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IONTOPHORETIC TRANSPORT OF MODEL COMPOUNDS FROM A GEL MATRIX ACROSS A CELLOPHANE MEMBRANE

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ABSTRACT

Drug release rates from hydrogels through cellophane membranes were determined using custom-built diffusion cells which were modified to allow the application of current across the membranes. In the absence of a current the results obtained using different concentrations of drug and of the gel indicate the release to be matrix-controlled with a linear relationship between the quantities of drug released and the square root of release time. When a range of direct currents was applied enhanced transport was observed and as the current was increased the release curves became linear with time. The rate of release was also found to increase linearly with the current strength. These results show that an electrical current may be used to increase

the rate of drug transport and to alter its release profile under conditions when the unassisted release is matrix rather than membrane controlled.

INTRODUCTION

The use of electrical current to transport ions through the skin was apparently first described by Veratti in 1747[1]. Most of the work on iontophoretic drug transport has centred on local delivery of drug ions into surface tissues.[2,3,4,5] Recent development of transdermal drug delivery systems[6,7,8] has promoted interest in the possible use of electrical current to enhance the rate of drug absorption across the skin and into the systemic circulation[9]. Iontophoresis, as a means of promoting transdermal delivery has many advantages and is certainly preferable to the use of chemical penetration enhancers. For example, the rate of delivery can be varied by varying the current used to transport the drug and this may be exploited to modulate and control the release of the drug from the device. For the future, such an electrically controlled system offers the possibility of being coupled directly to feedback from a suitable biosensor to provide a self-regulating drug delivery module.

A number of recent *in vitro* studies of drug transport across a rate controlling membrane separating two well-stirred aqueous compartments and some *in vivo* studies have highlighted the importance of ionic composition and degree of ionization in optimizing current assisted transdermal delivery using a two electrode system[10,11,12]. The effect of voltage on flux enhancement through hairless mouse skin was investigated using a four electrode system[13] and good agreement between the experimental and theoretical fluxes was observed at low voltages (0-0.25V). These mechanistic studies involved drug permeation in situations where the membrane controlled the mass transfer.

In contrast, the aim of the present work is to study matrix controlled passive transport from transdermal discs through a cellophane membrane into an aqueous sink and to determine the effect of using an electrical current to enhance the transport of the drug.

EXPERIMENTAL METHODS AND MATERIALS

Permeation Studies

Custom-built glass diffusion cells were used, as illustrated in Figure 1. The cellophane membranes were secured and supported by a specially designed teflon cap. The cell hydrodynamics were controlled using a magnetic stirrer with star-head follower and the temperature was maintained at 310 K by immersing the cell in a constant temperature water bath. The diffusion cells were filled with distilled water and allowed to equilibrate at the required temperature. A transdermal disc was placed on the membrane and at predetermined time intervals samples were withdrawn from the cell and replaced with distilled water.

The samples which were removed from the cells were analysed using a Pye Unicam SP 200 uv/vis spectrophotometer. In each case the concentration of drug was calculated by comparison with a linear calibration curve which was establised using reference standard solutions. Each experiment was done at least in duplicate and conducted over either a 2 or 5 hour period.

Electrically Assisted Transport

The procedure was similar to that used to study the passive transport but the migration of the ions was now assisted by an electrical current. The diffusion cells were modified to

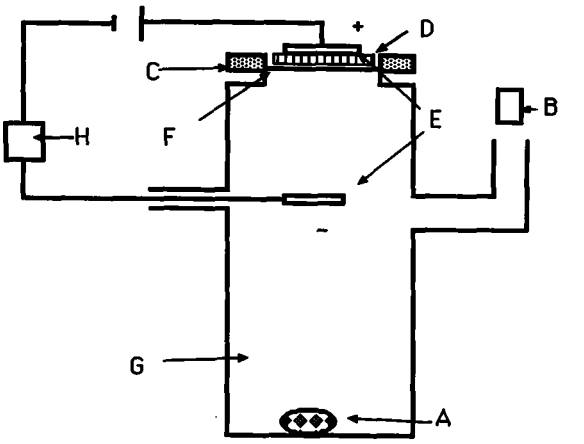

FIGURE 1

Schematic Representation of the diffusion cell used in the experiments. A. starhead magnet, B. Glass stopper, C. Teflon cap, D. loaded gel disc, E. Electrodes, F.Membrane, G. Receptor Solution and H. Ammeter.

accommodate a platinum electrode approximately 3cm below the membrane in the receptor compartment: the counter electrode was implanted at the back of the transdermal disc.

A direct current in the range 0.1-1.25mA was applied between these electrodes using a suitable power supply. The polarity was chosen so that migration of the positive drug ions was into the receptor compartment of the cell. A digital multimeter was connected in series to monitor the current. The voltage was adjusted as was necessary so that the current was maintained at a constant value throughout the experiment.

Systems Investigated

All of the permeation experiments employed Visking 18/32 cellophane membranes which were boiled several times in distilled

water before being used[14]. The hydrogel discs were freshly prepared for each experiment and had a cross-sectional area of 2.67 cm^2 with a volume of 1.81 cm^3. The transport of benzoic acid, salicylic acid, nicotine, and clonidine was investigated with the compounds being used in their "as received" states.

These compounds were chosen to provide examples of acids and bases as well as for their potential in transdermal devices. The majority of the work reported here concerns nicotine.(Sigma Chemicals, purity, 98-100%.)

RESULTS AND DISCUSSION

Passive Transport

The experimental data measured when the compounds were allowed to permeate the Visking membranes without electrical assistance are shown in Figure 2 where the relationship between the percentage of the drug released and the time is seen to be non-linear. When the release of a dissolved solute from a gel matrix is diffusion controlled the relationship

$$q/A = Q = 2C_o(Dt/\pi)^{\frac{1}{2}} \qquad (1)$$

may be expected to hold for up to 30% release[14], where q is the weight released, A is the surface area, C_o is the initial concentration of the solute in the gel and D is its diffusion coefficient. A plot of Q versus $t^{\frac{1}{2}}$ will be linear and indeed the release data shown in Figure 2 do yield such linear plots. These indicate that, in each case, the rate of drug release is controlled by diffusion within the matrix rather than by transport through the membrane. As a further test of equation (1) the effect of the initial concentration of drug on its release rate

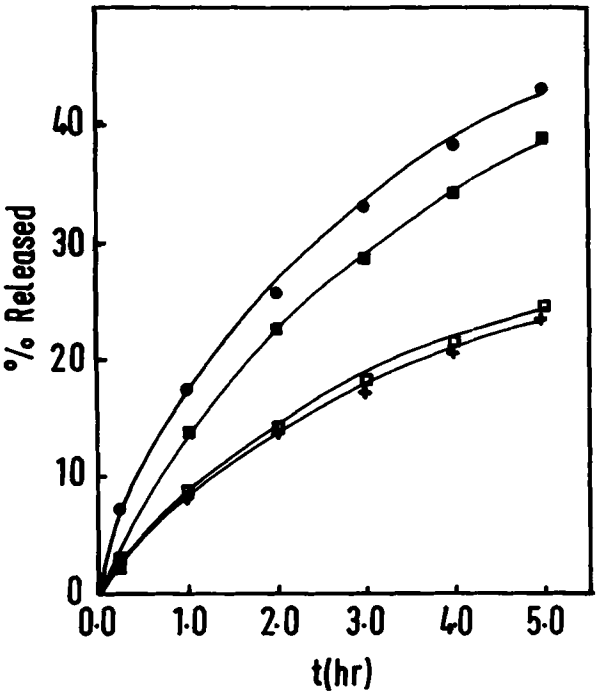

FIGURE 2

The Relationship between the percentage of each of the compounds released from the gel and the elapsed time, t. ○ progesterone, △ Nicotine, □ Salicylic acid, ■ Clonidine and ● Benzoic acid.

was examined for gels containing nicotine in the concentration range 5.52-55.2mg cm^{-3}. Plots of the quantity released versus $t^{\frac{1}{2}}$ are shown in Figure 3 where their linearity is evident. The small intercept reflects an initial period of boundary layer/membrane control. Consideration of equation (1) shows that a linear relationship should also exist between $Q/t^{\frac{1}{2}}$ and C_o and this is shown to be true for the present data in Figure 4. From the slope of this plot the diffusion coefficient of nicotine in the matrix can be estimated to be 2.4×10^{-6} cm^2 s^{-1}. Similar data for gels of different concentrations indicate a linear decrease in this

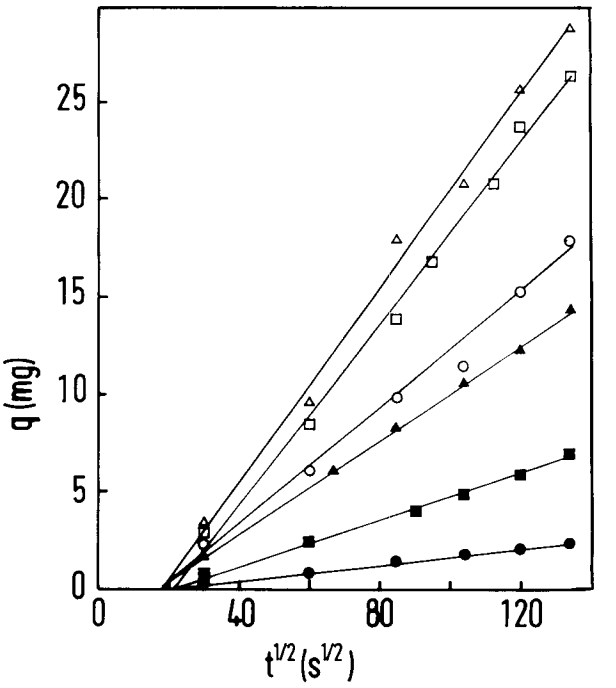

FIGURE 3

An illustration of the relationship between the quantity of nicotine released, Q, and the square root of the elapsed time, $t^{\frac{1}{2}}$, for a series of gels in which the initial concentration of nicotine was varied: ● 5.52 mg/cm^3, ■ 11.04 mg/cm^3, ▲ 22.09 mg/cm^3 ○ 0.30.39 mg/cm^3, □ 44.16 mg/cm^3, △ 55.2 mg/cm^3.

diffusion coefficient as the concentration of the gelling agent was increased in the concentration range 2 - 10% w/v.

It has been pointed out previously[16] that it is necessary to clearly distinguish between matrix control of the rate of drug release and first order release according to the equation.

$$\log W = kt/2.303 + \log Q \qquad (2)$$

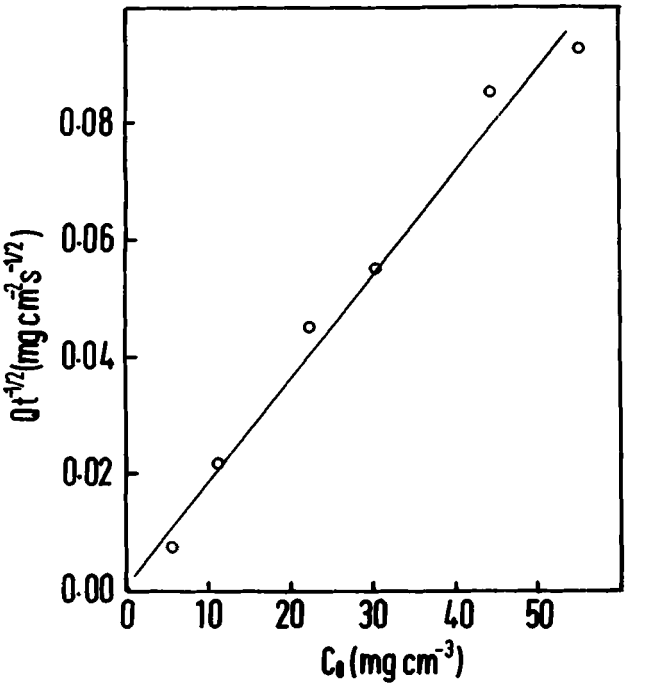

FIGURE 4

The linear relationship between $Q/t^{\frac{1}{2}}$ and C_0 for the release of nicotine through cellophane membranes.

where W is the quantity of drug remaining in the disc at time t. In the present work the first order plots (i.e.,log W versus t) resulted in poorer fitting of the data than did fitting to equation (1). Furthermore, as is evident from equation (1), a linear relationship should exist between log Q and log t with the expected slope being equal to 0.5. Tests of this type when applied to the present data revealed linear plots with slopes which were very close to 0.5 for the data points taken at the later stages of the drug release. The failure of the data taken earlier to fit as well to this equation again suggests that although it is clear that the release rate is predominantly

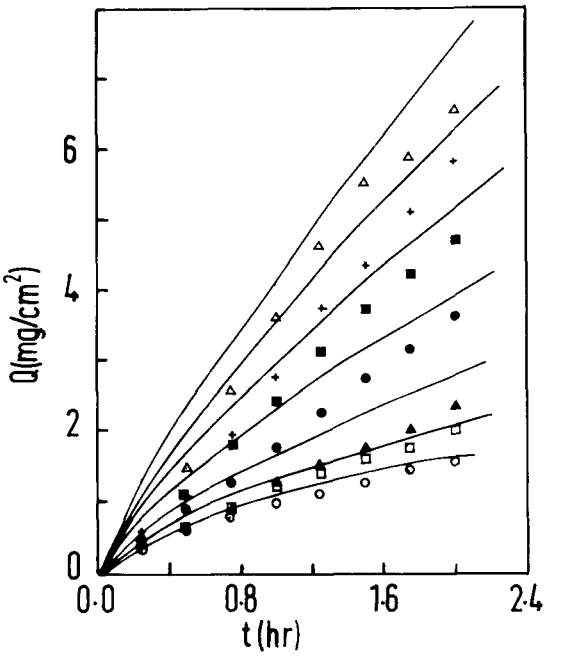

FIGURE 5

Release profiles for nicotine when the transport process is electrically assisted. The experimental data correspond to the currents which were used as follows: ○ 0.0mA; □ 0.1mA; ▲ 0.25mA; ● 0.5mA; ■ 0.75mA; + 1.0mA; and △ 1.25mA. The solid lines show the corresponding theoretical profiles calculated using equation (7).

determined by matrix diffusion there is, nonetheless, an initial contribution to the process from a boundary layer/membrane effect.

Electrically Assisted Transport

The effects of applying an electrical current in the range 0.1 to 1.25mA to assist the drug transport process is illustrated in Figure 5. As is evident, enhancements of up to 4-fold were obtained. As the current is increased the rate of drug transport into the cell also increases and the release profiles tend to

become linear. Zero order rates, R(mg/hr), may be obtained from the slopes of these plots and the overall rate may, as a first approximation, be considered to consist of two components, an iontophoretic rate, R_i, and a passive contribution, R_p, so that

$$R = R_p + R_i \qquad (3)$$

Furthermore we may consider that the rate due to the iontophoresis may be expressed as the product of the current i and an iontophoretic constant, f_i, such that

$$R_i = f_i i \qquad (4)$$

If R_p is independent of the iontophoretic contribution, or at least affected only negligibly by this process, then a combination of equations (3) and (4) show that R should vary linearly with i to yield a line of slope equal to f_i. Such a plot for the present experiments is shown in Figure 6 where f_i is found to have the value of 1.74×10^{-3} (s.d. $\pm 0.06 \times 10^{-3}$) mg s^{-1} mA^{-1}.

Faraday's laws of electrolysis provide the usual basis for consideration of the electrolytic movement of charged ions. For a univalent ion the passage of 96485 C will result in the transport of the molecular weight of the substance if its transport number is unity. Hence, the maximum rate of transport, R_F, is given in mg s^{-1} by

$$R_F = Mi/96485 \qquad (5)$$

where M is the molecular weight in grams and i the current in mA. For nicotine the proportionality constant between R_F and i has the value 1.68×10^{-3} mg $s^{-1}mA^{-1}$. This is within experimental error of the value found for f_i and would indicate an effective

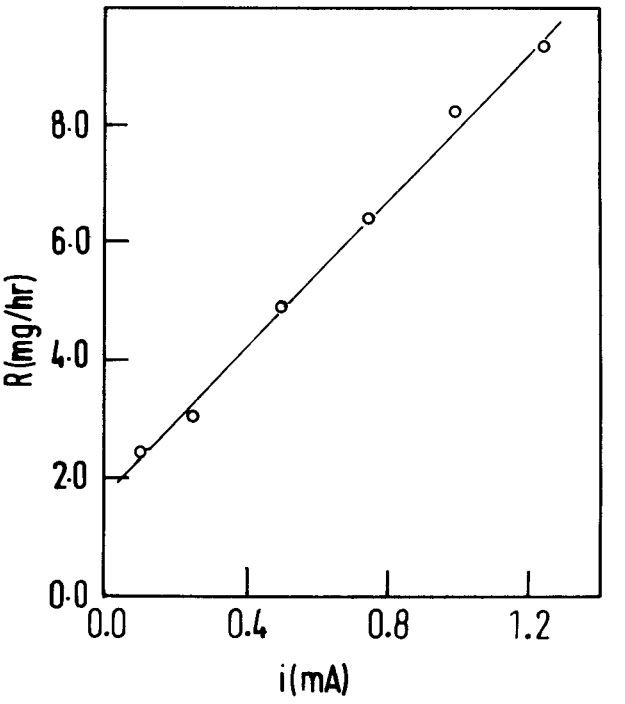

FIGURE 6

The relationship between the rate of assisted transport of nicotine into the diffusion cell and the iontophoretic current used.

transport number of close to unity for the iontophoretic process in this case. However, it should be emphasized that the experiments reported provide no information on the mechanism involved.

The quantity of drug delivered iontophoretically is given by

$$Q_i = f_i i_d t \qquad (6)$$

where i_d is the current density in mA/cm^2 so that using the simple model in which the total quantity entering the cell, Q_t, is considered to be the sum of Q_i and quantity of drug transformed

via the non-assisted process, Q_p, we have, by reference to equation (1).

$$Q_t = Q_p + Q_i = 2C_o(Dt/\pi)^{\frac{1}{2}} + f_i i_d t \qquad (7)$$

Release profiles calculated using equation (7) are shown as solid lines in Figure 5 where they are compared with the relevant experimental data. In spite of the assumptions made in this very simple model the level of agreement is reasonable. We have already commented on the discrepancies evident at the initial stages of the release: these are almost certainly due to effects arising at the boundaries which exist between the gel, membrane and receptor sink. The slight fall-off in the experimental release profiles at the longer times, when compared with the almost linear calculated curves, is probably due to the fact that iontophoretic removal of the drug from the matrix must be expected to influence the rate of passive release. Thus these data demonstrate that the simple model, which does not take such interactive effects into consideration, is inadequate and that it is very unlikely to provide a basis for the prediction of release rates from systems in which either the initial concentration of the drug or the iontophoretic currents used are widely varied. Work is continuing which will provide data from a more extensive range of systems and operating conditions so that a more comprehensive and exact model can be evaluated.

Conclusions

Electrical current was used successfully to increase the rate of drug transport from a gel matrix across an artificial membrane under conditions where the unassisted release was predominantly matrix rather than membrane controlled. As the current was increased the profiles were transformed to linear from their

original square root of time dependence. A simple model for the current-assisted process in which the passive and iontophoretic release rates were added to predict the total release profile was tested over a limited range of experimental data.

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