three solvents compared, followed by water, with PEG 400 being the least and even negative in some solvent systems. This is consistent with the fact that alcohol is known to be a better enhancer for skin penetration. However, this phenomenon might also be attributed to the necessity for the solvent partitioned in the skin to express its effects on the skin in order to influence the penetration of minoxidil. Solvent partitioning is dependent on the overall escaping tendency of the solvent from the vehicle to the skin which may have been modified by the presence of TPGS in the solvent mixture.

**TABLE 5** **Coefficients of Model Fitting for the Effect of TPGS on the Corrected Flux of Minoxidil**

| TPGS (%) | A | B | C | AB | AC | BC |
|---|---|---|---|---|---|---|
| 0 | 7.51 | 14.09 | –1.49 | 0 | 0 | 0 |
| 0.1 | 5.54 | 22.48 | 5.90 | –7.50 | –17.92 | –49.79 |
| 0.5 | 4.61 | 24.74 | 4.09 | –0.65 | –15.68 | –55.36 |
| 1 | 4.38 | 24.22 | 3.97 | –18.36 | –7.52 | –42.05 |
| 2 | 2.83 | 13.93 | 1.01 | 0 | 0 | 0 |
| 5 | 4.43 | 11.48 | –0.42 | 0 | 0 | 0 |
| 10 | 4.75 | 8.21 | 2.33 | 0 | 0 | 0 |
| 15 | 3.37 | 12.17 | 3.49 | 12.00 | –13.01 | –29.19 |
| 20 | 5.16 | 7.04 | 2.88 | 34.05 | –17.71 | –18.48 |

A = water; B = alcohol; C = PEG400

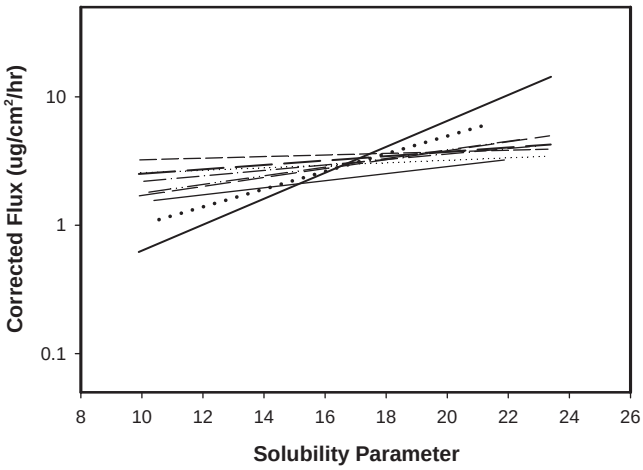


**FIGURE 5** **Semi-logarithmic Relationship Between the Corrected Flux of Minoxidil and the Solubility Parameter of Solvent Formulations with the Addition of Various Amounts of TPGS (% w/v) (Key: 0%, ——; 0.1%, ——; 0.5%, ——; 1.0%, ————; 2.0%, ……; 5.0%, —…—…; 10.0%, —·—··; 15.0%, ——; 20.0%, ····).**

Figure 5 describes the semi-logarithmic relationship between the corrected flux of minoxidil and the solubility parameter of these ten solvent formulations with the addition of various amounts of TPGS. A linear relationship was observed of an increasing logarithmic corrected flux with the increasing solubility parameter of the solvent formulation. Results also revealed that increasing amount of TPGS added gradually increased the corrected flux from solvent formulations with lower solubility parameters, but decreased that from solvent systems with higher solubility parameters. This might also be explained by the addition of TPGS probably making the partitioning of solvent formulations into the skin more favorable for those solvent formulations with lower solubility parameters and less favorable for those with higher solubility parameters as regards expressing the solvent effects on the skin.

The retained amounts (R) of 2% and 5% Regaine in the skin were 6622 ± 1925 and 10795 ± 9846 μg, respectively. Table 3 also lists the amount retained in skin of the ten solvent formulations containing 2% minoxidil in the presence of various amounts of TPGS. Plots of the amounts of minoxidil retained in the skin versus the flux ($J_{ss}$) and the corrected flux ($J_{corrected}$) are shown in Fig. 6A and B, respectively, for the ten solvent formulations with the addition of different amounts of TPGS. A proportional increase in the amount of minoxidil retained in the skin with increasing concentrations of from 2% to 5% is apparent for Regaine. The amounts of minoxidil retained

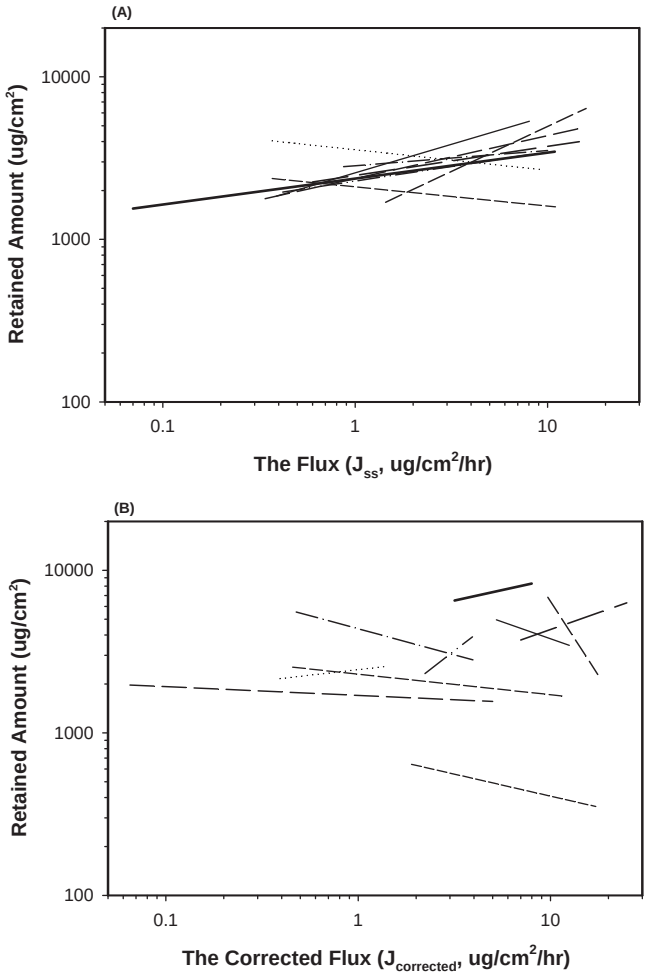


**FIGURE 6** **Logarithmic-logarithmic Plot of the Amount of Minoxidil Retained vs. (A) Flux and (B) Corrected Flux (Key: F1, —; F2, ——; F3, ——; F4, --------; F5, ……; F6, —·—·; F7,—··—·· ; F8, - -; F9, - - - -; F10, ——).**

for F1 and F5 were greater than and for F2 and F7 were lower than that for 2% Regaine, and the addition of TPGS to those four formulations led to the amount retained proportionally increasing with increases in both $J_{ss}$ and $J_{corrected}$. The amounts retained for the remaining formulations were lower than that for 2% Regaine, and the addition of TPGS to formulations F4, F6, F8, and F10 resulted in the retained amount increasing, and its addition to formulations F3 and F9 slight increases with decreasing $J_{ss}$ and $J_{corrected}$.

The increase in the amount of minoxidil retained by increasing the flux ($J_{ss}$) was probably caused by an increase in the concentration gradient leading to an increase in the concentration of minoxidil inside the skin adjacent to the solvent formulation, whereas that with decreasing the flux could have had a reservoir effect on the skin resulting in an increase in the amount of minoxidil retained. This explains why the amount of minoxidil retained increased with an increasing flux for formulations F1, F5, and F7 since 2% minoxidil was in excess of the solubility in the respective solvent formulations. In contrast, that with a decreasing flux for formulations F4, F6, F8, and F10 was because 2% minoxidil was below the solubility of the respective formulations. For formulations F3 and F9, both mechanisms were possibly operating simultaneously causing the amount retained to correlate insignificantly with the change in the flux. The viscosity effect due to the larger fraction of PEG 400 in both solvent formulations could not be ignored. Since $J_{corrected}$ indicates the overall effects of the solvent formulation with TPGS on the skin, the same correlation between the amount retained and $J_{corrected}$ as that for $J_{ss}$ reveals that the amount retained in the skin is a result of the effect on the skin regardless of which mechanism is operating.

Figure 7 depicts the semi-logarithmic relationship between the amount of minoxidil retained in the skin and the solubility parameter of these ten solvent formulations with the addition of various amounts of TPGS. Similarly, the influence of the solubility parameter with the addition of TPGS on the amount of minoxidil retained in the skin followed the same pattern as those for the corrected flux. The lowest amount of minoxidil retained in the skin was noted for those formulations with a solubility parameter close to 15. This might also be explained by the addition of TPGS probably making the partitioning of the

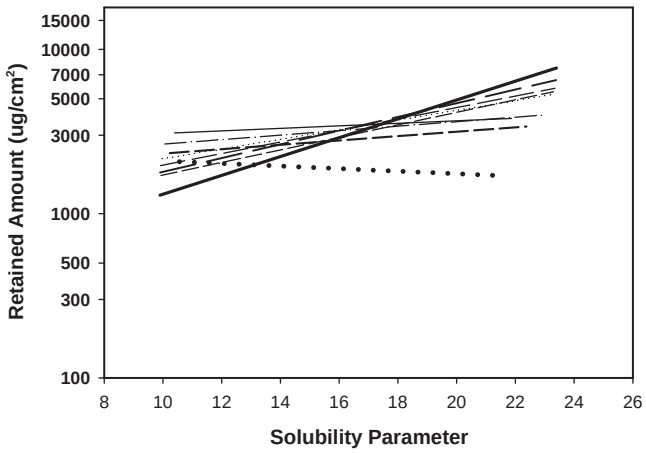


**FIGURE 7** **Semi-logarithmic Relationship Between the Amount of Minoxidil Retained and the Solubility Parameter of Solvent Formulations with the Addition of Various Amounts of TPGS (% w/v) (Key: Refer to Fig. 5).**

solvent mixture into the skin more favorable for retaining minoxdil in the skin for those with a lower solubility parameter and less favorable for those with a higher solubility parameter.

In order to minimize the systemic absorption of minoxidil and to localize its effect on the skin, the amount of minoxidil retained in the skin should increase as the flux decreases. The ratio of the amount retained to the flux was calculated for 2% Regaine as a reference to compare the systemic effects and local effects. The relative values of this ratio for the ten solvent formulations with various amounts of TPGS added were calculated with reference to that for 2% Regaine. Results are also listed in Table 4. The relative value being greater than, close to, and less than 1 indicates that the solvent formulation causes a greater local than systemic effect, equal systemic and local effects, and greater systemic than local effect, respectively, compared to Regaine. Results in Table 4 demonstrate that the relative values for solvent formulations F3 and F9 were greater than 1, and the addition of TPGS caused them to change from greater than 1 to less than 1, indicating that the local effect decreased as compared to Regaine. The relative value for solvent formulation F5 was slightly greater than 1, but the addition of TPGS only caused the relative value to change slightly (either to decrease to 0.87 and 0.74 or to increase to 2.47 and 2.25), revealing that the local effect had improved. The relative values for solvent formulations F2, F4, and F10 were all less than 1, and the addition of TPGS was unable to increase the relative values to greater than 1. This reveals that the addition of TPGS to those solvent formulations could not improve the local effect or hinder the systemic effect compared to Regaine. The relative values for solvent formulations F1, F6, F7, and F8 were less than 1, but the addition of TPGS gradually increased their relative values, and they reached maximal at different amounts of TPGS added, indicating that the addition of an optimal amount of TPGS can improve the local effect for the corresponding solvent formulation.

For attempts to improve the local retention of minoxidil with minimal penetration into the systemic circulation, those solvent formulations with relative values of greater than 1 and fluxes lower than that for Regaine would be the choice. Based on this, solvent formulations F3, F5, and F9 without TPGS fulfill the criteria. With the addition of TPGS, solvent formulation F6 would be expected as it has an improved local effect and a reduced system effect compared to Regaine.

The effect of TPGS on the SC was further elucidated by measuring the appearance of TPGS through the skin in the receptor compartment and the retention of TPGS in the skin. A sample from the receptor compartment and a corresponding skin sample after the 96-h penetration study were assayed for minoxidil by a validated HPLC method. The skin sample was divided into two parts: one was full skin and the other had the SC stripped off. The result of our analysis indicated that TPGS did not penetrate across the skin in its intact form or as its degradation product of vitamin E. Tocopheryl polyethylene glycol succinate (TPGS) was mainly localized in the SC and the retained amount was proportional to the increase in the added amount of TPGS in these ten solvent formulations. Therefore, the influence of TPGS on the skin only occurred through the interfacial interaction and partition phenomena in the SC layer.

## CONCLUSIONS

In attempts to improve the local effect for minoxidil delivered percutaneously, the addition of various amounts of TPGS in ten solvent formulations was examined. Compared to that for Regaine, the local effect was improved using solvent formulations F3, F5, and F9 to percutaneously deliver minoxidil. With the addition of TPGS, solvent formulation F6 would be an optimal choice. The local effect of promoting hair growth and the reduction in systemic absorption of minoxidil into the general circulation for these solvent formulations with or without the addition of TPGS are currently being evaluated using an in vivo animal model.

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