Vehicle Effects in Percutaneous Absorption: *In Vitro* Study of Influence of Solvent Power and Microscopic Viscosity of Vehicle on Benzocaine Release from Suspension Hydrogels

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Abstract □ The release through silicone rubber membranes of benzocaine suspended in carbomer hydrogels containing different concentrations of low molecular weight polyols (ethylene glycol, propylene glycol, glycerol, and sorbitol) was studied to establish general principles and procedures for control of the effects on percutaneous absorption caused by changes in drug solubility and/or diffusivity in the vehicle. The effect of the additives on the release is expressed in terms of the relative released amount, *i.e.*, the ratio, Q/Q_W, of the amount of drug released from each additive-containing gel to the amount released at the same time from the additive-free gel. The experimental Q/Q_W values are correlated with values calculated by a simple equation involving known or readily measurable parameters such as the drug concentration in the gel, the drug solubility in the pure liquid phase, and the viscosity of this phase. Derivation of such a relationship from a known equation describing the vehicle-controlled release of suspended drugs was possible because an inverse proportionality was observed between drug diffusivity in the gels and the viscosity of the respective solvents. This relationship is interpreted with respect to current theories on drug diffusion in diluted gels.

Keyphrases □ Absorption, percutaneous—benzocaine, release from suspension hydrogels, influence of solvent power and microscopic viscosity of vehicle, *in vitro* □ Benzocaine—percutaneous absorption, release from suspension hydrogels, influence of solvent power and microscopic viscosity of vehicle, *in vitro* □ Hydrogels, suspension—percutaneous absorption of benzocaine, influence of solvent power and microscopic viscosity of vehicle, *in vitro* □ Vehicles—suspension hydrogels, percutaneous absorption of benzocaine, influence of solvent power and microscopic viscosity of vehicle, *in vitro* □ Percutaneous absorption—benzocaine, release from suspension hydrogels, influence of solvent power and microscopic viscosity of vehicle, *in vitro*

Low molecular weight polyols are used extensively as humidity conditioners in dermatological hydrogels. Propylene glycol, glycerol, and sorbitol usually are introduced in these dosage forms to prevent undesirable solid films from forming on the skin following water evaporation. In addition to vehicle stability, drug bioavailability can be affected profoundly by these additives through their effect on physicochemical factors controlling passive absorption, such as the solubility and diffusivity of the drug in the vehicle and the resistance of the skin barrier to drug penetration.

The effect of varying the solubility of the penetrant in the vehicle on transepidermal penetration was investigated thoroughly (1–3). Other investigators (4) found that drug diffusion in the vehicle may provide a rate-limiting step in absorption if the drug is suspended in the vehicle. On the other hand, *in vivo* studies have not fully clarified, except in certain cases, the effect of excipients on skin resistance to drug penetration.

From the results of *in vivo* studies on propylene glycol, the most studied of these polyols (5), a precise conclusion cannot be drawn as to whether this substance exerts its effect on drug penetration by influencing the physicochemical properties of the vehicle or those of the skin or both. This uncertainty is due to the fact that, in most of these studies, the physicochemical parameters relative to the vehicle and the drug, namely, the solubility and apparent diffusivity of the drug in the vehicle, were not controlled suitably to allow assessment of the effects of the excipient on the skin barrier. These parameters must be considered for an appropriate evaluation of the release properties of topical vehicles.

This paper discusses an *in vitro* study of drug release from hydrogels containing low molecular weight polyols. The purpose of this study was to establish general principles and procedures for control of the effects on percutaneous absorption caused by the additive-induced changes in drug solubility and diffusivity in these vehicles. Although convenient methods for determining the solubility and the diffusion coefficient of drugs in semisolid media have been developed (6–9), investigation of possible correlations of these parameters with the more readily measurable drug solubility in the liquid phase of gels and the viscosity of this phase, respectively, was desired.

Propylene glycol, ethylene glycol, glycerol, and sorbitol were the additives studied because they are used widely in commercial preparations. Benzocaine (ethyl *p*-aminobenzoate) was selected as a model of a neutral, topical drug with low water solubility.

THEORETICAL

The effect on drug release to the skin by variations of the solubility and/or diffusivity of the drug in the vehicle depends on whether the rate-controlling step of release occurs in the skin (Case A), in the vehicle (Case B), or in both the skin and the vehicle (Case C).

In Case A, such variations are expected to exert no effect on the release rate since this rate depends on skin parameters, which are presumed constant, and on the thermodynamic activity of the drug in the vehicle, which is independent of the vehicle properties, above saturation (10). For two vehicles characterized by different values of drug solubility and/or diffusivity, $Q_2/Q_1 = 1$, where the ratio Q_2/Q_1 of the amount of drug released per unit area at any given time from Vehicle 2 to that released at the same time from Vehicle 1 is defined as the relative released amount from Vehicle 2 with respect to Vehicle 1.

Higuchi (11) derived the following equation for Case B:

$$Q = \sqrt{(2A - S)SDt} \qquad \text{(Eq. 1)}$$

where D, A, and S are the apparent diffusivity, the total concentration, and the solubility of the drug in the vehicle, respectively. Equation 1 is valid for vehicles in which the apparent diffusion coefficient is constant, the suspended drug is finely dispersed, the dissolution of the drug is much faster than its diffusion through the vehicle, and the total drug concentration is at least threefold greater than the solubility. With Eq. 1, the following expression for the relative released amount can be derived:

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$$Q_2/Q_1 = \sqrt{\frac{(2A - S_2)S_2D_2}{(2A - S_1)S_1D_1}} \quad \text{(Eq. 2)}$$

where the drug concentration is assumed to be the same in the two vehicles.

In Case C, Q_2/Q_1 is expected to vary from 1 to the value expressed by Eq. 2, depending on the resistance the drug encounters in its diffusion through the respective vehicles relative to that in the skin[1].

Equation 2 should be suitable for evaluating the maximum effect on the *in vivo* release of a drug to the skin attributable to variations of drug solubility and/or diffusivity in the vehicle. Greater or opposite effects should be ascribed to modifications of the barrier properties of skin due to skin–vehicle interactions.

The convenience of Eq. 2 for controlling the solubility and diffusivity effects obviously is connected with the ease of determination of these parameters. For gels, Eq. 2 can be modified to contain such readily measurable parameters as drug solubility in the solvent of the gel and the viscosity of this solvent. If the gel substance does not interact significantly with the drug, the solubility and diffusion coefficient of the drug in the gel should be practically the same as in the pure liquid. The diffusivity in homogeneous liquids, D_l, can be expressed through the viscosity of the liquid, η, and can be expected to range from:

$$D_l = \frac{kT}{4\pi\eta}\left(\frac{4\pi}{3v}\right)^{1/3} \quad \text{(Eq. 3)}$$

for solutes whose molar volume, v, is equal to the molar volume of the solvent, to:

$$D_l = \frac{kT}{6\pi\eta}\left(\frac{4\pi}{3v}\right)^{1/3} \quad \text{(Eq. 4)}$$

when the molar volume of the solute is significantly greater than that of the solvent[2] (12).

Substitution in Eq. 2 of the appropriate expressions of D_l (*i.e.*, Eq. 3 or 4) in place of the respective D and of the drug solubility in the solvent of the gel, Sl, in place of the respective S leads to:

$$Q_2/Q_1 = \sqrt{\frac{(2A - Sl_2)Sl_2\eta_1}{(2A - Sl_1)Sl_1\eta_2}} \quad \text{(Eq. 5)}$$

for Solvents 1 and 2, having either similar or different molecular volumes approximately equal to or smaller than that of the drug in the former case and considerably smaller than that of the drug in the latter, or to:

$$Q_2/Q_1 = \sqrt{\frac{2(2A - Sl_2)Sl_2\eta_1}{3(2A - Sl_1)Sl_1\eta_2}} \quad \text{(Eq. 6)}$$

where the molecular volume of Solvent 1 is significantly greater than that of Solvent 2 and approaches the value of the diffusing particle.

As stated, Eqs. 5 and 6 are applicable to gels where the interactions of the drug with the chains of the gel polymer are either absent or unimportant. Actually, these equations also are valid where such interactions are strictly mechanical if the volume fraction of the gel substance is the same in Gels 1 and 2, and is not so high that the diameter of the gel pores approaches the diffusing particle diameter. In these conditions, the diffusion coefficient in the gel is proportional to that in the solvent, D_l (12):

$$D = \frac{D_l}{1 + 2/3\phi} \quad \text{(Eq. 7)}$$

If ϕ, the volume fraction of the gel substance, is the same in Gels 1 and 2, then Eq. 2 for these gels again may be transformed into Eq. 5 or 6. On the other hand, the complications arising when the drug or some components of the liquid phase undergo complexation by the gel polymer rule out the application of simple Eq. 5 or 6 to such systems.

EXPERIMENTAL

Materials—Ethylene glycol[3], propylene glycol[3], glycerol[3], sorbitol[4], and carboxypolymethylene[5] (carboxyvinyl polymer) were used as received. The neutral sodium salt of carboxypolymethylene was prepared as described in the literature (13). Benzocaine[3] was crystallized to a constant melting point of 91.5° and micronized[6]. The average diameter of the particles (microscopic analysis) was 2.0 μm (geometric). Simethicone[7] (dimethyl polysiloxane, silicone rubber) sheeting in a labeled thickness of ~127 μm was used as the membrane.

Vehicles, Apparatus, and Procedures—Hydrophilic gels containing 1% (w/v) carboxypolymethylene sodium salt were obtained from water (Gel W) and from the following aqueous polyols: 25% (w/w) ethylene glycol (Gel EG 25), 36% (w/w) ethylene glycol (Gel EG 36), 17.5% (w/w) propylene glycol (Gel PG 17.5), 30% (w/w) propylene glycol (Gel PG 30), 50% (w/w) glycerol (Gel G 50), 66% (w/w) glycerol (Gel G 66), and 54.5% (w/w) sorbitol (Gel S 54.5).

Solution gels, each containing benzocaine concentrations corresponding to 20 and 40% of the solubility in the respective solvents, and suspension gels, each containing 11 mg of micronized benzocaine/ml, were prepared following literature procedures (7, 8). The apparatus and procedures used for the release experiments with the solution (9) and suspension (7) gels were reported previously.

The apparent impermeability of the membrane to the polyols was demonstrated by the use of a previously described permeation cell and an apparatus (14) where the nongelled polyol–water mixtures without the drug were the internal solutions and water was the external phase. The periodic acid test (15) performed on this phase after 8-hr runs gave a negative result in all cases. Each release experiment was performed at least three times, and the averaged data were used for the individual plots.

Solubility Determinations—Benzocaine solubility in the solvent systems of the gels was determined by equilibrating excess benzocaine with the solvent at 30°. Samples then were withdrawn and rapidly filtered through a 0.22-μm pore filter[8]. The clear solutions were diluted with distilled water and spectrophotometrically[9] analyzed at 286 nm.

Diffusivity Determinations—The diffusion coefficient of benzocaine in the gels at 30° was calculated from the release data obtained from the solution gels according to a reported numerical method of analysis (9). The computations were executed with a computer[10].

Table I—Solubility, Diffusivity, and Viscosity Data at 30°

Gel	Drug Solubility in Solvent, Sl, mg/ml	Drug Diffusivity in Gel, D, $cm^2/sec \times 10^6$	Solvent Viscosity, η, cps	$D\eta$, cm^2/sec cps $\times 10^6$
W[a]	1.31	8.6	0.8	6.88
EG 25	2.37	4.5	1.60	7.2
EG 36	3.35	4.1	2.08	8.53
PG 17.5	2.44	4.7	1.58	7.33
PG 30	4.07	3.7	2.16	7.99
G 50	2.50	1.7	4.60	7.8
G 66[a]	3.77	0.79	11.8	9.32
S 54.5[a]	1.05	—	12.3	—

[a] The solubility and diffusivity data for this gel were obtained from previous reports (7–9).

RESULTS AND DISCUSSION

Solubility of Drug, Microscopic Viscosity of Gels, and Drug Diffusivity in Gels—The values of the solubility, Sl, of benzocaine in the solvents of the gels studied are listed in Table I, together with the viscosity[11] of the solvents, η, and the diffusion coefficient, D, of drug in the gels. These values were determined by a recently developed method based on numerical analysis of release data (9). Accordingly, two drug concentrations, corresponding to 20 and 40% solubility in the solvent, were run for each gel; the respective values of diffusivity obtained from the computations were compared to ascertain the independence of concentration. This independence existed for all gels investigated since the diffusivity values determined at the two drug concentrations were within experimental error. Table I reports the average values. The diffusion coefficient of benzocaine in the gel containing sorbitol was not determined since previous work showed concentration dependence of this parameter (9).

[1] This analysis assumes the same release mechanism for the two vehicles being compared. The case of different mechanisms is not considered since it generally would require large variations of solubility and diffusivity.

[2] Strictly speaking, a correction for nonsphericity of the diffusant should be introduced in the expression of D for large particles. However, this correction has been ignored since it amounts to <10% for all but the most elongated structures (12).

[3] Carlo Erba S.p.A., Milan, Italy.

[4] Istituto Chemioterapico Italiano, Milan, Italy.

[5] Carbopol 934, B. F. Goodrich Chemical Co., Cleveland, Ohio.

[6] Jet mill model JMRS-80, Fryma Maschinen AG, Rheinfelden, Switzerland.

[7] Silastic, Medical Products Division, Dow Corning Corp., Midland, Mich.

[8] GSWP 01300, Millipore Filter Corp., Bedford, Mass.

[9] Beckman DU spectrophotometer.

[10] IBM 370/168.

[11] Rheomat-30 viscosimeter, Contraves, Zurich, Switzerland.

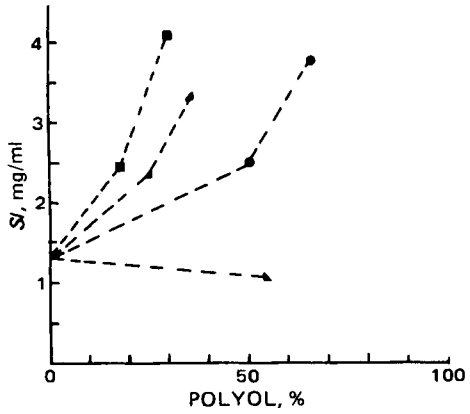

Figure 1—*Solubility of benzocaine in polyol–water mixtures at 30°. Key: ■, propylene glycol; ◢, ethylene glycol; ●, glycerol; and ◣, sorbitol.*

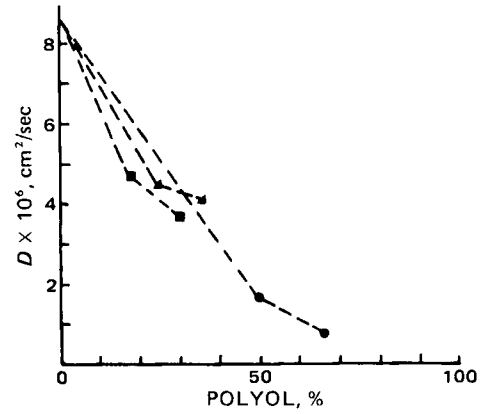

Figure 3—*Diffusivity of benzocaine in the polyol-containing hydrogels. Key: ■, propylene glycol; ◢, ethylene glycol; and ●, glycerol.*

The concentration independence of diffusivity in Gels W, G 50, G 66, EG 25, EG 36, PG 17.5, and PG 30 points to the absence of self-aggregation of the benzocaine molecules over the concentration ranges investigated (12). Complexation of the drug by the gel substance also can be excluded, because previous work indicated that the addition of carboxypolymethylene sodium salt to solutions of benzocaine in water or in water–glycerol did not alter the thermodynamic activity of the drug (8). Then the values reported in Table I for the solubility in the solvents also may be referred to as the drug solubility in the corresponding gels.

The dependence of the parameters in Table I on solvent composition can be visualized best in Figs. 1–3. Table I and Fig. 1 show that the solubility of benzocaine in the solvent mixtures increased with increasing content of propylene glycol, ethylene glycol, or glycerol, but the opposite effect was produced by sorbitol. For a given composition of the water–additive mixture, ascent in the polyol series from ethylene glycol to sorbitol resulted in a progressive solubility decrease. Such a decrease was more evident for higher additive concentrations. The greater solvent power of propylene glycol with respect to ethylene glycol probably was due to the moderately lower polarity of the propylene glycol molecule.

A substantial inverse proportionality between the diffusion coefficient in the gels and the viscosity of the respective solvents can be noticed on comparing the data in Figs. 2 and 3. This relationship is confirmed in Table I by the $D\eta$ products approximating a constant and in Fig. 4 by the linear trend of the D *versus* $1/\eta$ plot with a least-squares intercept approximating zero. Such a relationship agrees with the theory. Once complexation is excluded, only mechanical interactions between the diffusing species and the gel substance can be anticipated. Then, at the low concentrations of the gel polymer used in the present work, a proportionality between the diffusion coefficient of the drug in the gel and that in the solvent should exist and should be expressed by Eq. 7. Compliance of the latter coefficient with (or, in fact, an approximation to) Eq. 3 or 4 should account for the relationship between D and η emerging from the present data. Equation 4 seems more appropriate since the molecular volume either of water or of the polyols is in all cases smaller than that of the diffusing particle.

According to the foregoing considerations, the viscosity of the solvent mixtures should represent the effective microscopic viscosity of the respective gels; in turn, the composition of the liquid phase of gels should be substantially the same as that of the corresponding nongelled solvents. The assumption of an inverse proportionality between D and η, although substantially reasonable, is in fact an approximation. The nonzero intercept of the D *versus* $1/\eta$ plot in Fig. 4 hardly is attributable only to experimental errors. This observation may be better explained by admitting that in the presence of increasing additive concentrations, the diffusion coefficient in the liquid phase of gels deviates toward higher values than those expressed by Eq. 4. Furthermore, the volume fraction of solvent immobilized by the polymer might decrease, thus causing a decrease of the mechanical interactions of the diffusing particle with the gel network and, consequently, an increase of the diffusion coefficient in the gel with respect to that in the solvent (Eq. 7).

Influence of Solubility and Microscopic Viscosity on Release—Silicone rubber membranes similar to those used in this investigation were employed previously (4) for simulating skin. Their permeability to the drug is not supposed to be influenced by the polyols since none of them was found in the receiving phase. The degree of fineness of the suspended benzocaine, the concentration of the drug, and the concentration of the gel polymer all were kept constant so that the differences in release could not be attributed to these variables.

The plots in Fig. 5 show that either the solubility of the drug or the microscopic viscosity of the gels markedly affected release. Substantially

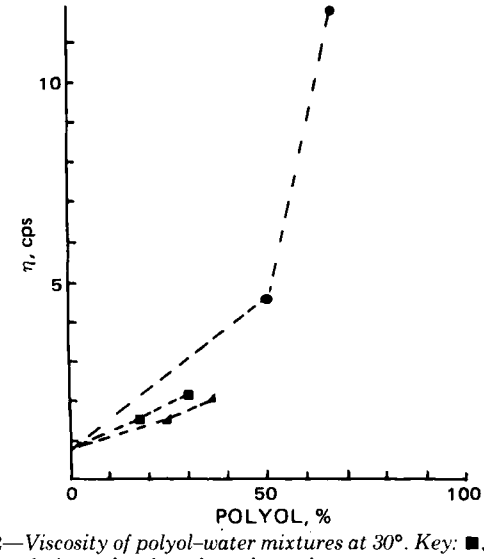

Figure 2—*Viscosity of polyol–water mixtures at 30°. Key: ■, propylene glycol; ◢, ethylene glycol; and ●, glycerol.*

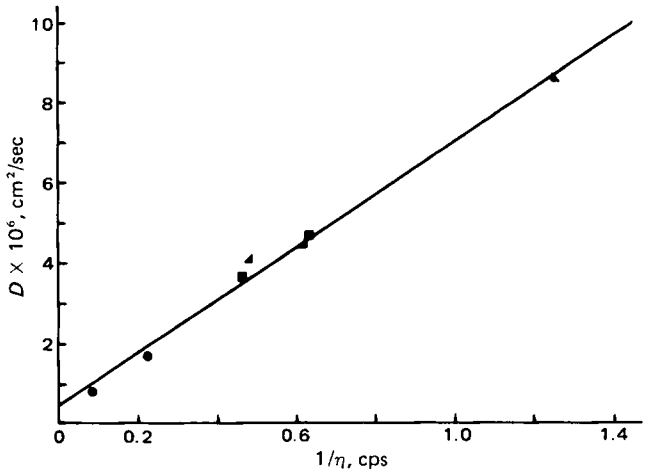

Figure 4—*Plot of benzocaine diffusivity in the hydrogels* versus *the inverse viscosity of the respective solvents. Key: ■, propylene glycol-containing gels; ◢, ethylene glycol-containing gels; ●, glycerol-containing gels; and ◣, additive-free Gel W. The linear regression parameters are slope = 6.65 and intercept = 0.44.*

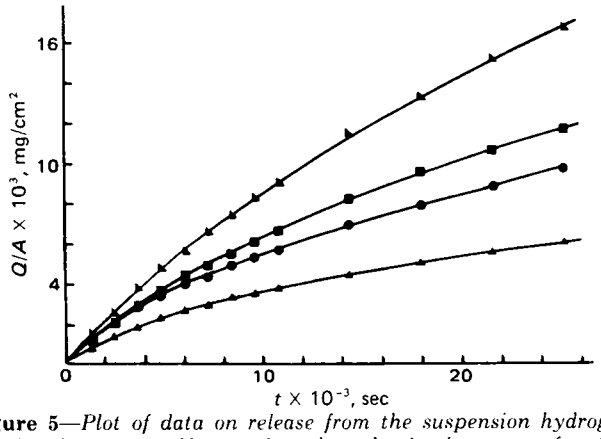

Figure 5—*Plot of data on release from the suspension hydrogels showing the amount of benzocaine released per unit area as a function of time. The total drug concentration was 11 mg/ml. Key: ◣, Gel W; ▲, Gel S 54.5; ●, Gel G 66; and ■, Gel G 50. The plots for Gels EG 25, EG 36, PG 17.5, and PG 30 are nearly superimposable on that for Gel W.*

distinct release patterns were shown by gels differing only in a single parameter (compare the data in Table I and Fig. 5 for Gels G 66 and S 54.5 and for Gels PG 17.5 and G 50). The data also indicate that the drug solubility and the gel microviscosity exerted their effects in opposite directions, with the former related directly and the latter related inversely to release. This effect can explain the substantially identical release pattern shown by gels differing in both parameters such as Gels W, EG 25 (or PG 17.5), and PG 30 (or EG 36) since any increase in the drug solubility was paralleled by an increase in the microscopic viscosity.

In light of the considerations stated under *Theoretical*, the results point to possible utilization of Eq. 5 for controlling the effect on release of varying the described parameters. Such an effect may be represented through the relative released amount, *i.e.*, the ratio, Q/Q_W, of the amount of drug released from each additive-containing gel to the amount released at the same time from the additive-free Gel W. The plots in Fig. 6 were intended to verify the time dependence of Q/Q_W for each gel; a comparison of the values of Q/Q_W determined at the end of the release experiments ($t = 25.2 \times 10^3$ sec) with those calculated by Eq. 5 is given in Table II.

The relative released amount was time dependent for gels (G 50, G 66, and S 54.5) that showed a marked deviation from the Q/Q_W value of unity determined at $t = 25.2 \times 10^3$ sec. Such a deviation was essentially less than that calculated by Eq. 5. On the other hand, a fair correspondence existed at all times between the experimental and the calculated Q/Q_W values when the latter value approximated one (see the data for PG 17.5, PG 30, EG 25, and EG 36). These results are in compliance with the theoretical considerations for Case C, and they appear to substantiate a vehicle–membrane-controlled release for the present gels. The increasing deviation of Q/Q_W from unity with time toward the value ex-

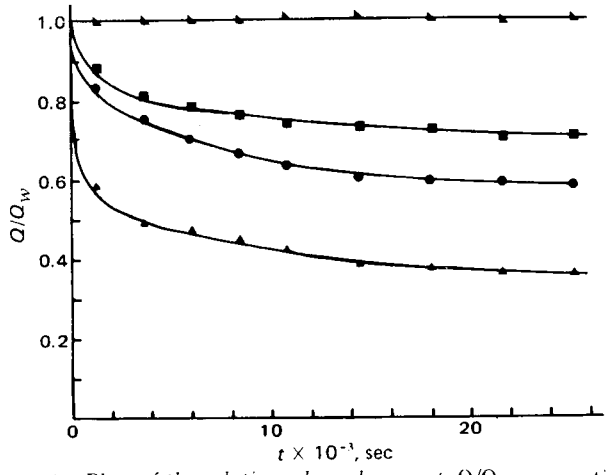

Figure 6—*Plots of the relative released amount, Q/Q_W, versus time. Key: ▲, Gel S 54.5; ●, Gel G 66; ■, Gel G 50; and ◣, Gel PG 17.5. The plots for Gels PG 30, EG 25, and EG 36 are nearly superimposable on that for Gel PG 17.5.*

Table II—Comparison of Experimental Relative Released Amount, Q/Q_W, with Values Calculated by Eq. 5

Gel	Experimental ($t = 25.2 \times 10^3$ sec)	Calculated
EG 25	1.04	0.93
EG 36	1.07	0.94
PG 17.5	1.01	0.94
PG 30	1.06	0.99
G 50	0.69	0.56
G 66	0.58	0.41
S 54.5	0.36	0.22

pressed by Eq. 5 is in agreement with the statement in previous reports (7, 16) that the vehicle–membrane-controlled release model evolves with time toward the vehicle-controlled model. Also, the present experimental evidence supports the view that Eq. 5 expresses the maximum effect on release produced by variations of the drug solubility and/or the gel microviscosity.

In Fig. 7, the experimental values of the relative released amount determined at $t = 1.2 \times 10^3$ sec, $t = 3.6 \times 10^3$ sec, and $t = 25.2 \times 10^3$ sec for all gels are plotted *versus* the values calculated by Eq. 5. The alignment of points clearly indicates that a definite relationship existed between the experimental vehicle–membrane-controlled Q/Q_W and the calculated vehicle-controlled values. This result points to the usefulness of such plots as calibration curves of the effects of the solubility and the diffusivity of the drug in the applied phase on quasi-steady-state[12] drug penetration through a membrane. Curves of this type, if obtained from *in vivo* experiments, should be indicative of the absence of vehicle-induced changes in skin permeability to drug; in this event, they could enable the prediction of the relative released amount once the parameters in Eq. 5 are determined. The more general Eq. 2 should be used to construct similar calibration curves when dealing with vehicles not meeting the requirements of Eq. 5.

CONCLUSIONS

In summary, Eq. 5 is proposed as a tool for controlling the effects of polyol additives, usually introduced in dermatological hydrogels, on important physicochemical factors influencing drug release such as the solubility and diffusivity of the drug in the vehicle. This equation has been shown to predict the maximum effect on benzocaine penetration through silicone rubber membranes associated with changes in the described parameters. A precise correlation exists between the experimental values of the relative released amount and the values calculated by Eq. 5. This finding points to the potential usefulness of this equation for constructing calibration curves of the effects of drug solubility and diffusivity in the vehicle on quasi-steady-state drug penetration through skin.

Although a silicone rubber membrane is far from being perfectly rep-

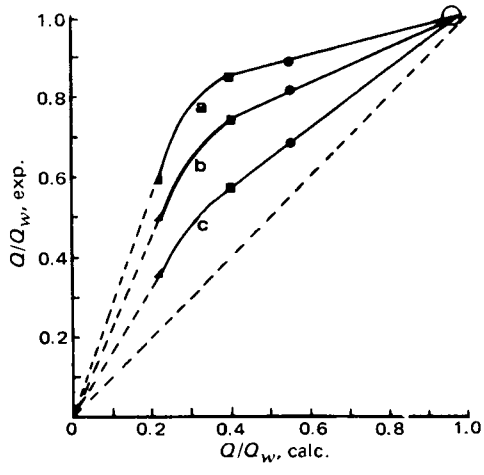

Figure 7—*Plots of the experimental relative released amount, Q/Q_W, versus the values calculated by Eq. 5. Key: a, $t = 1.2 \times 10^3$ sec; b, $t = 3.6 \times 10^3$ sec; c, $t = 25.2 \times 10^3$ sec; ○, Gels EG 25, EG 36, PG 17.5, and PG 30; ■, Gel G 66; ▲, Gel S 54.5; and ●, Gel G 50.*

[12] According to the results of a previous work (7), linear concentration gradients of the drug in the membrane should exist after the early times of the release experiments.

resentative of skin with regard to drug penetration, it nevertheless provides the requirements for the present comparative study where the following assumptions were made:

1. Skin transport is passive.
2. The skin parameters relevant to drug penetration are not influenced by the vehicle.
3. The vehicle composition does not change significantly during release.

Derivation of Eq. 5 from Higuchi's Eq. 1 (11) was possible because an inverse proportionality was observed between the diffusivity of drug in gels and the viscosity of the respective solvents. Such a relationship is justifiable considering the current theories on diffusion in diluted gels, as long as the viscosity of each solvent is accepted as the microscopic viscosity of the corresponding gel and self-aggregation or complexation of the drug is excluded. All of the gels studied in the present work (except, perhaps, the gel containing sorbitol) met the requirement of Eq. 5 that the molecular volume of the components of the liquid phase be substantially smaller than that of the diffusing drug. The cases of molecular volume of solvent approaching or exceeding that of the drug might deserve investigation for the applicability of Eq. 5 or 6.

It is hoped that the present study will help to rationalize the compounding of pharmaceutical gels and, furthermore, that the suggested principles and procedures for controlling the vehicle parameters will be useful in *in vivo* studies intended to assess the effects of excipients on skin permeability to drugs.

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Effect of Particle Size on Ophthalmic Bioavailability of Dexamethasone Suspensions in Rabbits

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Abstract □ Three suspensions of 0.1% [^{3}H]dexamethasone were prepared with mean particle sizes of 5.75, 11.5, and 22.0 μm. The suspensions were dosed topically to the right eyes of rabbits. Their bioavailability was compared by measuring aqueous humor and corneal levels over 5 hr. A statistically significant rank-order correlation was observed between increasing drug levels and decreasing particle size.

Keyphrases □ Dexamethasone—ophthalmic suspensions, bioavailability, effect of particle size, rabbits □ Bioavailability—dexamethasone, ophthalmic suspensions, effect of particle size, rabbits □ Ophthalmic preparations—dexamethasone suspensions, bioavailability, effect of particle size, rabbits

In the development of an aqueous suspension for topical use in the eye, the size of the suspended particles often is governed by their irritation potential. Although the particle size is an important consideration in irritation and comfort, the ophthalmic bioavailability of the drug can be influenced by particle size according to one or two possible *in vivo* mechanisms. If the particle induces tearing, rapid drainage of the instilled dose could reduce bioavailability (1, 2). In addition, the dissolution rate of particles residing in the conjunctival sac just after dose instillation should influence ophthalmic bioavailability.

Few published articles have indicated the importance of particle size in ophthalmic bioavailability. Sieg and Robinson (2) studied the bioavailability of a 0.1% ophthalmic fluorometholone suspension and demonstrated that the particles were retained within the conjunctival sac longer than the corresponding saturated solution and contributed significantly to the quantity of drug penetrating the cornea. By comparing the area under the aqueous humor–time curve for the 0.1% suspension and the saturated solution, ~78% of the area was determined to come from the retained particles. Therefore, the dissolution rate for poorly soluble drugs may influence the rate and extent of penetration into eye fluids.

The present study was conducted in rabbits to determine the importance of particle size in the ophthalmic bioavailability of a 0.1% dexamethasone suspension. Dexamethasone was chosen because of its clinical significance and because of the availability of tritiated dexa-

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