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Iontophoretically assisted in vitro membrane transport of nicotine from a hydrogel containing ion exchange resins

O.M. Conaghey [a,1], J. Corish [a,*], O.I. Corrigan [b]

[a] *Department of Chemistry, Trinity College, Dublin 2, Ireland*
[b] *Department of Pharmaceutics, Trinity College, Dublin 2, Ireland*

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Abstract

The iontophoretically assisted transport of nicotine across artificial and human skin membranes from heterogeneous gel vehicles comprising mixtures of ion exchange resins, to which the nicotine had been bound, and agar hydrogel has been investigated. Both strong and weak resins were used and the effects of resin bead size, the degree of cross-linking in the polymer, the medium in which the drug was bound, the drug concentration and the magnitude of the current were determined. The heterogeneous vehicles were shown to have advantages over comparable simple hydrogel vehicles in their versatility, in their capacities to store the drug and to control both its delivery rate and the pH of the vehicle during iontophoresis. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Transdermal; Iontophoresis; Hydrogel; Ion exchange resins; Drug delivery

1. Introduction

The design of composite vehicles, which extend the possibilities for the storage and controlled release of drug molecules, presents one route to the realisation of more flexible transdermal delivery systems. Ion exchange resins are utilised in a number of drug delivery techniques and the effects of their incorporation into a thoroughly-tested hydrogel-based system for the passive transdermal delivery of nicotine have recently been reported (Conaghey et al., 1998). The method used to prepare agar/resin gels which exhibited reproducible behaviour was to first load the resins with nicotine and then to add these to the liquid hydrogel before setting. A range of strong and weak acid resins were investigated and the rate of passive release from the composite

* Corresponding author.
[1] Present address: Elan Corporation plc., Athlone, Co. Westmeath, Ireland.

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vehicles across a Visking™ membrane into a Franz (1975) type cell was shown to be controlled by matrix diffusion of the drug through the vehicle. Substantial lag times were observed before this transport process commenced and these were attributed to the need to exchange the drug ions bound on the resins into the hydrogel. Indeed when no ions suitable to effect this exchange were available, i.e. when the receptor was deionized water, the release rates from the composite vehicles were found to be extremely small when compared to those from the corresponding simple agar hydrogel (Bannon et al., 1987). For this reason the composite vehicles investigated were found, again in in vitro experiments, to be unlikely to be useful for the passive transdermal delivery of nicotine.

The use of an electrical current to enhance drug delivery has received considerable attention in recent years (Gangarosa et al., 1980; Burnette and Ongpipattanakul, 1986; Siddiqui et al., 1989; Wearley and Chien, 1990). Iontophoresis can broaden the range of drugs that can penetrate the skin in both ionized and unionized forms and offers the possibility of better control of delivery rates particularly when coupled with feedback from a suitable biosensor. Linear relationships between the fluxes of drugs from electrically-assisted transdermal devices and their iontophoretic current densities have been demonstrated by a number of investigators under different experimental conditions (Burnette and Marrero, 1986; Bannon, 1989; Del Terzo et al., 1989; Wearley et al., 1989; De Nuzzio and Berner, 1990; Wang et al., 1993). The use of inert electrodes such as platinum metal in electrically-assisted transdermal devices may cause the electrolysis of water which results in the production of hydroxyl ions at the anode and hydroxonium ions at the cathode and thus give rise to pH changes in the vehicle. The pH range of solutions that can be applied to the skin is normally limited to between 3 and 8: outside of this range the *stratum corneum* is damaged and irritation can occur (Ledger, 1992). Various buffers can be used both to ensure that most of the drug species are in the ionized form and also that significant pH changes do not occur during the iontophoresis. However such buffer ions will compete with drug ions in the iontophoretic transport process and so decrease the effective transport number of the drug ion. This disadvantage, associated with the presence of a buffer to control changes in pH, can be overcome by the use of ion exchange resins in the vehicle. Johnson and Richfield (1990) used a pH buffered electrode in which the pH buffer layer was comprised of a buffer bound to resin beads. They reported that problems associated with mobility of buffer ions in the presence of an electric field were eliminated by their adsorption in the ion exchange resin.

This paper presents the results from a series of experiments in which the release of nicotine across Visking™ and human skin from the agar/resin composite vehicles described previously (Conaghey et al., 1998) was investigated in vitro when these vehicles were made to be part of an iontophoretically-assisted drug delivery system. Drug-loaded resins prepared both in deionized water and in buffer were tested and the changes in the pH of the vehicle as the delivery progressed were also monitored in some cases. Additionally, in a limited number of experiments, the inert platinum electrodes were replaced by Ag/AgCl electrodes for which the electrochemical reactions do not involve the electrolysis of water. The presence of the ion exchange resins, which may be considered as concentrated electrolytes in which one ionic species (the fixed ionic group) is immobile, complicates the response of the composite vehicles to the applied electrical potential. The fact that the conductivity of the ion exchanger is typically much larger than that of a dilute solution means that an applied electrical potential can be used to regenerate ion exchange beads and for ionic separations (Speigler and Coryell, 1951, 1952). In the present agar/resin system the consequences of the application of the potential, over and above iontophoretic assistance to the drug transport, is the electrochemical release of the nicotine bound to the resin so that it becomes available for transport from the device. As in any complex electrolytic system all of the mobile ions present are available to transport the current with

the more mobile species making the greater contributions. Such effects, which are evident when the resins are loaded in buffer solutions, have also been investigated as have the effects of drug concentration in the devices and of the particle sizes and degree of cross-linking of the resins.

2. Experimental

The nature of the composite vehicles and their methods of preparation, including details of the types of ion exchange resins used, have been previously described (Conaghey et al., 1998). The modification of the custom-built Franz type diffusion cell necessary to permit the passage of an electric current through the vehicle between an electrode placed on the surface of the gel furthest from the membrane and a second electrode placed within the receptor solution has also been described (Bannon et al., 1987). The silver/silver chloride electrodes were prepared by deposition onto pure silver foil and wire (Grade 1 Johnson Matthey) in a KCl solution (Burnette and Bagniefski, 1988). Deionized water from a Millipore Milli-Q water-purification system (pH $\sim$ 6.5) was used to prepare the gels and in the receptor compartment. Custom-built galvanostats were used to maintain the iontophoretic currents at constant values during the experiments. Each skin sample was visually inspected for integrity before use and all experiments were carried out in triplicate so that any failure in these membranes was immediately obvious. The nicotine levels in the receptor solutions and in analyses of other components of the drug-delivery systems were again measured using High Performance Liquid Chromatography (HPLC). The details of the method have been reported previously (Bannon et al., 1989). A Leica-Cambridge S360 Scanning Electron Microscope was used to examine and determine the size ranges of the Amberlite IR-120 resin beads and in the Energy Dispersive X-Ray Analysis (EDXRA) mode to determine the elements present in the carboxylic and sulphonic acid resins used.

3. Results

Because Visking is known not to present any real barrier to the passage of nicotine (Bannon et al., 1987; Bannon, 1989) the experiments in which it is used in reality provide information of the rates at which the nicotine is released from the complex vehicles. The following two sections describe this process for the strong sulphonic acid-based and weak carboxylic acid-based ion exchange resins, respectively. The remainder of the results refer to the assisted transport of nicotine from the composite vehicles across human skin.

3.1. Iontophoretic release of nicotine from sulphonic acid resins

3.1.1. Comparison of resins loaded in water and buffer pH 5.0

The differences between the passive and assisted release of nicotine from agar gels containing Dowex $\times$ 8 (200–400) resins which were loaded with nicotine in deionized water or in phosphate-citric acid buffer (pH 5.0) are shown in Fig. 1. The overall concentrations of nicotine in the two composite systems were very similar being 22.76 and 25.70 mg/cm^3 for those containing resins loaded in deionized water and buffer, respectively. It is clear that when the ion exchange resin is loaded in the buffer medium the subsequent release of the nicotine is significantly hindered. In the initial stages of the release the rate achieved increases slightly on increasing the magnitude of the current but in each case a plateau occurs when approximately 7% of the nicotine content has been released. For the resin loaded in deionized water the initial release rate is greater with the higher current, 1.97 mg/h for a current of 0.5 mA compared to 1.66 mg/h for 0.25 mA. For these systems plateaux are observed when some 55–60% of the nicotine has been transported from the disc.

3.1.2. Effects of bead sizes and degree of cross-linking

These effects were examined using Dowex resins loaded in deionized water and with ion-

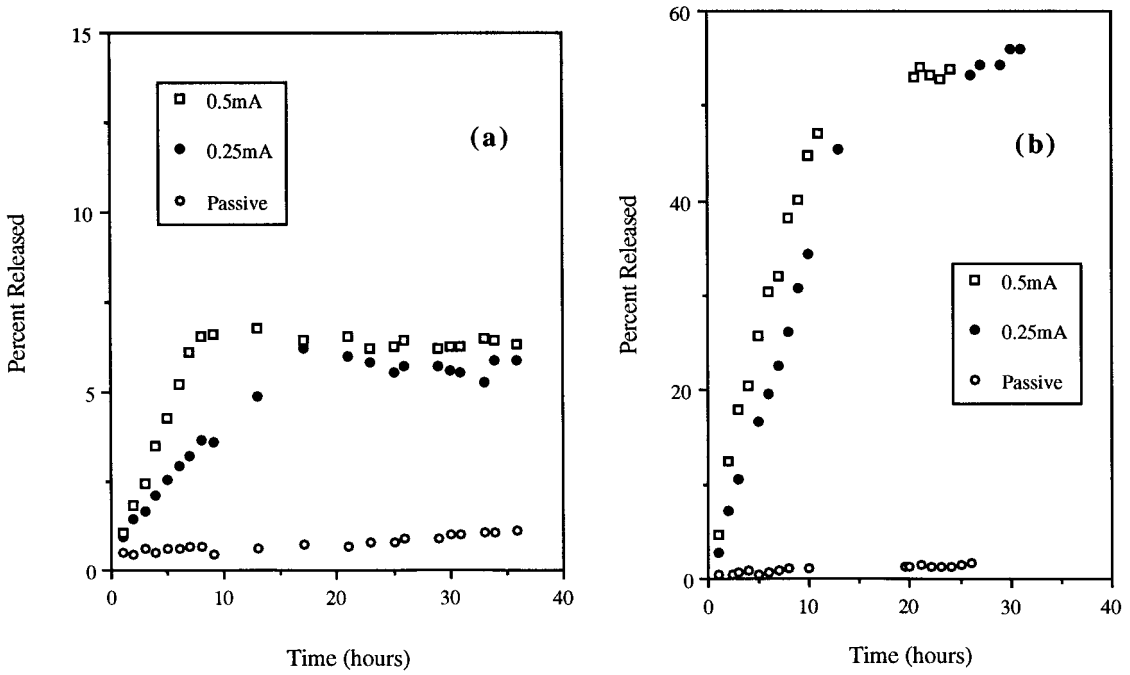

Fig. 1. Comparisons of the release across Visking into water of nicotine, passively and at the currents marked, from Dowex × 8 (200–400) resin held in 4% hydrogel and loaded in a buffer of pH 5.0 (a) and in deionized water (b). The concentrations of nicotine in the discs were 22.76 and 25.7 mg/cm^3 for those containing resin loaded in water and buffer, respectively.

tophoretic currents in the range of 0.1–1.0 mA. The concentration of the drug in each resin-hydrogel was the same for each experiment. Considerable enhancement over the passive release was observed with all the systems and at all current densities and during the initial stages the profiles are approximately linear with time. These initial release rates increase, in every case, with increasing current but each system shows a characteristic plateau above which no further release of nicotine occurs. The resins with the smaller particle size release up to 60% of their nicotine content, which is very significantly more than is released from the larger sized particles under the same conditions. The degree of cross-linking in the resin polymer is also a factor with the higher nicotine release occurring from the polymer that is more highly cross-linked.

Fig. 2 shows the iontophoretic rates of nicotine transport across Visking as calculated from the first 5 h linear portions of the release profiles. It is evident that the release rates for all the systems were found to increase linearly with the magnitude of the iontophoretic current but with each rate depending on the particular resin being used. The resin-hydrogel with the smallest size of resin bead and with the higher degree of cross-linking in the polymer released the drug at the highest rate. This result is partly at variance with literature reports that the most rapid release of drug is obtained from smaller resin particles of resins with lower cross-linking (Schacht et al., 1982; Irwin et al., 1990) but there are insufficient data available to provide a detailed explanation of our observations.

Attempts were made to achieve a greater release of nicotine than is represented by the various plateaux by switching off the current and allowing the device to stand for time periods of up to 1 h. The current was then switched on again but no further release of nicotine was observed. When the platinum electrodes used for the majority of the experiments were replaced by Ag/AgCl electrodes there were no significant differences in the

range of release rates measured for the various resins.

3.1.3. Drug concentration effects

When additional quantities of nicotine-loaded Dowex × 2 (200–400) resin were added to the hydrogel so that the overall drug concentrations in the vehicle were increased, the rates and quantities of nicotine released increased for any particular fixed iontophoretic current. The extent and effect of these additions are illustrated in Fig. 3 for a constant current of 0.5 mA. At each concentration a specific plateau was attained but the fraction of the drug content released in every case lay between 35 and 45%. Similar results were observed for the Dowex × 8 (200–400) and Dowex × 8 (50–100) resins with percentages of approximately 60 and 13% being released, respectively. These results confirm that the large sized beads release significantly less nicotine. Table 1 provides a summary of the results and it is important to state that a full recovery of all the nicotine was possible in every case when the used resin-hydrogels were leached into a dilute sodium hydroxide solution. The possibility that a build-up of nicotine in the receptor was hindering its further release was examined by replacing the receptor solution with pure deionized water and resuming the passage of the iontophoretic current. No further release of nicotine beyond the characteristic plateau values was observed.

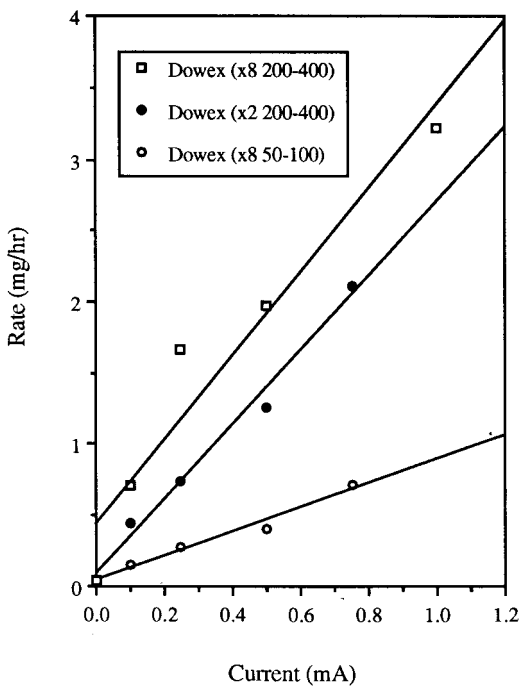

Fig. 2. The relationship between the measured iontophoretic release rates over the first 5 h of operation and the corresponding current densities for the different types of Dowex resins investigated.

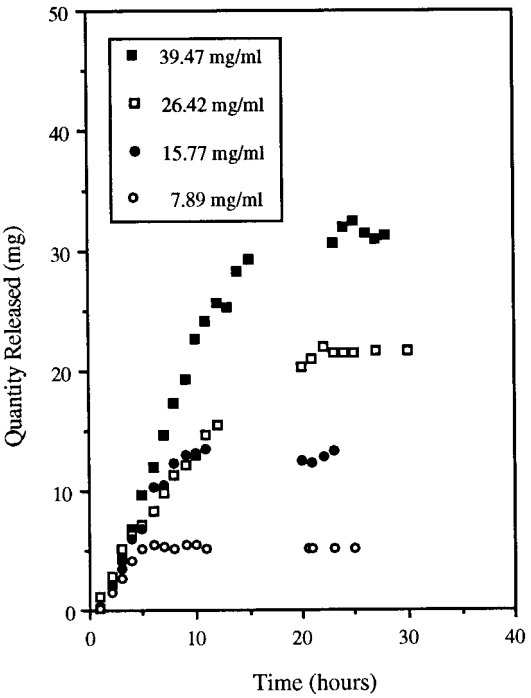

Fig. 3. The release rates across Visking of nicotine, iontophoretically assisted at a current of 0.5 mA, from resin-agar gels in which the overall concentrations of the drug has been varied to the values shown in the key by changing the quantities of nicotine-loaded Dowex × 2 (200–400) resin added to the hydrogel.

3.2. Iontophoretic release of nicotine from carboxylic acid resins

3.2.1. Resins loaded in phosphate-citric acid buffer pH 5.0

The iontophoretically assisted release of nicotine from Amberlite IRC-50 carboxylic acid resins loaded in the buffer was studied extensively

Table 1
The percentages of nicotine released from the Dowex resin-hydrogel vehicles for a variety of initial overall concentrations and ionic currents

Dowex resin type	Initial overall conc. (mg/cm^3)	Iontophoretic current (mA)	Percentage of nicotine released
×2 (200–400)	26.42	0.10	41.1
		0.25	43.7
		0.50	44.3
		0.75	44.1
	7.89	0.50	37.9
	15.78	0.50	46.1
		1.00	41.0
	39.50	0.50	42.4
		1.00	41.6
×8 (200–400)	25.67	0.25	55.8
		0.50	53.9
		1.00	59.8
×8 (50–100)	22.09	0.25	13.4
		0.50	14.5
		0.75	15.1
	9.09	0.05	12.1

for periods of up to 50 h and over a range of currents. Enhancement of the release was seen to occur only after an initial time period has elapsed during which the release was almost negligible. The length of this time period depended on the magnitude of the current being used and the release of nicotine during this initial period of iontophoresis was very similar to its passive release from a corresponding vehicle. The magnitudes of the iontophoretic currents and the periods of the lag times were measured so that the charge that was required to pass through the cell before enhanced release of nicotine was observed could be calculated. This charge was found to lie between 5.9 and 7.2 C in every case for the vehicles used here. Release profiles at a constant current of 0.5 mA were also determined for a series of devices each of which had a total nicotine content of 15.0 mg/cm^3 but which were loaded in buffer solutions at pH 5.0 but with different ionic strengths in the range of 0.11–0.42 M. The ionic strength of the medium in which the drug was bound to the resin was found to have a significant effect. For resins loaded in the more concentrated buffer solutions (ionic strength = 0.21 and 0.42 M) the initial release rates were very small at 0.03 mg/h but with a significant increase to 2.23 mg/h after approximately 4 h. In contrast, the resin loaded in the buffer of lowest ionic strength (0.11 M) displayed an almost linear profile after a very brief time interval of $\sim$0.15 h had elapsed. These results suggest that as the concentrations of ions other than nicotine are increased in the resin, the initial release of nicotine is decreased.

This interpretation was confirmed by a series of EDXRA made on resin-hydrogel vehicles. The initial measurements compared spectra from vehicles prepared using resins loaded in buffer with those using resins loaded in deionized water. These showed that the former contained a significant quantity of sodium whereas only negligible quantities of ions, principally calcium, were found in the latter. All the vehicles were dried overnight at 313 K before analysis. Fig. 4 shows the relationship between the sodium content of the vehicle and the quantity of nicotine released: the EDXRA determinations of the sodium were made on vehicles removed from experiments after the time intervals shown during the first 10 h. Observation of the peak at 1.2 keV, which corresponds to the presence of sodium, indicates that the concentration of sodium in the hydrogel decreased significantly as the iontophoretic current is passed through the device. The sodium content

of the gel after each time interval was then related to the quantity of nicotine released. The greater mobility of the sodium ion is responsible for this preferential electrochemical transport and an efficient release of nicotine is not achieved until the availability of sodium ions as carriers has been greatly reduced.

3.2.2. Resins loaded in deionized water

The application of iontophoretic currents in the range of 0.1–1.0 mA on the release of nicotine from a weak ion exchange resin which had been loaded in water before its incorporation into the heterogeneous vehicle again resulted in considerable enhancements over the corresponding passive rates. The release was seen to take place without the initial time delay. The rates observed depended on the magnitude of the current applied and the profiles were linear with time except at the highest current density where the effect of depletion was evident. As with the simple hydrogel vehicle the rates of the electrically assisted release (Bannon, 1989) were found to vary linearly with the current used but the rate of release from the resin/hydrogel was significantly slower. At an approximate nicotine concentration of 23 mg/cm^3 the iontophoretic transport rates were 1.20 and 8.50 mg/h for the carboxylic acid resin/agar and simple hydrogel, respectively, at a current of 0.5 mA. The latter value is consistent with that reported for the same system by Bannon (1989). The corresponding values measured in this work for the sulphonic acid resins were 0.20, 0.63 and 0.99 mg/h for the Dowex (× 8 50–100; × 2 200–400; and × 8 200–400) resin/hydrogels, respectively.

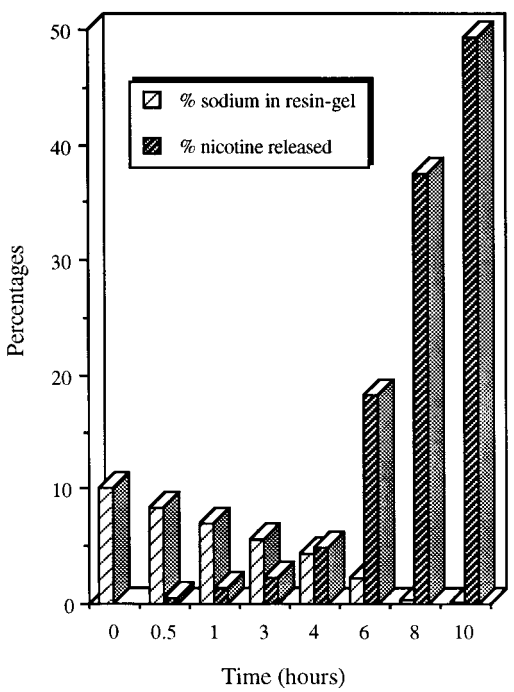

Fig. 4. Variations in the percentage of sodium in the Amberlite IRC-50 carboxylic acid resin-hydrogel vehicle and the percentage of nicotine released during iontophoretic delivery at a current of 0.5 mA. The overall concentration of the nicotine was 15 mg/cm^3.

3.2.3. Drug concentration effects

As the quantity of drug-loaded carboxylic acid resin added to the hydrogel was progressively increased the effect on the iontophoretic release rate was found to be similar to that observed for the sulphonic acid resins (Fig. 3). Fig. 5 shows the variation in the iontophoretic rates of delivery at 0.5 mA, as determined from the linear portions of the release profiles, from the carboxylic acid resins as a function of the overall concentration of the nicotine in the vehicle. The rates show the appearance of a plateau as the concentration of nicotine is increased.

3.3. Iontophoretically-assisted release across human skin

The passive release of nicotine from the heterogeneous vehicles used here across human skin was found to be essentially negligible (Conaghey et al., 1998). The initial results for iontophoretically-assisted delivery from vehicles containing sulphonic acid based resins showed that the same limitations applied as had been observed for the delivery across Visking, i.e. only a limited percentage of the nicotine content could be released. The variation in the delivery rates with time was also found to be complex and, as a consequence, only data relating to carboxylic acid resins/hydrogel vehicles will be presented here.

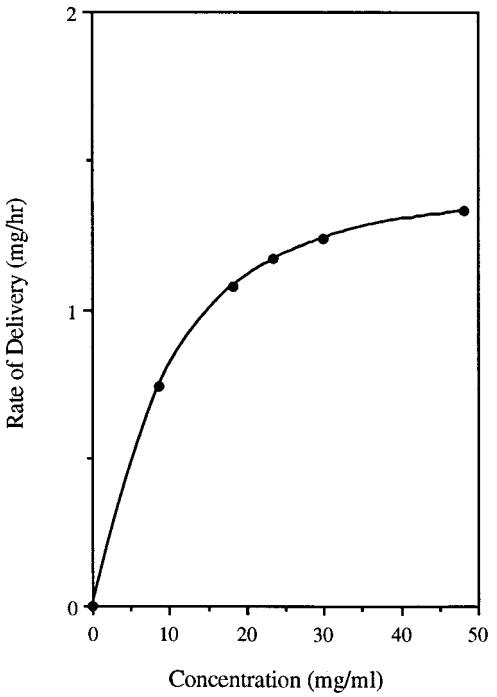

Fig. 5. The relationship between the iontophoretically assisted delivery rate at 0.5 mA from the Amberlite IRC-50/hydrogel vehicle and the overall concentrations of the nicotine in the vehicle as given in the key.

3.3.1. Effect of the magnitude of the dc current

A series of experiments in which the current density was varied in the range of 0.0375–0.375 mA/cm^2 was carried out to deliver the nicotine across full thickness human skin from Amberlite IRC-50/hydrogel vehicles loaded in deionized water to an overall concentration of 40.1 mg/cm^3. The results are shown in Fig. 6. After a lag time of some 50 min it is evident that significant quantities of nicotine are transported across the barrier and that these increase with the current used. Determinations of the rates of delivery at hourly intervals showed that in all cases the release rates increased with time. This was attributed to an increasing passive contribution as the concentration of 'free' nicotine built up in the gel. It is well established that the barrier presented by the skin is altered by iontophoretic delivery (Foley et al., 1992) and the build-up of nicotine in these systems following iontophoresis was demonstrated by measuring the rates of passive release through Visking when the currents were switched off.

The quantities delivered in 10 h, as shown in Fig. 6, indicated rates that are very similar to the corresponding rates measured earlier for transport across Visking. This shows that the delivery to the receptor is being controlled by the device. In addition, as has been found for other compounds being delivered from simple vehicles (Bellantone et al., 1986; Del Terzo et al., 1989; Phipps et al., 1989; Foley, 1991), the rate of delivery increases linearly with the magnitude of the current. Taken together these data suggest that the system may be suitable for use in a transdermal delivery system.

3.3.2. Drug concentration effects

A series of Amberlite 150 resin/hydrogel vehicles were prepared in which the overall concentration of the nicotine was varied from 5.35 to 40.19 mg/cm^3 by increasing the quantity of nicotine-

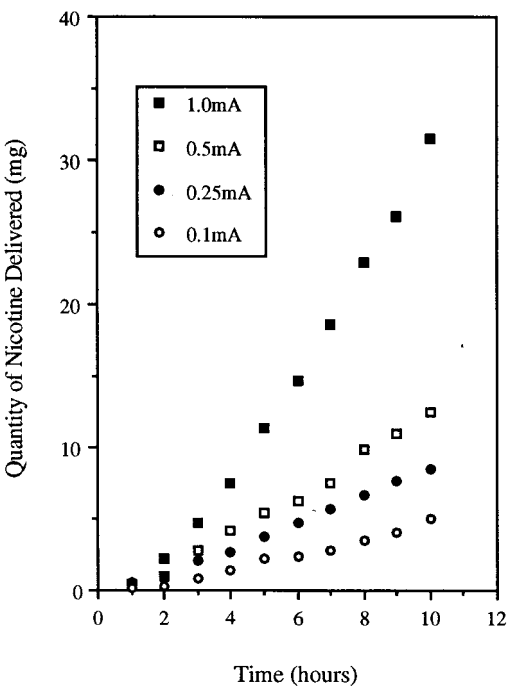

Fig. 6. The effect of current at the values shown in the key on the delivery rate of nicotine across full thickness human skin from an Amberlite IRC-50/hydrogel vehicle containing 40.1 mg/cm^3 of the drug. The receptor compartment contained phosphate buffer at pH 7.4.

loaded resin added to the gel. The release profiles were determined at a current of 0.5 mA, chosen because it was mid-range of the currents used and because it corresponded to a current density of 0.187 mA/cm^2 which is easily tolerated in humans (Singh and Roberts, 1989). Because the nicotine is initially bound to the ion exchange resin the quantities released during the early stages of the experiment were all quite similar. However, as the experiment proceeds the build-up of the 'free' nicotine concentration leads to an additional passive contribution so that the release profiles changed after approximately 2 h. A plot of the relationship between the average rates of delivery determined from the slopes of the linear parts of the release profiles and the concentrations of nicotine in the vehicle was almost exactly the same as that shown in Fig. 5 for the analogous transport through Visking. As has also been reported for the release of nicotine from a simple agar hydrogel (Bannon, 1989), the relationship is not linear and shows a fall off in the delivery rates at the higher concentrations. In contrast to these results, linear relationships between the iontophoretic delivery rate and the drug concentration have been reported for verapamil (Wearley et al., 1989). Even though the percentage of the load that is released diminishes with increased nicotine concentration, it is evident from Fig. 5 that the more concentrated systems do lead to a greater delivery of nicotine by the same iontophoretic current.

3.3.3. Resins loaded in buffer at pH 5.0

As was reported earlier for the iontophoretic transport of nicotine across Visking the delivery rate across skin was significantly reduced when the resin was loaded with nicotine in a phosphate-citric acid buffer at pH 5.0. The explanation is also the same: the initial low release is due to the presence of sodium ions in the resin.

3.4. Changes in pH during the iontophoresis

When platinum electrodes are used to effect iontophoretic transport of drugs in aqueous-based systems, as is the case with most of the experiments reported here, the electrolysis of water can lead to an increase in the concentration of protons in the donor compartment with a subsequent drop in pH. The production of hydrogen ions also leads to a reduced efficiency in the transport of positive drug ions. The pH of simple hydrogel vehicles was found to decrease to values as low as 2 or 3 during the iontophoretic transport of nicotine. The pH of the gel is important not only because it affects the ratio of charged to uncharged species but because it may also affect the permselectivity of the skin (Burnette and Ongpipattanakul, 1986) and cause damage and irritation (Allenby et al., 1969).

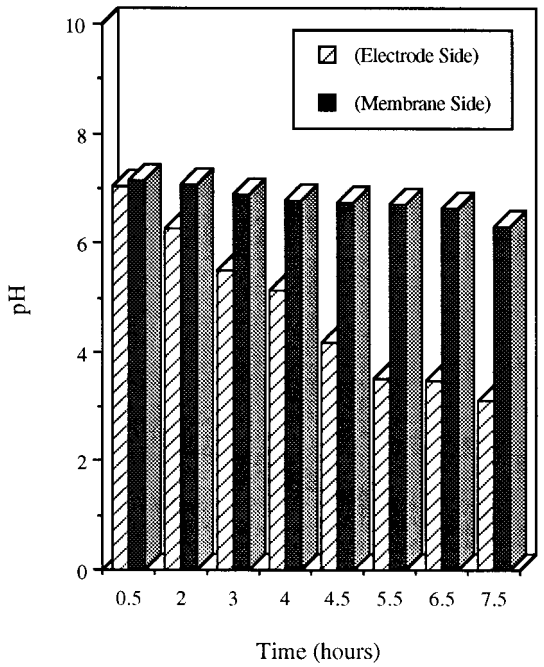

Fig. 7. The variation with time in the pH measured at both sides of a carboxylic acid resin/hydrogel vehicle during iontophoresis at 0.187 mA/cm^2.

It has previously been pointed out by Johnson and Richfield (1990) that ion exchange resins can be used to overcome the problem of pH decrease within a gel during iontophoresis. In the present work the pH of the gel was measured both at the upper surface which was directly in contact with the platinum electrode and on the lower surface which was in contact with the membrane. The results are shown in Fig. 7 for a carboxylic-acid

resin/hydrogel over an 8-h period. The effect of the presence of the resin is quite dramatic in maintaining an almost constant pH at the membrane side of the vehicle over the period of the iontophoresis. The lowest pH value to which the skin was exposed during these experiments was pH 6.31 whereas iontophoresis in the simple hydrogel resulted in values as low as pH 3.0.

3.5. The use of Ag/AgCl electrodes

An alternative method to avoid deleterious pH changes during iontophoresis is to use reversible electrodes. One such favoured electrode system is silver/silver chloride which has a redox potential lower than that for water. For example, Phipps et al. (1986) used this electrode in their demonstration of an electrochemically optimized delivery system while investigating the transport of Li^+ ions. The Ag/AgCl electrode behaved as a non-polarizable reversible electrode: there was little or no change in the donor pH and the efficiency of delivery of the lithium was increased relative to that achieved using other electrode systems.

Ag/AgCl electrodes were used in the work reported here both to seek to enhance the release of nicotine from the Dowex × 8 (200–400) resins across Visking and to increase the transport of nicotine from the carboxylic acid resin across human skin. For a Dowex/hydrogel system containing an overall concentration of nicotine of 25.67 mg/cm^3 the use of the reversible electrode resulted in essentially no change in the release profile from that achieved using the inert platinum electrode. The plateau occurred when some 26% of the nicotine content had been released. The behaviour of the Amberlite IRC-50/hydrogel system, which contained an overall concentration of 19.25 mg/cm^3 of nicotine, is illustrated in Fig. 8 for delivery across full thickness human skin using both inert and reversible electrode systems. Initially the delivery from the platinum electrode is more efficient but then both systems show linear profiles and the quantities released after approximately 6 h are essentially the same. Since weak ion exchange resins have a preference for hydrogen ions (Nachod, 1949) the greater initial release using the inert electrode would be expected. In addition the mobility of the Ag^+ ions through the gel would be expected to be less than that of H^+ ion.

4. Discussion

The experimental measurements reported here establish the principles that govern the iontophoretically-assisted delivery of nicotine-loaded vehicles based on a hydrogel containing particles of an ion-exchange resin into which the drug has been previously loaded. The use of an iontophoretic current has been shown to enhance the rates of delivery from these vehicles over the corresponding passive transport. In the case of human skin these enhanced rates mean that the vehicles could potentially be used in an electrically assisted transdermal drug delivery system.

The release profiles observed for the sulphonic acid based resins exhibit an initial linear release followed by a plateau region which is characteris-

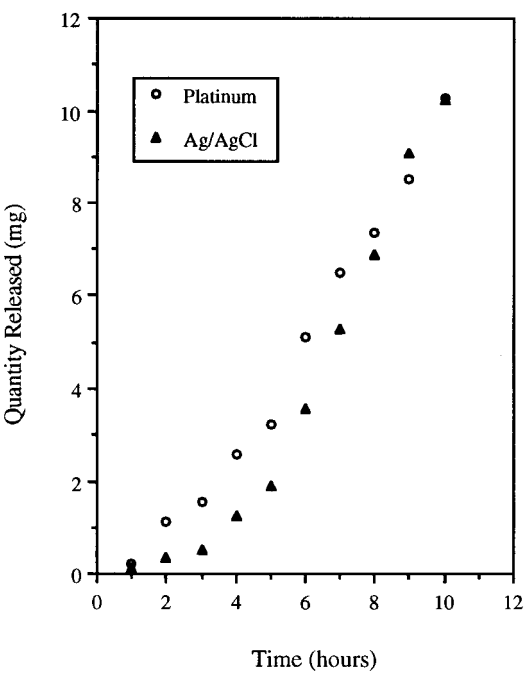

Fig. 8. A comparison of the release profiles of nicotine from an Amberlite IRC-50/hydrogel vehicle containing an overall concentration of 19.25 mg/cm^3 using a current of 0.5 mA with platinum and Ag/AgCl electrodes.

tic of the medium in which the resin had been loaded. For drugs loaded in a buffer medium of pH 5.0 the plateau was reached when approximately 7% of the nicotine was released. When loaded in deionized water a more significant fraction (up to 60%) of the nicotine content was released. Notwithstanding possible effects of the passage of the current on the electrical behaviour of the resin and of the changes induced in the pH of the hydrogel, the explanation for the observed behaviour lies in the fact that ions are known to be bound to sulphonic acid ion exchange resins by two processes (Borodkin and Yunker, 1970; Gupta et al., 1986; Bhat et al., 1988; Farag and Nairn, 1988; Plaizier-Vercammen, 1992): (i) they can be loosely bound by adsorption on the surface of the beads; and (ii) they can be more strongly bound by chemical bonds in the interior of the beads, where the concentration of the sulphonic acid groups may be very high. At a pH of 5.0, i.e. when bound in the buffer solution, nicotine (pK_a 8.3 and 3.2) is ionized and will bind ionically to the resin. However in the deionized water the nicotine will be present in both ionized and non-ionized form and will be likely to bind both ionically and via other weaker intermolecular forces. (Helfferich, 1962; Borodkin and Yunker, 1970; Bhat et al., 1988; Gupta et al., 1986).

Further evidence for this interpretation is provided by the variation in the delivery as a function of the sizes of the resin beads. The difference between the quantities released iontophoretically from 0.15 to 0.42 mm and the 0.02–0.07 mm particle-sized Dowex resins (10 and 60% of the totals, respectively) is much greater than would be expected from the respective loadings of 316 and 451 mg/g. This difference in release is explained by the fact that the area available for surface-bound nicotine is substantially larger on a weight for weight basis with the smaller particles. The unexpected result in which increasing the degree of cross-linking from 2 to 8% resulted in the release of approximately 13% additional nicotine suggests that the increased cross-linking may hinder the movement of nicotine through the matrix thus increasing the proportion that is weakly bound on the surface.

The data for the carboxylic acid resin also show that the nicotine ions were displaced efficiently from the resin/hydrogel vehicle when they had been bound in deionized water. The fact that the rate of release increased with the current and remained relatively constant throughout the iontophoretic period suggests that the iontophoresis is controlling the rate of ion exchange. For resins loaded in buffer there was an initial lag time, which depended on the magnitude of the current used, and during which the delivery of nicotine was negligible. EDXRA analyses showed that sodium ions were preferentially exchanged from the resin before the release of nicotine could take place efficiently.

When the concentration of nicotine-loaded resin of either type in the hydrogel was increased, no corresponding increase was observed in release rates: this was due to the absence of the corresponding passive contributions during the iontophoresis. This behaviour is in contrast to that observed when the nicotine is held in the simple hydrogel and is a very useful property of the heterogeneous vehicles. It provides a means of increasing the content of drug in a device while retaining control of its rate of release through the iontophoretic current. The iontophoretically-assisted rates measured were somewhat lower than the corresponding transport from simple hydrogels but, at least in the case of nicotine, could be varied over a wide range.

Another significant advantage of the resin/hydrogel vehicles is the fact that the pH of the system remains almost constant during the iontophoretic delivery process. This will alleviate the problem of skin irritation, which can occur with the simple hydrogel during iontophoresis. The removal of hydrogen ions also means that they cannot compete with the nicotine ions to carry the current and so efficiency of the iontophoretically-assisted delivery is increased. A further consequence is that the delivery rate can then be more easily maintained at a chosen constant value.

Given the range of ion exchange resins that are available, the results presented here demonstrate clearly that heterogeneous resin/hydrogel mixtures can be designed to offer a very wide-ranging and flexible series of vehicles for the iontophoretic

delivery of different types of drug molecules. This flexibility, coupled with their ability to control the pH during delivery and to sustain increased drug loading while maintaining a very good control of the drug delivery rate, mark these systems as significantly superior to the corresponding simple hydrogels. To fully evaluate their potential a series of in vivo experiments will be necessary.

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References

Allenby, A.C., Fletcher, J., Schock, C., Tees, T.F.S., 1969. The effect of heat, pH and organic solvents on the electrical impedance and permeability of excised human skin. Br. J. Dermatol. 81, 31–39.

Bannon, Y.B., 1989. A Study of the Transport Processes Governing Passive and Iontophoretic Transdermal Drug Delivery. Ph.D. Thesis, University of Dublin.

Bannon, Y.B., Corish, J., Corrigan, O.I., 1987. Iontophoretic transport of model compounds from an a gel matrix across a cellophane membrane. Drug Dev. Ind. Pharm. 13, 2617–2630.

Bannon, Y.B., Corish, J., Corrigan, O.I., Devane, J.G., Kavanagh, M., Mulligan, S., 1989. Transdermal delivery of nicotine in normal human volunteers: a single and multiple dose study. Eur. J. Clin. Pharmacol. 37, 285–290.

Bellantone, N.H., Rim, S., Francoeur, M.L., Rasadi, B., 1986. Enhanced percutaneous absorption via iontophoresis I. Evaluation of an in vitro system and transport of model compounds. Int. J. Pharmacol. 30, 63–72.

Bhat, C.V., Bhat, B.S., Shiv, S., Rehana, S., 1988. Ion exchange kinetics of nicotine and nicotinamide with gel type sulphonic acid cation exchange resin: exchange mechanism. Oriental J. Chem. 4 (2), 147–151.

Borodkin, S., Yunker, M.H., 1970. Interaction of amine drugs with a carboxylic acid ion exchange resin. J. Pharm. Sci. 59, 481–486.

Burnette, R.R., Bagniefski, T., 1988. Influence of constant current iontophoresis on the impedance and passive and Na^+ permeability of excised nude mouse skin. J. Pharm. Sci. 77 (6), 492–497.

Burnette, R.R., Marrero, D., 1986. Comparison between the iontophoretic and passive transport of thyrotropin releasing hormone across excised human skin and nude mouse skin. J. Pharm. Sci. 75, 738–743.

Burnette, R.R., Ongpipattanakul, B., 1986. Characterisation of the permselective properties of excised human skin during iontophoresis. J. Pharm. Sci. 76, 765–772.

Conaghey, O.M., Corish, J., Corrigan, O.I., 1998. The release of nicotine from a hydrogel containing ion exchange resins. Int. J. Pharm. 170, 215–224.

De Nuzzio, J.D., Berner, B., 1990. Electrochemical and iontophoretic studies of human skin. J. Control. Release 11, 105–112.

Del Terzo, S., Behl, C.R., Nash, R.A., 1989. Iontophoretic transport of a homologous series of ionized and non-ionized model compounds: influence of hydrophobicity and mechanistic interpretation. Pharm. Res. 6, 85–90.

Farag, Y., Nairn, G.J., 1988. Rate of release of organic carboxylic acids from ion exchange resins. J. Pharm. Sci. 77 (10), 872–875.

Foley, D., 1991. Transdermal Drug Transport: Its Enchancement by Iontophoresis and its Effect on the Electrical Properties of the Skin. Ph.D. Thesis, University of Dublin.

Foley, D., Corish, J., Corrigan, O.I., 1992. Iontophoretic delivery of drugs through membranes including human *stratum corneum*. Solid State Ionics 53–56, 184-196.

Franz, T.J., 1975. Percutaneous absorption on the relevance of in vitro data. J. Invest. Dermatol. 64, 190–195.

Gangarosa, L.P., Park, N.H., Wiggins, C.A., Hill, J.M., 1980. Increased penetration of non-electrolytes into mouse skin during iontophoretic water transport (iontohydrokinesis). J. Pharmacol. Exp. Ther. 212, 377–381.

Gupta, P.K., Hung, C.T., Perrier, D.G., 1986. Albumin microspheres. 1. Release characteristics of adriamycin. Int. J. Pharm. 33, 137–146.

Helfferich, F.G., 1962. Ion Exchange. McGraw-Hill, New York.

Irwin, W.J., MacHale, R., Watts, P.J., 1990. Drug delivery by ion exchange. Part VII: Release of acidic drugs from anionic exchange resinate complexes. Drug Dev. Ind. Pharm. 16 (6), 883–898.

Johnson, M.T.V., Richfield, N.H.L., 1990. pH buffered electrode for medicinal electrophoresis. US Patent, 4,973,303.

Ledger, P.W., 1992. Skin biological issues in electrically enhanced transdermal delivery. Adv. Drug Deliv. Rev. 9, 289–307.

Nachod, F.C., 1949. Ion Exchange. Academic Press, New York.

Phipps, J.B., Padmanabhan, R.V., Gillispie, L.J., Suram, J.M., 1986. Iontophoretic delivery of propranolol across excised rabbit, pig and human skins. In: Chaudry, I.A., Theis, C. (Eds.), Proceedings of the Thirteenth International Symposium on Controlled Release of Bioactive Materials. CRS, Lincolnshire IL, p. 179.

Phipps, J.B., Padmanabhan, R.V., Lattin, G.A., 1989. Iontophoretic delivery of model inorganic and drug ions. J. Pharm. Sci. 78 (5), 365–369.

Plaizier-Vercammen, J.A., 1992. Investigation of the bioavailability of coedine from a cationic exchange sulphonic acid. 2. Evaluation of release kinetics of coedine from the resin and uptake of Na^+ from solution. Int. J. Pharm. 87, 31–36.

Schacht, E., Goethals, E., Gyselinck, P., Thienpont, D.J., 1982. Polymer drug combinations VI. Sustained release of levamisole from ion exchange resins. J. Pharm. Belg. 37 (3), 183–188.

Siddiqui, O., Roberts, M.S., Polack, A.E., 1989. Iontophoretic transport of weak electrolytes through excised human stratum correum. J. Pharm. Pharmacol. 41, 430–432.

Singh, J., Roberts, M.S., 1989. Transdermal delivery of drugs by iontophoresis: a review. Drug Des. Deliv. 4, 1–12.

Speigler, K.S., Coryell, C.D., 1951. Electromigration in a cation exchange resin. Science 113, 546–547.

Speigler, K.S., Coryell, C.D., 1952. Electromigration in a cation exchange resin. II Detailed analysis of two-component systems. J. Phys. Chem. 56, 106–113.

Wang, Y., Allen, L.V., Li, L.C., Tu, Y.H., 1993. Iontophoresis of hydrocortisone across hairless mouse skin; investigation of skin alteration. J. Pharm. Sci. 82, 1140–1144.

Wearley, L.L., Chien, Y.W., 1990. Enhancement of the in vitro permeability of azidothymidine (AZT) via iontophoresis and chemical enhancer. Pharm. Res. 7, 34–40.

Wearley, L.L., Liu, L.-C., Chien, Y.W., 1989. Iontophoretically-facilitated transdermal delivery of vepramil. II. Factors affecting the reversibility of skin permeability. J. Control. Release 9, 231–242.