drugs that intrinsically dissolve slowly ($k_i/pM = 0.0667$), a decrease in disintegration time cannot greatly improve the tablet dissolution (curve b → b'), whereas the effect is great for fast dissolving drugs ($k_i/pM = 0.333$, curve a → a'). The T_d and k_i/pM values influence an overall dissolution profile in different ways, so that the evaluation of the dissolution properties of solid dosage forms merely from an overall dissolution profile might lead to an erroneous conclusion. Therefore, to evaluate the dissolution properties of solid dosage forms, disintegration measurements and dissolution tests of the powder before or after inclusion in a tablet should be carried out separately.

The developed equation is based on the simple disintegration–dissolution model. Actually, more complex factors may affect tablet dissolution. For instance, disintegration is not always the deaggregation into primary particles and particle-size distribution is not always log-normal. The equation also would not be applied to the case where drug particle-size distribution changes after compression. In spite of such restrictions, the proposed equation might still be useful to predict or examine tablet dissolution.

APPENDIX

Let the integration with respect to $\ln a_0$ in Eqs. 9*b* and 11*b* be $I(T)$:

$$I(T) = \frac{\int_{\ln[(2k_i/p)(t-T)]}^{\infty} pV_{(t-T)}N_0 f(m/T_d{}^m)T^{m-1}\, d(\ln a_0)}{\int_{-\infty}^{\infty} pN_0 v_0 f\, d(\ln a_0)} \quad \text{(Eq. A1)}$$

By letting $(m/T_d{}^m)T^{m-1} = r(T)$ and $(2k_i/p)(t - T) = \tau(T)$ for simplification and employing the method similar to that used by Brooke (11), Eq. A1 becomes:

$$I(T) = r(T)\left\{\left[1 - F\left(\frac{\ln[\tau(T)/M] - 3\sigma^2}{\sigma}\right)\right]\right.$$
$$-3[\tau(T)/M]\exp(-5\sigma^2/2)\left[1 - F\left(\frac{\ln[\tau(T)/M] - 2\sigma^2}{\sigma}\right)\right]$$
$$+3[\tau(T)/M]^2\exp(-4\sigma^2)\left[1 - F\left(\frac{\ln[\tau(T)/M] - \sigma^2}{\sigma}\right)\right]$$
$$\left.-[\tau(T)/M]^3\exp(-9\sigma^2/2)\left[1 - F\left(\frac{\ln[\tau(T)/M]}{\sigma}\right)\right]\right\} \quad \text{(Eq. A2)}$$

For numerical computation of $I(T)$, the following approximation (15) was used for $F(x)$:

$$F(x) = 1 - \frac{1}{\sqrt{2\pi}}\exp(-x^2/2)(ay + by^2 + cy^3 + dy^4 + ey^5) \quad \text{(Eq. A3)}$$

where $y = 1/(1 + 0.2316419x)$, $a = 0.319381530$, $b = -0.356563782$, $c = 1.781477937$, $d = -1.821255978$, and $e = 1.330274429$. Finally, Eqs. 9*b* and 11*b* can be given by:

$$\int_0^t I(T)\, dT \qquad (t < T_d)$$
$$\int_0^{T_d} I(T)\, dT \qquad (t \geq T_d)$$

For numerical computation, it can be approximated by the trapezoidal rule based on dividing T_d by a large number of n; for $t < T_d$:

$$\int_0^t I(T)\, dT \fallingdotseq \frac{h}{2}[(I_0 + I_{n'}) + 2(I_1 + I_2 + \ldots + I_{n'-1})] \quad \text{(Eq. A4)}$$

for $t \geq T_d$:

$$\int_0^{T_d} I(T)\, dT \fallingdotseq \frac{h}{2}[(I_0 + I_n) + 2(I_1 + I_2 + \ldots + I_{n-1})] \quad \text{(Eq. A5)}$$

where $I_i = I(T_i)$ $(i = 0, 1, 2, \ldots.)$, $h = T_d/n$, $n' = (nt)/T_d$, and $T_n = T_d$.

The double integration is evaluated practically by dividing disintegration time into about 500 intervals.

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Conductivity of Drugs Used for Iontophoresis

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Abstract □ The electrical conductivities of drugs were measured *in vitro* using a conductivity MHO-meter. These experiments indicate that local anesthetics, vasoconstrictors, some corticosteroids, several anticancer drugs, and several antiviral agents are suitable for iontophoresis. The contribution to conductivity of buffers and nonspecific ions in the same solution with the drug also was defined.

Keyphrases □ Conductivity, electrical—various drugs measured *in vitro*, suitability for iontophoresis □ Iontophoresis suitability—various drugs, electrical conductivity measured *in vitro*

Iontophoresis is a simple, well-documented method of drug application for medication of tissues (1). It assures the penetration of electrically charged drugs into surface tissues. It is possible to medicate electrically any surface tissue with drugs having a positive or negative charge (1). The technique involves transporting selected ions electrically into a tissue by passing a direct electrical current through a medicating solution and the patient, using selected electrode polarity.

BACKGROUND

Iontophoresis has many advantages as a drug administration method. Systemic toxicity is virtually eliminated since only a minute amount of

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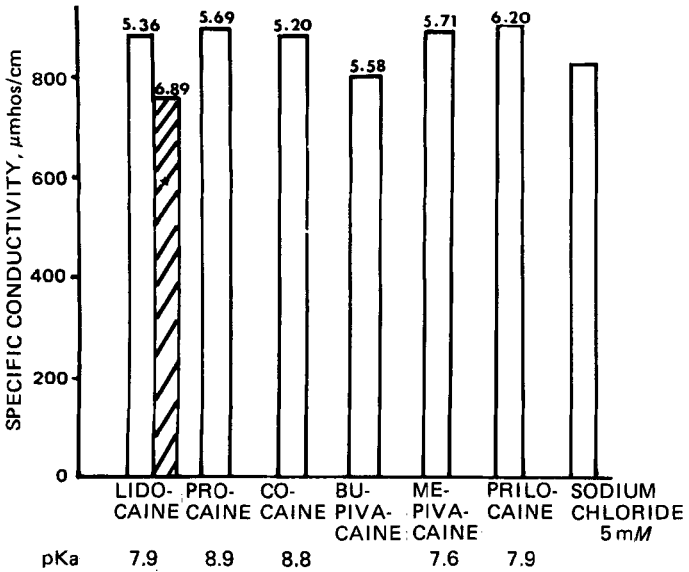

Figure 1—*Specific conductivities of several local anesthetics. The numbers above the bars are pH values of local anesthetic solution. The concentration of local anesthetics was 10 mM.*

drug is delivered. Nevertheless, a relatively high drug concentration is administered locally (2). Patient acceptance is excellent, and fear of administration is eliminated, especially in comparison to administration by syringe and needle.

Iontophoresis is a method of choice for the administration of pilocarpine in a diagnostic test for cystic fibrosis (3) and of lidocaine and epinephrine for external ear canal anesthesia (4). Loose deciduous teeth have been extracted following a profound surface anesthesia induced by iontophoretic application of a local anesthetic (2% lidocaine) containing epinephrine (1:50,000) to the oral mucosa (5). Iontophoresis also has been used to administer vasodilators such as methacholine and histamine for peripheral vascular disease (6).

Iontophoresis frequently has been used in dentistry as a method of choice to aid in the penetration of fluoride ions for the treatment of exposed ultrasensitive (hypersensitive) dentin (7–10). Treatment of recurrent herpes labialis using idoxuridine iontophoresis results in abortion of the lesions and rapid healing (2, 11). Other uses of iontophoresis in medicine have been reviewed (1).

Several conditions are necessary for iontophoretic medication to be achieved. The drug should be charged or modified to carry a charge, and the area medicated must be at a body surface. The drug is applied under an electrode of the same polarity; a return electrode, opposite in charge to the drug, is placed at an indifferent site on the body. Then current is allowed to flow below the level of the pain threshold for an appropriate time (2).

This paper reports on the electrical characteristics of various drugs so that proper conditions for use may be achieved. The drugs studied include local anesthetics, vasoconstrictors, corticosteroids, antiviral agents (including some nucleosides and nucleotides), and anticancer agents.

EXPERIMENTAL

Apparatus—A lectro MHO-meter[1] equipped with a conductivity measuring cell[2] and a pH-millivolt meter[3] were used.

Chemicals—Local anesthetics were lidocaine hydrochloride[4], procaine hydrochloride[5], cocaine hydrochloride[6], bupivicaine hydrochloride[7], mepivacaine hydrochloride[8], and prilocaine hydrochloride[9]. Vasoconstrictors were epinephrine bitartrate[7], levarterenol bitartrate[7], and

[1] Model MC-1, Mark IV, Lab-Line Instruments, Melrose Park, Ill.
[2] Model 3403, Yellow Spring Instrument Co., Melrose Park, Ill.
[3] Model 701, Orion Research, Cambridge, Mass.
[4] Xylocaine Hydrochloride Monohydrate, Astra Pharmaceutical Products, Worcester, Mass.
[5] Novocaine Hydrochloride, Medical College of Georgia Pharmacy, Augusta, Ga.
[6] Medical College of Georgia Pharmacy, Augusta, Ga.
[7] Sterling-Winthrop Research Institute, Rensselaer, N.Y.
[8] Carbocaine Hydrochloride, Sterling-Winthrop Research Institute, Rensselaer, N.Y.
[9] *Citant Hydrochloride*, Astra Pharmaceutical Products, Worcester, Mass.

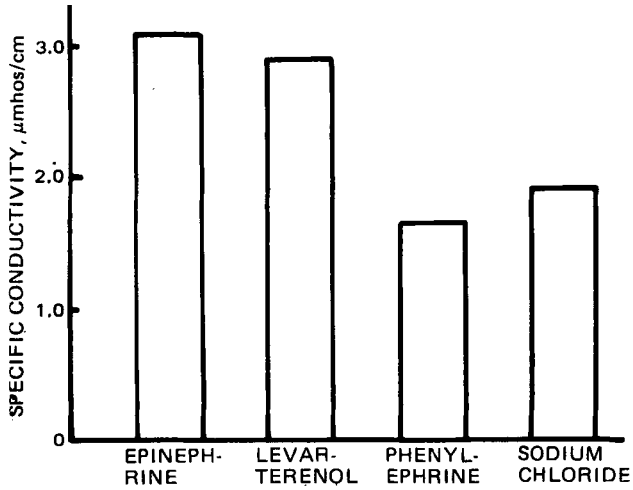

Figure 2—*Specific conductivities of vasoconstrictors. The concentration studied was 0.12 mM (about 1:25,000). The concentration of sodium chloride was the same as that of vasoconstrictors.*

phenylephrine hydrochloride[10]. Corticosteroid hormones were hydrocortisone sodium succinate[11], methylprednisolone sodium succinate[12], and hydrocortisone sodium phosphate[13]. Anticancer drugs were methotrexate[14], cyclophosphamide[15], bleomycin[16], and doxorubicin[17].

Nucleotides were adenosine 5′-monophosphate (AMP)[18], adenosine 5′-diphosphate (ADP)[18], adenosine 5′-triphosphate (ATP)[18], adenosine 3′,5′-cyclic monophosphate (cAMP)[18], uridine 5′-diphosphate (UDP)[18], uridine 5′-triphosphate (UTP)[18], and thymidine 5′-monophosphate (TMP)[18]. Antiviral agents were idoxuridine[19], vidarabine[20], thymine arabinoside[21], vidarabine monophosphate[22], and phosphonoacetic acid[23].

Conductivity Measurement Procedures—Various concentrations of chemicals were prepared with double-distilled water. Some chemicals were dissolved in buffers having different pH values. The prepared solutions were placed in a water bath (25°) for maintaining the temperature of chemical solutions. An aliquot of the solution was taken for measuring the specific conductivity, using the lectro MHO-meter, and the remaining portion of the solution was used for the pH determination.

Specific conductivity, k, was measured by direct reading of the lectro MHO-meter. The formula for calculating k is $k = (l/A)\,L$, where l/A is the conductivity cell constant (l is the distance in centimeters between the electrodes and A is the area in square centimeters of the electrode) and L is the conductivity in reciprocal ohms. Equivalent conductance was calculated from the specific conductivity by using $\Lambda = (k \times 1000)/C$, where Λ is the equivalent conductance, k is the specific conductivity, and C is the concentration of electrolyte (molar).

RESULTS

Figure 1 shows the specific conductivities of several local anesthetics tested at a concentration of 10 mM (sodium chloride measured at 5 mM is shown for reference). The specific conductivities ranged from 800 to 900 μmhos/cm. If one considers the pKa values of local anesthetics (lower line of Fig. 1) and the pH of the local anesthetic solutions (above the bars), it can be calculated that almost all of the local anesthetic molecules were ionized. When the pH of the lidocaine solution was increased from 5.36 to 6.89 by adding 1 mM NaOH (crosshatched bar of Fig. 1), the specific conductivity of the solution was decreased by 15%, indicating that the

[10] Neosynephrine Hydrochloride, Sterling-Winthrop Research Institute, Rensselaer, N.Y.
[11] Solu-Cortef, The Upjohn Co., Kalamazoo, Mich.
[12] Solu-Medrol, The Upjohn Co., Kalamazoo, Mich.
[13] Merck Sharp & Dohme, West Point, Pa.
[14] American Cyanamid Co., Pearl River, N.Y.
[15] Cytoxan, Mead Johnson Laboratories, Evansville, Ind.
[16] Blenoxane, Bristol Laboratories, Syracuse, N.Y.
[17] Adria Laboratories, Wilmington, Del.
[18] Sigma Chemical Co., St. Louis, Mo.
[19] Calbiochem, La Jolla, Calif.
[20] Ara-A, Parke-Davis & Co., Ann Arbor, Mich.
[21] Ara-T, a gift of Dr. Glenn Gentry, University of Mississippi, Jackson, Miss.
[22] Ara-AMP, Parke-Davis, Ann Arbor, Mich.
[23] PAA, Abbott Laboratories, Chicago, Ill.

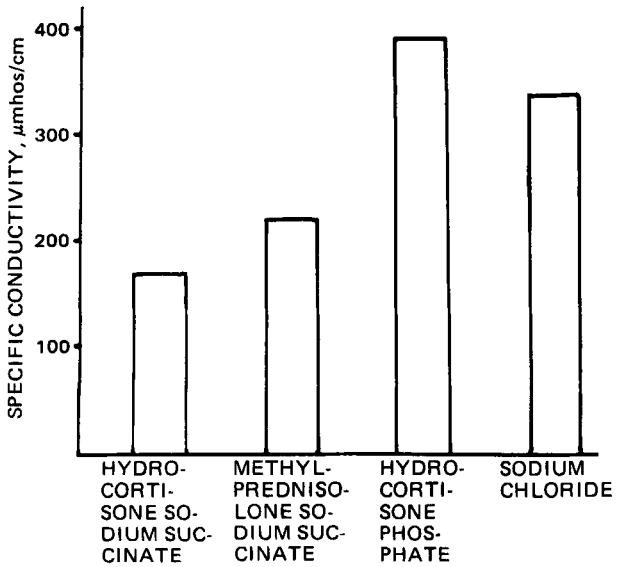

Figure 3—*Specific conductivities of some charged steroids. The concentration of steroids and sodium chloride was 2.0 m*M.

concentration of ionized lidocaine molecules was decreased by alkalization.

Figure 2 shows the specific conductivity of epinephrine bitartrate, levarterenol bitartrate, phenylephrine hydrochloride, and sodium chloride at 0.12 m*M*. This vasoconstrictor concentration is effective for iontophoresis in clinical practice. The conductivities of the two bitartrates were higher than the conductivity of the same concentration of sodium chloride, probably because of the presence of the divalent anion.

Figure 3 shows the specific conductivities of 2.0 m*M* steroids and sodium chloride. Hydrocortisone phosphate had the highest conductivity, methylprednisolone sodium succinate was intermediate, and hydrocortisone sodium succinate had the lowest. Hydrocortisone and methylprednisolone were nonconductive (data not shown).

Since some steroid solutions contain buffers, *e.g.*, phosphate buffer, the specific conductivity of the solution includes the conductivity of the buffer system. An experiment was performed to determine whether drug conductivity can be calculated by determining the conductivities of the drug and buffer followed by subtraction of the conductivity of the buffer alone. An additional amount of phosphate buffer, exactly as specified by the manufacturer, was added to the steroid–buffer solution, and the specific conductivity of the resultant solution as well as that of the buffer alone was measured.

When the same amount of phosphate buffer was added to the methylprednisolone sodium succinate–buffer solution, the conductivity was approximately increased by the conductivity of the phosphate buffer alone (Fig. 4). The pH of each of the three solutions was the same (7.0). The result indicates that there is no interaction between steroid and phosphate buffer and that each ion acts independently in terms of its contribution to conductivity.

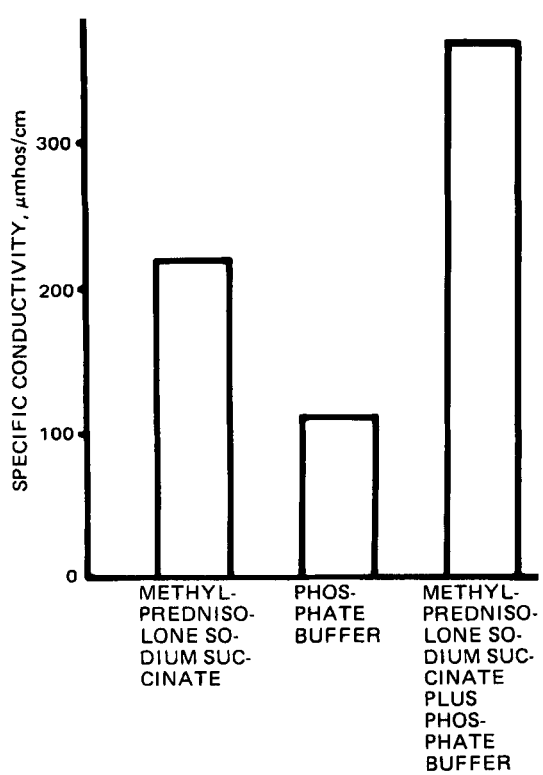

Figure 4—*Effect of phosphate buffer on the specific conductivity of methylprednisolone sodium succinate at 2.0 m*M.

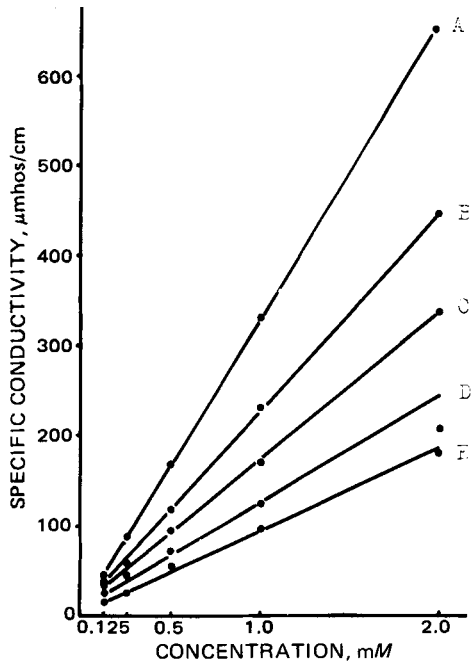

Figure 5—*Specific conductivities of anticancer drugs. Key: A, methotrexate; B, cyclophosphamide; C, sodium chloride; D, bleomycin; and E, doxorubicin.*

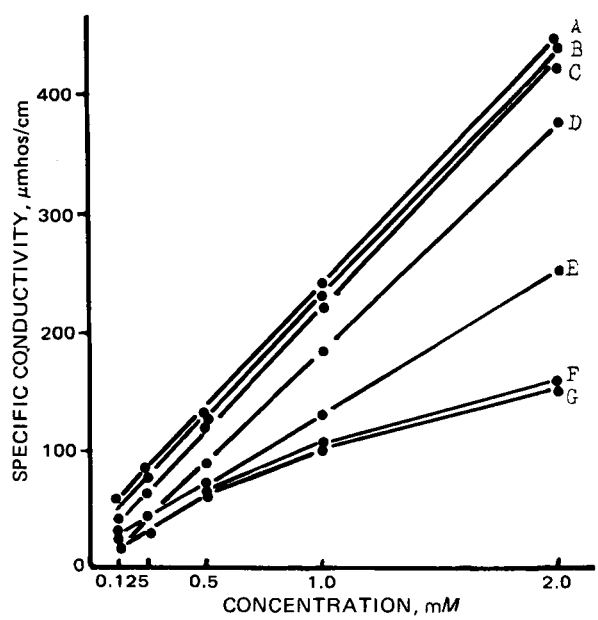

Figure 6—*Specific conductivities of nucleotides. Key: A, uridine 5′-triphosphate; B, adenosine 5′-triphosphate; C, adenosine 5′-diphosphate; D, uridine5′-diphosphate; E, thymidine 5′-monophosphate; F, adenosine 3′,5′-cyclic monophosphate; and G, adenosine 5′-monophosphate.*

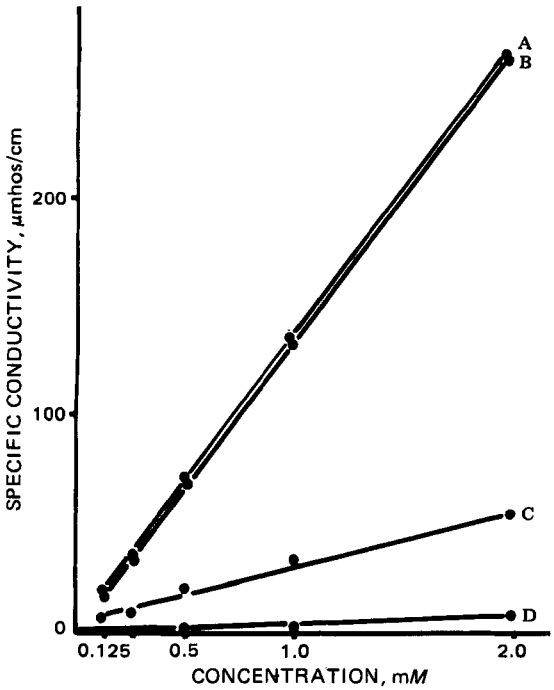

Figure 7—*Specific conductivities of antiviral agents. Key: A, phosphonoacetic acid; B, vidarabine monophosphate; C, idoxuridine; and D, vidarabine and thymine arabinoside. The conductivity of idoxuridine was measured in tromethamine buffer.*

Figure 5 is a plot of drug concentration *versus* specific conductivity for several anticancer drugs. A similar plot for sodium chloride is included for comparison. Drugs tested showed high conductivities. Methotrexate had the highest conductivity since it included a glutamate residue with two negative centers.

Figure 6 illustrates conductivity–concentration plots for several nucleotides. These compounds were studied because of their relationship to antiviral and anticancer drugs. The highly charged phosphate compounds showed high conductivities. The di- and triphosphates were more conductive than monophosphates. All nucleosides tested were nonconductive (data not shown).

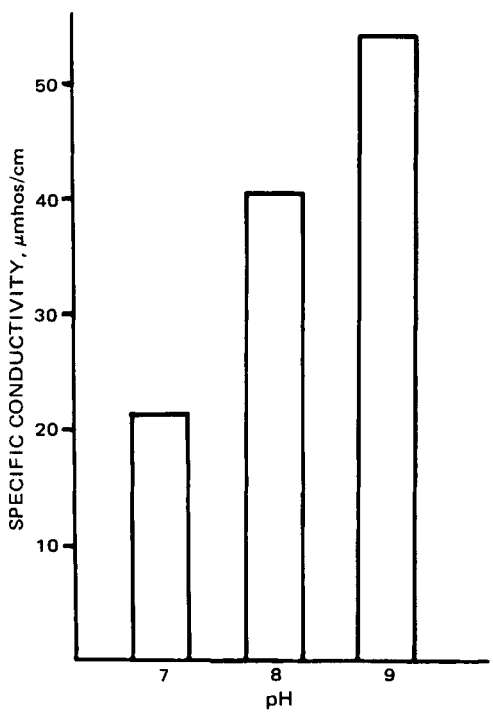

Figure 8—*Specific conductivity of idoxuridine at different pH values. Idoxuridine was dissolved in 0.02* M *tromethamine buffer solutions at pH 7, 8, and 9.*

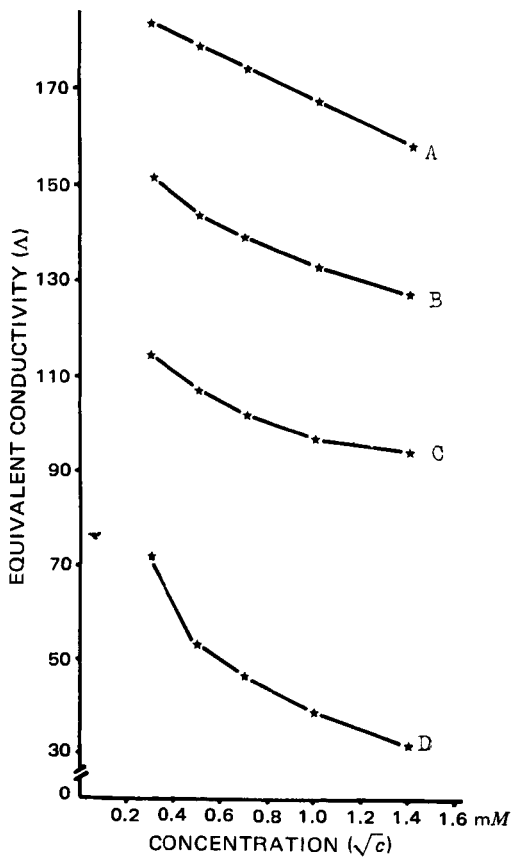

Figure 9—*Plot of equivalent conductivity,* Λ, versus $\sqrt{c}$ *for sodium chloride (A), vidarabine monophosphate (B), lidocaine (C), and idoxuridine (D). The value of* Λ *was calculated by the equation described in the text.*

Figure 7 illustrates the conductivities of several antiviral agents. Nucleoside analogs such as vidarabine, thymine arabinoside, and idoxuridine had almost no conductivity. However, the highly charged vidarabine monophosphate and phosphonoacetic acid had very high conductivities. When idoxuridine was dissolved in 0.02 *M* tromethamine buffer (pH 9.0), the conductivity of idoxuridine itself was highly increased by six times. As the pH increased, the conductivity of idoxuridine also increased (note the conductivity of the buffer alone at each pH subtracted) (Fig. 8). At pH 9, idoxuridine showed the highest conductivity. These data are consistent with the weak acid nature of idoxuridine (pKa 8.20).

Figure 9 shows the equivalent conductance, Λ, plotted against concentration for sodium chloride, vidarabine monophosphate, lidocaine, and idoxuridine. Sodium chloride solution formed a straight-line relationship when Λ was plotted against the square root of the concentration, $\sqrt{c}$; this relationship is typical of strong electrolytes, and the data agree with literature values (12). Idoxuridine showed the curvilinear pattern of a weak electrolyte while vidarabine monophosphate and lidocaine were intermediate.

DISCUSSION

Many drugs are appropriately charged for iontophoretic administration. Conductivity experiments conducted *in vitro* indicate which drugs are the best candidates for iontophoresis. Furthermore, the electrical properties of solutions with altered pH values and buffers added can be defined.

A literature search resulted in only one reference on the conductivity of drugs; it indicated that cocaine had 0.6 of the "tissue velocity" of sodium chloride (13). The conditions under which this measurement was made were not found. The present study reports the specific conductivity of a number of drugs of practical or theoretical usefulness for treatment of conditions or diseases of humans using iontophoresis as the administration method. The tissue to be treated must be at or near a body surface.

Drugs considered eligible for iontophoretic administration include local anesthetics (1, 4, 5) and anti-inflammatory (1), antiviral (2, 14, 15), and anticancer (16) agents.

All of the commonly used local anesthetic hydrochloride salts showed excellent conductivities. The conductivity of 10 m*M* lidocaine hydrochloride was about equal to that of 5.0 m*M* NaCl. Vasoconstrictors were also highly conductive; the conductivity of epinephrine bitartrate was greater than that of sodium chloride. Since local anesthetics and epinephrine are positively charged drugs, both can be introduced under the positive electrode (anode). The drugs can be properly balanced in concentration to obtain optimal vasoconstriction as well as deep topical anesthesia. In this clinic, 2% lidocaine with 1:12,500–1:50,000 epinephrine has been adequate for oral mucosa, ear canal, and skin anesthesia. The choice of epinephrine concentration depends on the vascularity of the tissue. One study (4) recommended 1:2000 epinephrine for ear canal anesthesia, but 1:12,500 was effective in this clinic.

Hydrochloride salts of local anesthetics conduct best at pH ~5. This pH keeps almost all local anesthetic molecules in the positively charged form. Increasing the pH tends to lower the conductivity by converting positively charged molecules to unionized molecules. However, iontophoresis of local anesthetics can be performed successfully even when the pH is close to the pKa since there will be adequate numbers of local anesthetic ions to carry the current.

Steroids are usually uncharged unless they have been chemically modified for high water solubility (intravenous use). Three anti-inflammatory steroids found to be highly conductive are methylprednisolone sodium succinate, hydrocortisone sodium succinate, and hydrocortisone phosphate. Since they are marketed for intravenous use, the solutions contain buffers to bring the solutions to proper pH and osmolarity. The present data indicate that highly ionic drug and buffer ions conduct current independently, each ion contributing to conductivity according to physicochemical factors operating in the solution of strong electrolytes. This conclusion was demonstrated by the finding that the buffer conductivity was equal to the conductivity of buffer in the mixture (Fig. 4).

The presence of buffer or salt ions is a negative factor for iontophoresis of moderate to strong electrolytes since extraneous ions compete with drug ions for the current. Nevertheless, iontophoresis seems to be successful when extraneous ions are present. It is preferable that more than one-half of the conductivity be due to drug ions. Aphthous ulcers, poison ivy, inflamed arthritic joints, and uninfected sores were treated successfully with the steroid iontophoresis.

A number of useful anticancer drugs have high conductivities, and iontophoresis of these drugs directly into the lesion may offer a new approach to treatment when surgical excision is impossible. This experimental hypothesis has not been tested, but studies with the closely related antiviral drugs indicate that experiments with anticancer chemotherapy using iontophoresis should be performed.

Nucleotides were tested for conductivity because of their chemical similarity to antiviral drugs. While nucleosides were nonconductive, the phosphorylated nucleotides were highly conductive because of the presence of phosphate groups. Triphosphates were about equal in conductivity to diphosphates, while monophosphates were less conductive. Adenosine monophosphate was almost equal in conductivity to sodium chloride at equal concentration. On the basis of these experiments, it was predicted that the antiviral nucleoside analogs (idoxuridine, thymine arabinoside, and vidarabine) would be nonconductive and that their respective nucleotide analogs would be highly conductive. These predictions, except for idoxuridine, were verified by the conductivity experiments; idoxuridine acts as a weak acid and becomes more conductive as the pH is increased. Experiments in mice (2, 14) showed that idoxuridine concentration in skin could be greatly increased by iontophoresis in comparison to topical administration. Both cathodal and anodal iontophoresis increased the skin penetration, but cathodal iontophoresis was ~20% more effective than anodal.

Subsequent experiments on penetration of uncharged compounds (tritiated water and thymidine) (17) indicated that sodium or chloride iontophoresis will carry other compounds in solution into the tissues, a process known as electro-osmosis. Anodal iontophoresis of idoxuridine is effective because of electro-osmosis while cathodal iontophoresis may act by both electro-osmosis and introduction of negative idoxuridine ions. On this basis, the commercial preparation of idoxuridine was applied at the anode to herpes simplex viral lesions of the lip (11). In all patients, the treatment was effective in aborting the viral lesions. In conjunction with medical specialists, herpes simplex viral lesions of the skin (recurrent or disseminated) and of the anus were treated successfully.

Many other agents could be suggested for iontophoresis. For example, antibacterial and antifungal agents may be introduced into localized lesions of skin more effectively than by topical administration and more safely than by systemic administration.

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