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Solubility and in vitro transdermal permeation of nifedipine

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Abstract

The solubilities of a hydrophobic drug, nifedipine, in a diverse panel of solvent and cosolvent systems were determined experimentally at room temperature. The observed solubilities were examined for deviations from regular solution solubilities as calculated by the Hildebrand and Scott Equation. When presented graphically, the observed solubilities showed a pattern of positive deviations from ideality. The influence of solubilities in a cosolvent system on nifedipine permeation through hairless mouse skin was evaluated in the four binary cosolvent systems. The solubility of nifedipine was measured in four dimethyl isosorbide (DMI)-based cosolvent mixtures and the theoretical skin:vehicle partition coefficients were calculated. The amounts of nifedipine permeated at 24 h post application from the representative donor systems administered as suspensions were measured across hairless mouse skin in vitro. For the systems studied, it was concluded that: (1) nifedipine solubility was enhanced in moderately polar cosolvent systems; (2) there was no correlation between the steady-state flux and drug solubility; and (3) nifedipine permeation was higher from systems that contain solvents known to readily pass the skin. © 1997 Elsevier Science B.V.

Keywords: Solubility parameters; Nifedipine; Water solubility; Partition coefficient; Hairless mouse; Transdermal delivery

1. Introduction

The dihydropyridine class of calcium channel blocking agents have received attention as candidates for transdermal delivery (Diez et al., 1991). The permeation of nicardipine (Seki et al., 1987) and nifedipine (Kondo and Sugimoto, 1987) were postulated to be strongly influenced by the thermodynamic activity of drug in the donor phase. Percutaneous flux of drug, J, is considered primarily a passive diffusion process driven by the difference between the thermodynamic activity, a,

Abbreviations: ACN, acetonitrile; BOH, butanol; CF, chloroform; DCM, dichloromethane; DEG, diethylene glycol; DMI, dimethyisosorbide; DMSO, dimethysulfoxide; ETOH, ethanol; EAC, ethyl acetate; EDC, ethylene dichloride; HEX, hexane; MEOH, methanol; MC, methylellosolve; MO, mineral oil; N9, nonoxynol-9; VOLPOL, PEG-5 oleyl ether; PEG400, polyethylene glycol; PG, propylene glycol; PIP, piperidine; THF, tetrahydrofuran.

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of drug in the vehicle and the skin. The thermodynamic formulation of the diffusion equation, using the standard expression for chemical potential, $\mu = \mu^0 + RT \ln a$, is (Scheuplein, 1978):

$$J = -\frac{DC}{RT}\frac{d\mu}{dx} = -\frac{DC}{a}\frac{da}{dx} \quad (1)$$

Eq. (1) suggests that one scheme for optimizing flux is to ensure that the medicament is at its maximum thermodynamic activity within the vehicle. It has been suggested that thermodynamic activity and chemical potential are simply a measure of the escaping tendency of a drug from a vehicle; the higher this property, the greater the amount of drug should partition from the vehicle into the epidermis (Kondo and Sugimoto, 1987). Assuming all terms in the model remain constant, maximal flux should occur when the penetrant has achieved maximal thermodynamic activity. By definition, maximal activity occurs when solid drug is in equilibrium with drug dissolved in the vehicle. If diffusion is neither rate limited by the intrinsic dissolution rate or affected by the partitioning characteristics of the drug then all vehicles that contain drug as a finely ground suspension should exist as a saturated solution which sustains constant, maximal escaping tendency for the duration of the experiment. For the case of a homogeneous membrane of thickness, h, constant diffusion coefficient, D, and activity coefficient, a/C, and partition ratio, K, at both interfaces, Eq. (1) simplifies to the familiar form of Fick's law:

$$J = -\frac{DK}{h}(C_d - C_r) \quad (2)$$

where C_d and C_r are the concentration of drug in the donor and receptor compartments of a Franz cell. Under sink ($C_r = 0$) conditions and partition equilibrium at the membrane-solution interface we have

$$J = -\frac{DC_m}{h} \quad (3)$$

where $C_m = KC_d$ is the drug concentration in the membrane immediately adjacent to the donor solution. It is evident from Eq. (3) that the predicted steady state flux across an ideal membane (for which D, C_m and h are not affected by the vehicle) depends solely on the diffusion coefficient of the drug and its solubility in the membrane.

A quick and reliable means of predicting flux would be of great value in the pairing of drug with excipients. Hancock and coworkers reviewed the solubility parameter for the prediction of material properties and assessment of interactions among components in pharmaceutical dosage form design (Hancock et al., 1997). Vaughan discussed the utility of employing the solubility parameter early in the drug development process to facilitate vehicle selection (Vaughan, 1985). Sloan and coworkers (Sloan, 1992) used solubility parameters to estimate theoretical stratum corneum:vehicle partition coefficients of topical formulations. This study employs nifedipine as a model permeant to examine the utility of solubility theory as a means of quickly predicting the effect of formulation changes upon both saturation solubility of drug in donor and drug permeation rate.

2. Materials and methods

2.1. Materials

Nifedipine, ethyl-*p*-amino benzoate (EPABA), propylene glycol, and fatty acids were purchased from Sigma, St Louis, MO. Long chain alcohols were purchased from Janssen Chimica (Spectrum, CA). Morpholine and its analogues (Texaco, TX); dimethyl isosorbide (ICI Specialty, DE); ethylene and propylene oxide block copolymers (BASF, Parsippany, NJ); Azone (Whitby Research, Richmond, VA); Volpols and Polychols (Croda, New York, NY); and polyethylene glycols and silicones (Dow Corning) were donated by the respective companies.

2.2. Preparation of solutions

In view of the high sensitivity of nifedipine to light, all experiments were carried out in a darkened room illuminated when necessary by gold fluorescent tubes (Westinghouse FC12T9 SW32W). All percentages were expressed on a weight:weight basis unless specified otherwise.

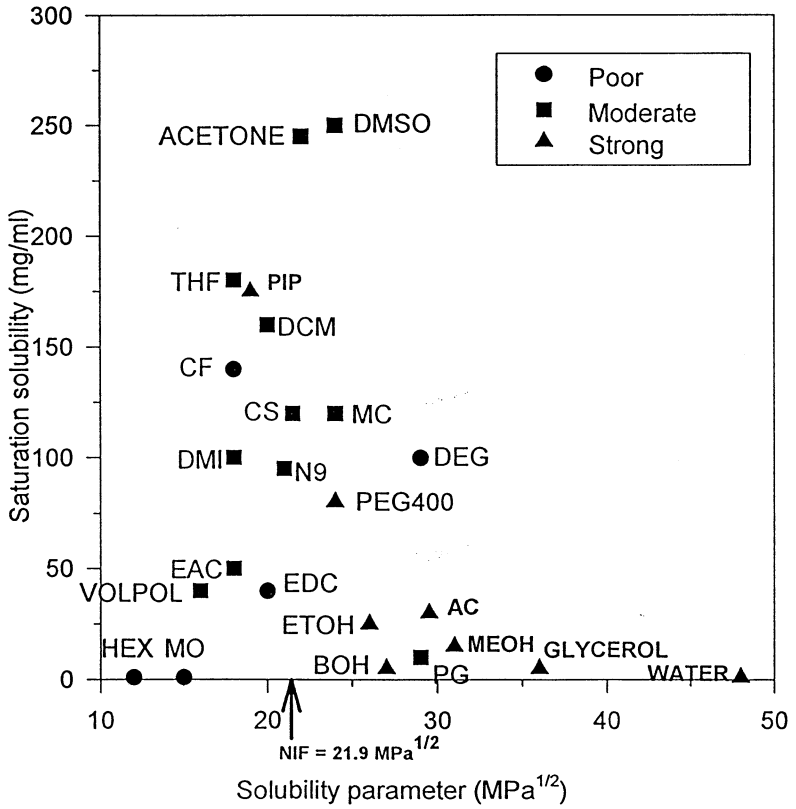

Fig. 1. Saturation solubility (mg/ml) versus total solubility parameter $(MPa)^{1/2}$ for the compounds studied.

Weight determinations were performed on a Metler A240 balance or Perkin-Elmer Model AD-14 microbalance. Four binary cosolvent mixtures were prepared from Volpol-3 (VOL:DMI), nonoxynol-9 (NX9:DMI), polyethylene glycol 400 (PEG:DMI) and propylene glycol (PG:DMI); dimethyl isosorbide was employed as the secondary solvent present in the binary mixtures. The composition of these binary mixtures ranged between 0 and 100% and was expressed in terms of the mole fraction percent of the DMI component.

2.3. Differential scanning calorimetry

The melting point and heat of fusion for nifedipine were obtained using a Perkin Elmer Model DSC-4 calorimeter and TADS software. Determinations were in triplicate using a scan rate of 10.0° per min and a sample weight of approximately 4 mg in vented pans.

2.4. Determination of drug content

All separations were performed on a Baseline 810 Chromatography Workstation (Dynamic Solutions Division of Millipore, CA) and Waters Model 484 Tunable Absorbance Detector set at 230 nm. A Hibar RT 250-4 LiChrosorb RP-18 (10 μm) column protected by a LiChrocart RP-18 (5 μm) precolumn (EM Separations, NJ) was kept at 37°C in a Model CH-30 HPLC Column Heater (FIAtron Laboratory Systems, WI). An isocratic mobile phase was prepared as follows: filtration of HPLC grade acetonitrile, methanol and water individually through 0.45 μm teflon filters; measured in a ratio of 1:1:2 by volume, respectively; sonicated and used at a flow rate of 1.3 ml/min.

Nifedipine concentrations were determined from peak areas by the external standard method using EPABA.

2.5. Solubility studies

Cosolvent blends were prepared on a mole fraction basis. Donor suspensions were prepared by adding excess nifedipine to the cosolvents and agitating in a Fisher Versa-Bath S Model 224 at 37°C until equilibrium was obtained (generally 72 h). The suspensions were centrifuged at $3514 \times g$ for 20 min, transferred to a 3 ml glass luerlock syringe fitted with a 0.2 μm Milex-FG filter (Milipore, Bedford, MA). The contents were expressed into amber glass tubes after having discarded the first milliliter of filtrate. A tared positive displacement syringe (Unimetrics, Anaheim, CA) was used to determine the density of the filtrate. Filtrates were diluted in methanol in triplicate and concentrations determined at 350 nm using a Hewlett-Packard 4105 spectrophotometer.

2.6. Diffusion cell experiments

Hairless mouse skin was chosen as the test membrane after initial studies showed that flux across silicone (Dow-Corning) and ethylene-vinyl acetate (90:10, 40 μm) copolymer (3M Corporation) was very low. Female hairless mice (26–28 g, 8–12 weeks of age) were the progeny of four females and one male SKH-1 obtained from Charles River Laboratories. A separate fresh skin sample was used for each individual cell. Following cervical dislocation, whole thickness, intact skin from the ventral region was removed using blunt dissection and immediately placed on the diffusion cells in contact with the receptor phase.

Four vertical diffusion cells with a surface area of 4.9 cm^2 (Crown Glass, Somerville, NJ) were used for each experiment, keeping one as control. The receptor phases of the diffusion cells were maintained at 37 ± 0.1°C with a circulating water bath. Receptor fluid (6:4 (v/v) mixture of 0.9% sodium chloride and polyethylene glycol 400) was used to ensure sink conditions. The diffusion cell was assembled, 17 ml of receptor solution was added, a reference (0-h) sample was taken, and a known weight of nifedipine:cosolvent suspensions were applied to the donor side of the diffusion cell. A control cell received the donor formulation without drug. At 24 h aliquots of receptor phase (1 ml) were transferred to 10 ml screw top test tubes containing 40 μg of EPABA methanolic solution and evaporated to dryness. Fifty μl of 10% trichloroacetic acid and 4 ml of chloroform were then added, the tubes gently agitated then centrifuged. The aqueous supernatant was aspirated, the organic phase evaporated to dryness, reconstituted with 0.25 ml of mobile phase, and analyzed by HPLC.

Mass balance was determined on the DMI-containing systems by washing each donor compartments with 10 ml of methanol, taking care to remove any solid nifedipine particles and to keep the time of contact of methanol to a minimum

Table 1
Saturation solubility in and permeability of nifedipine from binary mixtures prepared by the addition of propylene glycol or polyethylene glycol in dimethyl isosorbide

X_i	δ_T	C_s	J	Nifedipine permeated*
Fraction of PG in DMI				
0.00	18.5	85.0 ± 2.5	0.25 ± 0.08	29 ± 9
0.20	20.5	81.5 ± 2.7	0.17 ± 0.71	20 ± 84
0.43	22.8	57.5 ± 0.2	1.46 ± 0.60	50 ± 71
0.70	25.6	40.5 ± 5.0	0.61 ± 0.18	172 ± 21
0.87	26.0	19.1 ± 0.4	4.45 ± 1.02	523 ± 120
0.95	27.3	9.2 ± 0.01	3.84 ± 1.46	455 ± 172
1.00	28.1	10.0 ± 0.6	1.86 ± 0.76	219 ± 89
Fraction of PEG in DMI				
0.00	18.5	85 ± 2.5	0.25 ± 0.08	29 ± 9
0.05	18.7	98 ± 1.0	1.42 ± 0.23	165 ± 27
0.13	19.1	105 ± 2.8	1.51 ± 0.15	177 ± 18
0.30	19.8	106 ± 3.1	2.33 ± 0.11	275 ± 13
0.57	21.5	99 ± 3.6	5.78 ± 3.47	680 ± 408
0.80	22.7	92 ± 2.8	2.55 ± 0.87	300 ± 102
1.00	23.8	85 ± 1.5	0.09 ± 0.02	10 ± 2

X_i, mole fraction of PG or PEG in DMI; δ, solubility parameter expressed in units of $(MPa)^{1/2}$; C_s, saturation solubility of nifedipine in units of mg N/g cosolvent; J, flux, in units of $mg/h \cdot cm^2$; *, cumulative amount of nifedipine in μg permeated over a 24 h period (permeation results obtained over the interval = 0–24 h). Results represent the mean of three determinations $\pm$ 1 S.D.

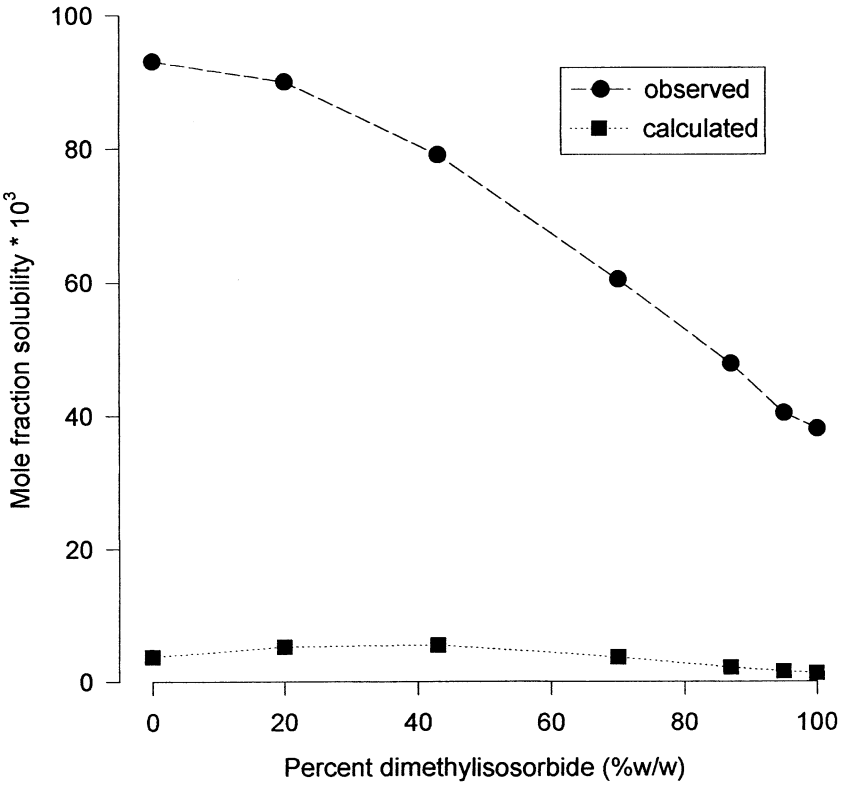

Fig. 2. Nifedipine observed and calculated (Eq. (6)) solubility in polyetheylene glycol 400:dimethyl isosorbide binary cosolvent mixtures.

(less than 3 min total). The methanol washes were combined, diluted and measured by HPLC. The receptor phase was changed and the skin kept in contact for 23 h with fresh receptor fluid to allow any residual drug to leach out. At the end of 23 h, the receptor phase was removed and analyzed. After another hour of contact between the skin and fresh receptor phase, the receptor phase was analyzed to assure that no additional nifedipine had leached from the skin. Recoveries of approximately 90% of the original applied dose were achieved. For the binary DMI-based vehicle only, donor was reapplied at the 48 h mark and sampling continued until 72 h to establish the long term effects of donor upon the barrier properties of skin.

2.7. Calculations

The properties of interest were assumed to be functionally related to the donor composition and thus by changing the proportion of ingredient the properties of the donor would change proportionately. The properties of the mixture were a simple linear combination of its component cosolvents, x_i, such that the solubility parameter, δ, for n solvents was

$$\delta = \sum_{i=1}^{n} \delta_i * x_i \quad (4)$$

Solubility parameter of mouse stratum corneum was 21.5 $MPa^{1/2}$, based on the estimate of 9.7–10 $(cal/cm^3)^{1/2}$ reported for full thickness porcine

skin (Liron and Cohen, 1984) [where 1 $MPa^{1/2} = 2.045\ (cal/cm^3)^{1/2}$)]. The solubility parameter for polyethylene glycol 400 (PEG400) was 19 $MPa^{1/2}$ (Dow Chemical). All other solubility parameters were obtained from the literature (Barton, 1983; Brandup and Immergut, 1975; Hansen and Skaarup, 1967) or, when unavailable, estimated using the method proposed by Fedors (1974). The logarithm of the skin:vehicle partition coefficient, $\log PC_{s,v1}$, was calculated by a published method (Sloan et al., 1986a) given by Eq. (5)

$$\log PC_{s,v_1} = [(\delta_2 - \delta_1)^2 - (\delta_2 - \delta_s)^2] - \frac{V_2}{2.3RT} \quad (5)$$

where δ_2 was the solubility parameter of solute, δ_1 was the solubility parameter of the vehicle, δ_s was the solubility parameter of the skin, V_2 was the molar volume of solute, R was the gas constant and T was absolute temperature. The logarithm of the mole fraction solubility of solute, $\log X_2$, according to regular solution theory was calculated from the Hildebrand equation (Martin and Swarbrick, 1983)

$$\log X_2 = \frac{-\Delta H_f}{1364}\frac{(T_m - T)}{T_m} - \frac{V_2\phi_1^2(\delta_1 - \delta_2)^2}{1364} \quad (6)$$

where X_2 was the mole fraction solubility of solute at temperature T, ΔH_f was the molar heat of fusion of the solute at its melting point T_m, and ϕ_1 was the volume fraction of the solvent.

The effect of mixture composition on non steady state permeation was compared by determining the average amount of nifedipine recovered in the receptor phase, V_r, after 24 h. The 24 h nifedipine receptor concentrations, $C_{r_{24h}}$ were averaged and the amount permeated at 24 h normalized for the surface area of skin in a 25 mm diameter cell, Q_{24h}, was calculated according to Eq. (7)

$$Q_{24h} = C_{r_{24h}} * \frac{V_r}{4.9\ cm^2} \quad (7)$$

The mean Q_{24h}-values were used to compare penetration from different cosolvent systems.

3. Results and discussion

3.1. Solubilities and partition coefficients

The aqueous solubility of nifedipine in phosphate buffer (pH 7.0) was determined to be 6 μg/ml and the solubility in *n*-octanol was 12.2 mg/ml. The observed partition coefficient of N was determined using *n*-octanol/phosphate buffer pH 7 at 37°C, and found to give a log K_{oct} of 3.31. This value lies between a range of values reported in the literature of 3.14 in *n*-octanol/water (Diez et al., 1991), 2.49 in *n*-octanol/phosphate buffer (McDaid and Deasy, 1996), and 4.00 (Ali, 1983). Nifedipine partition ratios vary greatly depending on the material chosen to represent the lipophilic phase (approximately 10:1 and 10000:1, when measured in cyclohexane-aqueous buffer and octanol:aqueous buffer (pH 7) systems, respectively (Ali, 1983). The solubility parameter of N (estimated via Fedor's method to be 21.94 $Mpa^{1/2}$) approximates the value of 21.5 $MPa^{1/2}$ reported by Liron and Cohen as the solubilty parameter for mouse skin (Liron and Cohen, 1984). Thus, it would appear that N has the prerequisite qualities of a 'good' candidate for transdermal therapy.

Saturation solubility should be maximal when the solubility parameter of solvent approximates that of solute. Fig. 1 shows a wide range of nifedipine saturation solubilities in various solvents that bracket the solubility parameter of N. Theory predicts that all solvents with a solubility parameter approximate to that of solute will act as strong solvents. It is readily apparent in Fig. 1 that overall the solubility parameter is a poor predictor of solubility. However, when the experimentally determined N saturation solubilities are subclassified according to their respective Burrell's H-index (Barton, 1983), which ranks their potential to form hydrogen bonds, a pattern amongst solvents of low, medium and high hydrogen-bonding is discerned: solvents of medium hydrogen-bonding capacity are generally the best solvents for N.

The total solubility parameter may be considered to be the sum of the three Hanson parameters which describe the dispersion (δ_d), dipolar (δ_p) and hydrogen bonding (δ_h) intermolecular forces. Partitioned in this manner the Keesom forces, described by the δ_p term, give rise to dipole–dipole interactions or 'orientation' forces that seem to exert a strong influence on nifedipine solubility. The pattern in the solubility data in Fig. 1 suggest that nifedipine interacts strongly with solvents primarily via Keesom forces. Further evi-

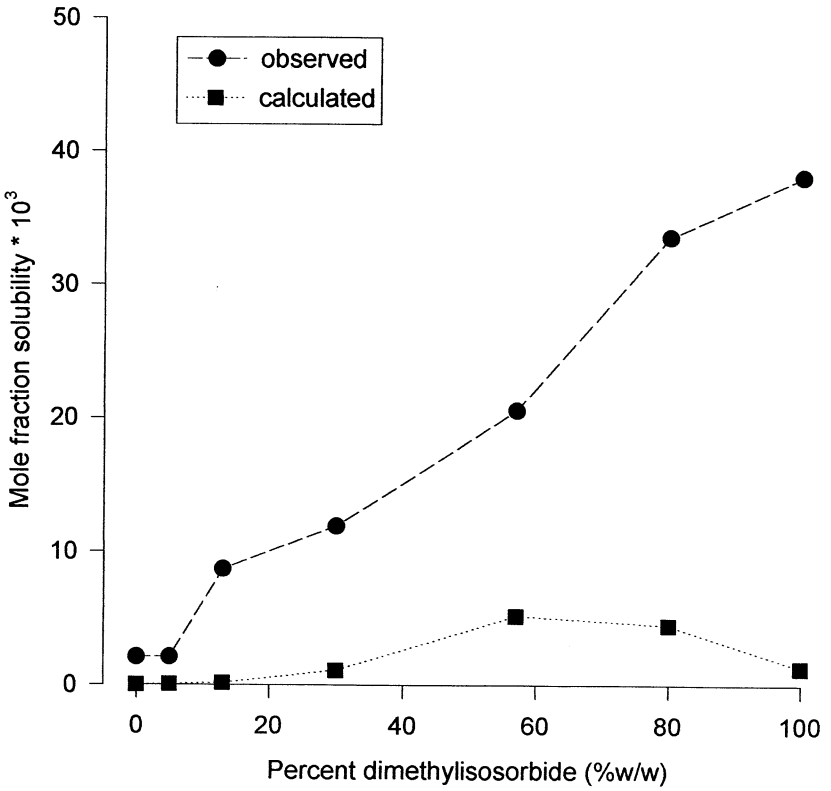

Fig. 3. Nifedipine observed and calculated (Eq. (6)) solubility in propylene glycol:dimethyl isosorbide binary cosolvent mixtures.

dence of significant Keesom interactions can be found in the disparity of nifedipine partition coefficients. As mentioned, the nifedipine partition ratio varies greatly depending on the material chosen to represent the lipophilic phase (approximately 10:1 and 10 000:1, when measured in cyclohexane-aqueous buffer and octanol:aqueous buffer (pH 7) systems, respectively). The disparity between the partition coefficient measured in octanol versus hexane may be explained by Keesom interactions. N has poor solubility in lipids (hydrocarbons, fixed oils, etc.), a low hexane:buffer partition coefficient, and equally poor solubility in environments solvents capable of forming strong hydrogen bonds. However, there is a distinct affinity of N for solvents that exhibit dipole-dipole intermolecular attractions. The pattern observed in Fig. 1 show that: (1) nifedipine appears to be a neutral compound with neither strong lipophilic nor hydrophilic character; (2) the best solubility (i.e. strongest solvent:nifedipine interaction) is in solvents with high δ_p values; and (3) nifedipine solubility is maximal in moderately polar solvents with dielectric constants between 20 and 30.

PG or PEG, in combination with DMI, are solvents with potential for use in a transdermal product and were studied in greater detail. The solubilities of N in binary solvent systems of these solvents are presented in Table 1. The regular solution mole fraction solubilities were calculated from Eq. (6) using our determinations of melting point (176°C) and enthalpy of fusion (9090 cal/mol) for N. The calculated mole fraction solubilities and the experimentally observed mole fraction

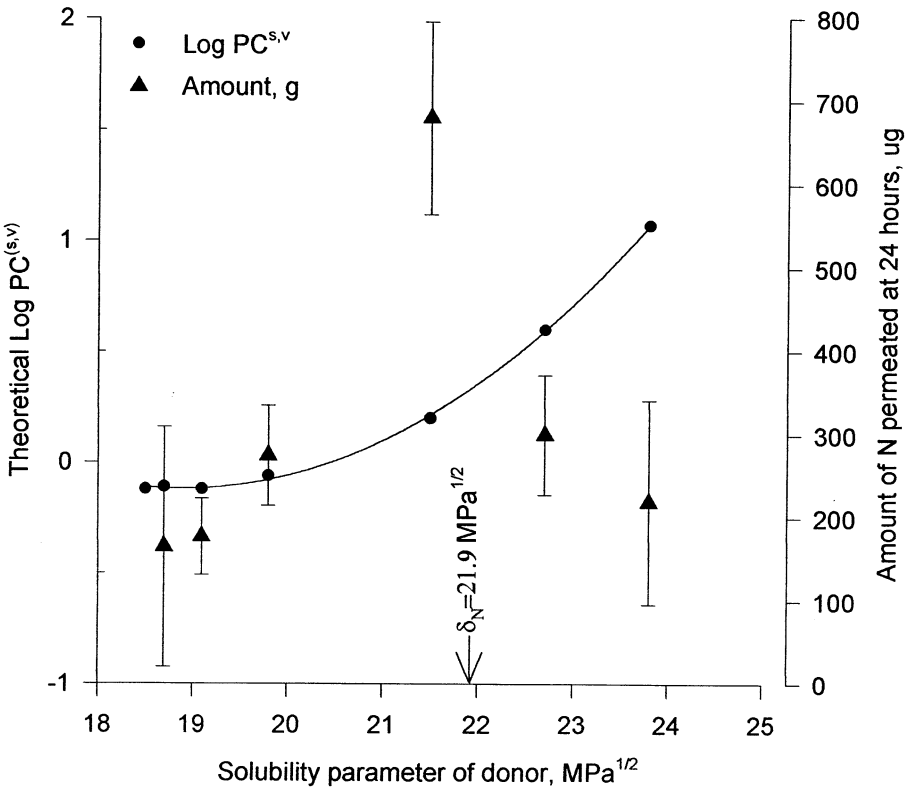

Fig. 4. Relationship between theoretical log skin-vehicle partition coefficient, amount permeated over 24 h and solubility parameter for PEG:DMI binary mixtures.

solubilities of nifedipine are compared for the binary cosolvents in Figs. 2 and (3). Regular solution theory consistently underestimates the experimentally determined solubilities. The departure of the observed from the calculated solubilities is further evidence of solvent–solute interaction.

3.2. Diffusion cell experiments

Application of regular solution theory to predict the partitioning process requires three essential features in the experimental design: (1) saturated solutions are applied to the skin; (2) after each initial application period, a 24 h washout period is used to determine the degree of accumulation in the skin; and (3) after the washout period, a second application of saturated drug solution is applied to determine the degree of damage to the barrier properties of the skin. For these conditions, Eq. (5) and its extensions have been successfully applied to predict the effect of vehicle on salicylic acid (Sloan et al., 1986b) and 5-fluorouracil (Sheretz et al., 1990) delivery through mouse skin. The surfactant-containing VOL:DMI and NX9:DMI binary mixtures, in which the solubility parameter ranged between 18.4 and 20.4 and 16.4 and 18.4 $(MPa)^{1/2}$, respectively, showed neglible N penetration and were excluded from further evaluation. Of the four binary systems tested, the PG:DMI and PEG:DMI based cosolvent donors, when reapplied to the cells following the washout period, exhibit no significant irreversible alteration of the intrinsic barrier properties of the skin. Since no difference is observed in the pre and post treatment steady state Q values we conclude that their effect on the intrinsic barrier properties of the

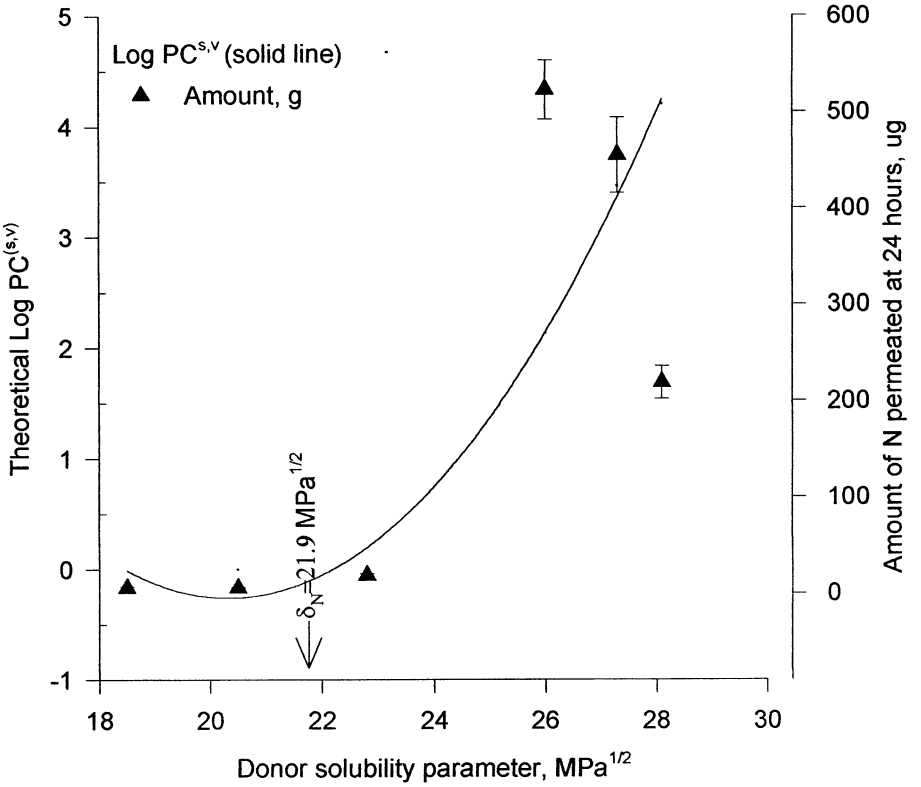

Fig. 5. Relationship between theoretical log skin-vehicle partition coefficient, amount permeated over 24 h and solubility parameter for PG:DMI binary mixtures.

skin are insignificant. Therefore, for these systems only, a methodology described by Sloan (Sloan et al., 1986a) could be employed to observe the effect of nifedipine solubility in cosolvent systems on in vitro diffusion through hairless mouse skin.

Four series of DMI-based binary mixtures were tested. Table 1 contains the composition and permeation results from a series of the PEG and PG containing DMI-based binary systems constituting a broad range of solubility parameters that bracket the point of maximal nifedipine solubility. The two binary mixtures containing DMI with either PG or PEG had better N permeation and Eq. (5) was used to calculate theoretical skin-vehicle partition coefficients. Fig. 4 summarizes the relationship between the theoretical skin vehicle partition coefficient, $\log PC_{s,v}$, and the total amount of nifedipine permeated in the 24 h study period, Q_{24h}, for the PEG:DMI binary systems. The data for the PG:DMI binary systems are treated in a similar manner in Fig. 5. Fluxes for the PG:DMI system are inversely dependent on drug solubility in the vehicles reported in Table 1. Minimum fluxes correspond to the point $\delta_2 = \delta_1$, as predicted by Eq. (5). The solubility of nifedipine is approximately constant in the PEG:DMI binary systems and the modest permeation rates from PEG:DMI systems did not differ significantly ($p = 0.05$). Those PG:DMI systems binary mixtures with low N solubility (i.e. high %PG) yielded higher fluxes which is again consistent with Eq. (5). Except for the 57% PEG formulation, permeation was up to fourfold greater from all PG:DMI formulations ($\delta_1 = 18–29$ MPa$^{1/2}$) compared to PEG:DMI formulations ($\delta_1 = 18–25$ MPa$^{1/2}$). Clearly, drug solubility in the donor is itself a poor indicator of permeation. Apparently, an optimal point for penetration, near the solubil-

ity parameter of drug and corresponding to the product of C_v and $PC_{s,v}$, exists after which drug is less easily released from donor vehicles.

All diffusion cell experiments utilized suspensions of nifedipine so that the thermodynamic activity of nifedipine would remain constant throughout the study period. Eq. (2) predicts maximal flux when the product of drug concentration in the vehicle, C_v, and $PC_{s,v}$ is optimal so that permeation is as much a function of the drug's skin:vehicle partition coefficient as its saturation solubility. The influence of strong intermolecular interactions is clearly evident in the solubility results and explains why N does not behave as an 'ideal' penetrant.

What the data do appear to establish is that high concentrations of PG lead to increased skin permeability to nifedipine. The solubility parameters of DMI, nifedipine, porcine stratum corneum, and propylene glycol are 18.4, 20.5, 20.5 and 28.6 $MPa^{1/2}$, respectively. When the solubility parameter of vehicle is much larger than than that of N, theoretical partition coefficients favoring movement of drug from the donor into the skin are predicted by Eq. (5). Better fluxes are predicted from binary mixtures high in PG and low DMI and the results shown in Fig. 5 are consistent with these predictions.

In summary, dipole–dipole interactions appear to be the primary determinant of nifedipine solubility. Saturation solubility or theoretical partition coefficient are poor predictors of the amount of nifedipine recovered from the receptor fluid at 24 h. Nifedipine permeation is higher from solvents that readily permeate the skin and further studies to establish the nature of this influence are underway.

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