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The release of nicotine from a hydrogel containing ion exchange resins

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Abstract

Parameters influencing the release rates of nicotine from a range of agar-based gel vehicles containing ion exchange resins to which the nicotine had been bound have been determined. Measurements were made using a Franz-type cell with transport across artificial and human skin membranes. Analysis of the data on the basis of feasible diffusion models show that the overall release process across Visking is best represented as being controlled by matrix diffusion through the hydrogel. Because the nicotine is bound to the resin its rate of release from the resin-containing gels is much less than that from the corresponding simple hydrogel. The availability of ions suitable to exchange with the nicotine, following their diffusion from the receptor buffer solution, is shown to substantially increase the delivery rate. The vehicles were found to be unsuitable for passive release across human skin.

Keywords: Nicotine; Hydrogel; Ion exchange resins

1. Introduction

The transdermal delivery of drugs can offer substantial advantages over the more traditional oral and parenteral routes (Guy and Hadgraft, 1988). The development of new transdermal devices is therefore an integral part of the current general research effort aimed at controlling and sustaining the delivery of drugs, so that the predictability and reproducibility of their release kinetics and their bioavailabilities are improved. The essential features of a transdermal device are a drug reservoir, in which a supply of the active constituent is stored, and a means by which the rate at which the drug passes from the device to the surface of the skin is controlled. The principal methods employed to effect this control involve either the use of a suitable semi-permeable mem-

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brane or membrane laminate as a rate-controlling barrier or the design of the vehicle itself (Corish and Corrigan, 1990). In the latter case the material of the vehicle may be chosen so as to provide a suitable rate of matrix diffusion for the drug molecules or these molecules may be microencapsulated so that their release into the vehicle proper determines the rate of delivery from the device.

There is a number of successful transdermal drug delivery systems commercially available at present but the need remains to extend their operating parameters so that more sustainable and variable delivery regimes can be achieved. This paper reports the results of a series of investigations in which a range of ion exchange resins with different characteristics were incorporated into the hydrogel vehicle of a thoroughly-studied transdermal system originally designed to deliver nicotine (Bannon et al., 1989). The objective was to study the kinetics of the release of nicotine from both weak and strong ion exchange resins held in a hydrogel so that more flexible devices, both in terms of their ability to store the drug and to control the rates of its subsequent delivery, could be developed. The work includes an evaluation of the techniques for the loading of the complex vehicles and a determination of the release profiles of the nicotine across Visking™ and excised human skin membranes. The effects of factors such as variations in the composition of, and concentrations of drug in the vehicles, the particle sizes of the resins and the nature of the receptor media have also been established in a series of in vitro drug release measurements using Franz-type cells (Franz, 1975).

Because most of the ions that result from drug molecules are cations the resins chosen for this work are cation exchangers. The complexation of drugs with ion exchange resins (Calmon and Kressman, 1957; Helfferich, 1962; Schacht, 1983) has proved a promising means of achieving their controlled release (Chaudhry and Saunders, 1956; Raghunathan et al., 1981), of taste masking (Borodkin and Sundberg, 1971), of enhancing stability (Calmon and Kressman, 1957) and of drug delivery (Irwin et al., 1990). The utilisation of ion exchange resins is attractive in sustained drug delivery because, at least in theory, drug release characteristics rely on the ionic environment of the resin-drug complex. Sustained release peroral dosage forms have also been developed (Jalsenjak et al., 1977; Baichawal and Abraham, 1980; Nixon and Hassan, 1980). The incorporation of sustained release microcapsules into aqueous vehicles can result in substantial loss of the drug core to the suspending media. This can be reduced through the use of diffusion-retarding polymers in the drug-resin complexes before encapsulation (Kelleher and Carpanzano, 1991) or by coating the resin beads to improve and control their release characteristics (Motycka and Nairn, 1978). Studies of this type related to peroral dosage often measure drug release rates into simulated gastric and intestinal fluids. In contrast in the present study, the release of drug bound to the resin takes place in the first instance into the bulk of the hydrogel vehicle from where it can subsequently pass to the surface of the membrane and be transported into the receptor.

The electrical properties of ion exchange resins have also been studied extensively and the regeneration process, with the implied release of bound ions, can be effected by the passage of an electric current (Helfferich, 1962). The behaviour of the hydrogels containing drug-loaded resins and described here, when used as vehicles in iontophoretically assisted transdermal systems, will be described in a forthcoming publication (Conaghey et al., 1998).

2. Experimental

2.1. Preparation of the vehicles

Two types of strong sulphonic acid-based resin were investigated. The first was Amberlite IR-120 (supplied by Aldrich Chemical, UK): this was used only in exploratory work that will not be described in detail. The second comprised Dowex 50 W resins (supplied by Dow Chemical, Germany) which are available commercially with varying degrees of crosslinking and as spherical particles of different sizes. The release properties of three of these resins: Dowex × 2 (200–400) and × 8 (200–400) (0.018–0.0073 mm) and × 8 (50–

100) (0.152–0.424 mm) were determined. The values $\times 2$ and $\times 8$ are the percentages of divinylbenzene in the resin which provide the degree of crosslinking and the numbers in brackets refer to the average particle sizes of the resin beads. Apart from the preparation described below the resin beads were used as received. They were not further fractionated according to their particle sizes. Two types of weak carboxylic acid-based resins, Amberlite IRC-50 (supplied by Aldrich Chemical, UK) and Purolite C115 (supplied by Healy Chemicals, Ireland), were also incorporated into hydrogel vehicles and tested.

Ion exchange resin-hydrogel discs were prepared in two ways. In the exploratory work the Amberlite IR-120 resin was added to a 4% agar (Code L28, Oxoid Ltd.) hydrogel mix to which nicotine at the required concentration had already been added. When the resulting resin-containing gel had set, discs with a cross-sectional area of 2.67 cm^2 and a volume of 1.87 cm^3 were cut out using a circular cutting tool. In all cases sufficient resin was added to potentially bind all of the nicotine contained in the hydrogel. The preliminary work with vehicles prepared in this way clearly showed that the presence of the resins changed the rates of delivery of nicotine from those observed with the simple hydrogel (Bannon, 1989). It was also shown that the quantity of resin added, the size of the resin particles and the nature of the receptor solution could all affect these delivery rates (Conaghey, 1994). However, the results were found not to be easily reproducible.

These difficulties were overcome by the second method of preparation which was that used for all the work reported in this paper. Prior to their use the ion exchange resins, which were all of pharmaceutical grade, were activated by successive elution of methanol, distilled water, 1 M NaOH and 1 M HCl through a bed of resin held in a Buchner funnel. Volumes of ~ 30 ml of each eluant were used per gram of resin (Irwin and Belaid, 1987) and the resins were then washed with distilled water until the eluate was neutral. The resins were then dried overnight at room temperature and subsequently at 313 K in an oven to constant weight. They were then loaded with nicotine by adding an excess of the drug made up in an 0.16 M solution. The solvents used were either deionized water or phosphate-citric acid buffer at pH 5.0 and with a range of ionic strengths. These nicotine solution/resin mixtures were stirred continuously with initial experiments indicating that overnight periods were necessary to ensure sufficient contact.

After filtration and washing with distilled water until the eluate was free of nicotine, the resin was dried overnight at room temperature. Treatment with dilute NaOH and subsequent analysis using UV spectrophotometry allowed the nicotine content of the resins to be determined. The quantities of nicotine in the solution before and after binding were also analysed by UV spectrophotometry to ensure a mass balance.

The final step in this second method of preparation of the transdermal discs was the addition of the appropriate quantities of drug-loaded resins to a 4% agar solution. The resulting viscous resin-hydrol mixtures were then allowed to set into petri-dishes and discs, with the same dimensions as before, were cut from the resulting cooled gels. The pH of the gel was measured at 7.0 and the agar used was supplied as ion free. Because there were small variations in the quantities of nicotine that were bound in the resin, individual potencies were determined for each batch of resin that was loaded and for each resin/agar gel that was prepared. For the work described in this paper all the resins were loaded in the phosphate-citric acid buffer of ionic strength 0.21 M which ensured that the nicotine was ionized.

The nicotine, which was 98–100% anhydrous, was supplied by Nicobrand, Coleraine, Northern Ireland. All buffer solutions were prepared using A.R. grade chemicals.

2.2. Release studies

The custom-built Franz (1975) type cells used to determine the release kinetics and the methodology have been described previously (Bannon et al., 1987). The transport of nicotine from the vehicles was studied across a synthetic barrier, i.e. Visking dialysis tubing (Visking, Chicago, IL) and across excised human skin. In the latter case full

thickness skin as well as samples of the *stratum corneum* prepared following the method of Kligman and Christopher (1963) were used. Some experiments were also carried out in which the release rates of nicotine from the complex vehicles or from loaded ion exchange resin beads directly into a receptor were determined. The nicotine levels in the receptor solutions were quantified using High Performance Liquid Chromatography (HPLC) and the method has been described in detail (Bannon, 1989).

2.3. Analysis of data

Extensive data analyses were carried out based on diffusion models that might be feasible to describe the processes whereby the drug molecules left the resins and were eventually transported across the membranes and into the Franz type cells. The first, which had been used in several analagous previous studies (Reichenberg, 1953; Motycka and Nairn, 1979; Bhaskar et al., 1986; Farag and Nairn, 1988; Irwin et al., 1990), derived from the work of Boyd et al. (1947). It ascribes the rate-controlling step to the diffusion of the drug molecules through the particles of resin. The second attributes control of the release rate to diffusion of the drug across a film, treated as a planar and relatively very thin layer, surrounding each particle. The rate of the exchange of drug ions between the resin and its surroundings would then be ultimately determined by the slower of these two processes, i.e. by diffusion out of the resin particle or through a surrounding film. A detailed comparison of the differences between these processes and the dependence of each on the properties of the ion exchanger and of the solution has been made (Helfferich, 1962).

Neither of these two models was found to be applicable to the data measured here where the drug ions, after release from the resin particles, also have to pass through the hydrogel before they diffuse across the membrane. For this reason all of the analyses reported later are based on the matrix diffusion control model (Higuchi, 1960) which was found to best describe the kinetics that were observed. In this, the quantity of drug, Q, released at time t is given by

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

in which C_o is its initial concentration in the reservoir, and D its diffusion coefficient through the matrix. Eq. (1) is a simplified form that is valid when less than 30% of the drug has been released.

3. Results

3.1. Effect of the receptor solution

To assess the presence in the vehicles of free nicotine that could diffuse passively across the membrane barriers the release rates into deionized water were first determined. These measurements were followed by experiments in which a phosphate buffer medium, the ionic strength of which was varied, was used as the receptor. Representative results are shown in Fig. 1. Diffusion from the complex vehicles across Visking into the deionized water is seen to be very significantly less than from an analogous simple agar disc containing the same drug concentration. The release rates from the complex vehicles were, however, enhanced by the phosphate buffer receptor with somewhat greater delivery taking place from the strong resins. The effect of increasing the ionic strength of this buffer on the release rates from the agar/Amberlite IRC-50 vehicle is a corresponding increase in the transport from the discs and is shown in Fig. 2. Data collected during the course of these measurements also showed that for the Dowex resin systems the release of nicotine did not vary significantly with particle size or degree of crosslinking.

The release of nicotine from the heterogeneous vehicles into phosphate buffer solution was found to be considerably faster in the absence of the Visking barrier. For example, in the case of release from an agar/Amberlite IRC-50 vehicle containing the same concentration as that shown in Fig. 2 into the buffer at an ionic strength of 0.22 M some 50% of the nicotine was released after approximately 8 h with just less than 80% released after 25 h.

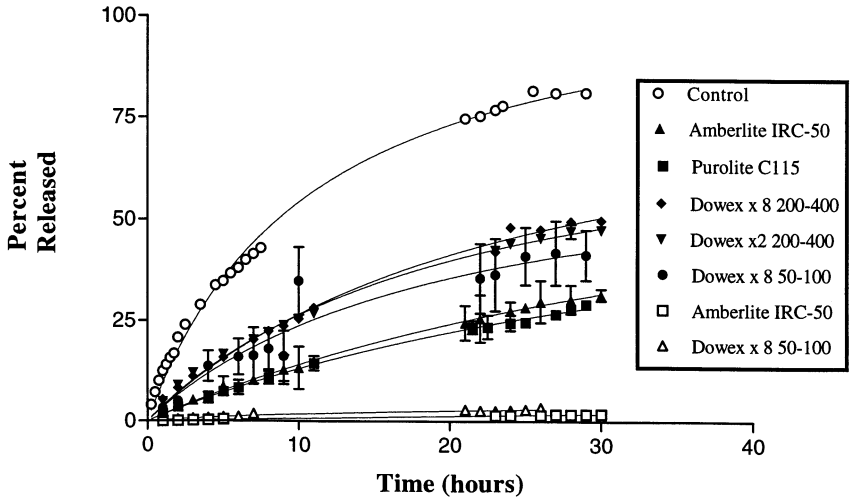

Fig. 1. The release profiles of nicotine into deionized water, shown as open symbols, from a simple 4% hydrogel, the control, compared with those from similar gels containing ion exhange resins to which nicotine has been bound. The release profiles of nicotine into phophate buffer (pH 7.4), shown as closed symbols, from both weak and strong ion exchange resins held within the same hydrogel are also shown. In all cases the concentration of the nicotine in the vehicles was 15.28 mg/cm^3 and the release rates were measured across Visking.

The release of nicotine from ion exchange resin beads in the absence of the hydrogel, i.e. directly into the phosphate buffer was found to be a very much more rapid process. Under the conditions described above some 90% of the nicotine in the Amberlite IRC-50 had been transferred to the buffer after only 0.75 h. These measurements show that the presence of the hydrogel surrounding the resin beads exerts a very significant controlling influence and slows down the release process.

3.2. Effect of nicotine concentration

The concentration and distribution of nicotine within the components of the complex vehicles was varied in the following two ways. In the first the quantity of drug-loaded resin used in the preparation of the discs was increased to give a higher overall concentration of nicotine in the vehicles. Fig. 3 shows release profiles from two agar/Amberlite IRC-50 discs in which the quantities of resin added differed by a factor of four. The corresponding overall concentrations of nicotine in these discs were 11.4 and 40.1 mg/cm^3, respectively. The initial nicotine release rates across Visking are seen to be similar but at longer times there is a fall-off evident in the release from the vehicle with the lower concentration as the nicotine is depleted. When the same data are shown in terms of the percentages of the nicotine contents that have been released, it is evident that a larger percentage is released from the vehicle with the lower overall concentration. This suggests that increasing the quantity of resin in the hydrogel reduces the effectiveness of the vehicle.

This conclusion is supported by release profiles measured from another two agar/Amberlite IRC-50 systems in which the distribution of the nicotine between the components of the vehicle was altered. These were prepared by loading resin to two different levels, 97 and 146 mg/g, respectively, but then adding sufficient of each loaded-resin to the hydrogel to give the same overall concentration, 15.3 mg/cm^3, of nicotine in each of the composite vehicles. The release profiles showed that the greater availability of free resin sites in the vehicle, i.e. in that containing the more lightly-loaded resin, slowed down the rate of release of nicotine.

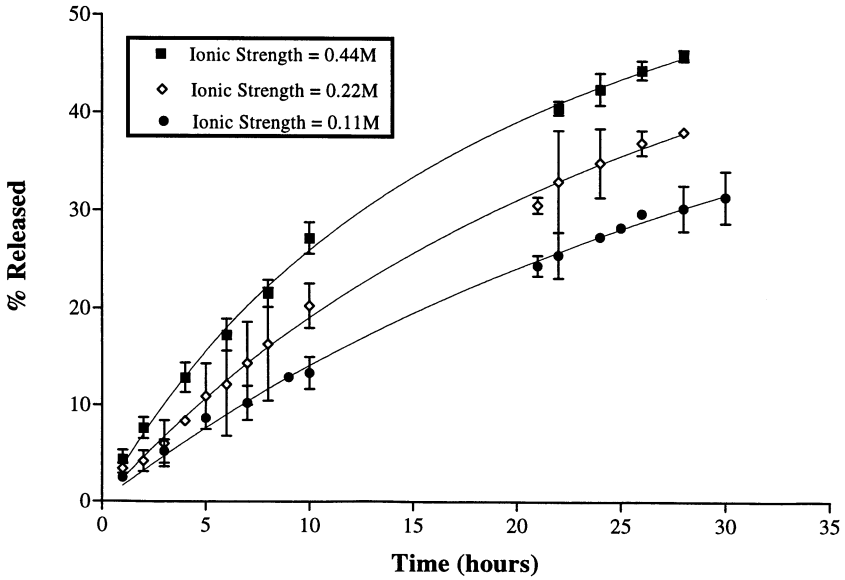

Fig. 2. The effect of changing the ionic strength of the phosphate buffer (pH 7.4) receptor solution on the passive release rate of nicotine from Amberlite IRC50 resin held in a 4% hydrogel across Visking. The concentration of the nicotine in the vehicles was 15.28 mg/cm^3.

3.3. Release kinetics

The release of nicotine from the simple hydrogel matrix which forms the basis of the vehicles investigated here has previously been examined in detail (Bannon, 1989) and was shown to follow Eq. (1) indicating matrix diffusion control. Table 1 lists the slopes of the release profiles measured here plotted according to this equation: lag times and correlation factors are also given. In general, the data appeared to fit the line a little better at longer times. These results indicate that the release rates of the nicotine from the complex vehicles are controlled primarily by its diffusion through the hydrogel matrix but with some perturbation during the early stages of the process. Non-zero intercepts on the time axes have been reported for the permeation of a number of compounds from the analogous simple hydrogel vehicle through Visking (Bannon, 1989). These lag times for nicotine diffusing from the agar gel were of the order of 5 min. In contrast, the initial rates of permeation from the hydrogel/resin systems investigated here are slower and the lag times are very substantially longer. In addition, these lag times were also found to depend on the ionic strength of the buffer that was in the receptor compartment. For example, for the release of nicotine from the agar/Amberlite IRC-50 vehicle the measured lag times were 26.7, 50.4 and 101.4 min for buffers of ionic strengths of 0.44, 0.22 and 0.11 M, respectively.

These observations indicate that the observed lag times are most likely to be the sum of the times taken for ions from the receptor solutions to diffuse to the resin particles, for their exchange with the drug ions and for the nicotine released to diffuse back to the surface of the vehicle. Our own observations for the exchange of nicotine directly from loaded ion exchange resin beads into a receptor solution show this to be a very rapid process with essentially total exchange having taken place within an hour. Earlier analogous measurements (Chaudhry and Saunders, 1956; Gyselinck et al., 1981; Schacht et al., 1982; Plaizier-Vercammen, 1992) confirm this view with diffusion coefficients of the order of 10^{-5} cm^2/s being reported. The rates of release were also found to increase with the ionic concentrations of the eluting solutions.

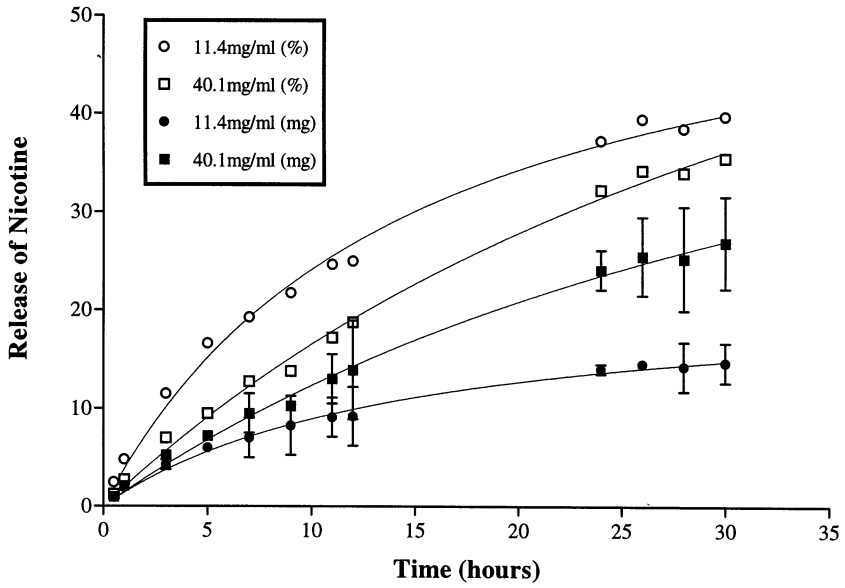

Fig. 3. A comparison of the release profiles of nicotine from Visking into phosphate (pH 7.4) buffer, shown both as percentage and weight released, from two agar/Amberlite IRC-50 vehicles containing quantities of the loaded resins that differ by a factor of four.

An approximate calculation (Crank, 1975) can be made to estimate the time taken for the diffusion of the ions from the receptor solution to the resin beads in the resin/agar vehicle. To do this the volume of the disc, the quantity of resin that it contains and the average particle sizes and density of the beads are used to calculate an average path length from the surface of the disc to the resin particles. This distance turns out to be ~ 0.064 cm and for a diffusion coefficient of 10^{-5} cm^2/s the average time for the ions to reach the resin when the ionic strength is 0.44 M is ~ 17 min. Because the diffusion coefficient for nicotine through the agar is also of the order of 10^{-5} cm^2/s (Bannon, 1989) this time should therefore be doubled to give an estimate of the lag time that would elapse before nicotine would be observed in the receptor. Given the relative simplicity and approximate nature of the model being used, the time of 34 min is in reasonable agreement with the observed lag time of 26 min. Because in this model the lag times scale inversely with the ionic strength of the ions in the buffer which are driving the diffusion process, a time of ~ 136 min will be calculated for the 0.11 M case and this is also in reasonable agreement with the observed time of 101 min.

3.4. Release across human skin

As is evident from Fig. 1 the release of nicotine from agar/resin gels across Visking into deionized water occurs at a rate that is very much less than its release from the corresponding simple hydrogel. Because Visking is essentially a non-rate-limiting barrier to the transfer of nicotine (Bannon, 1989) it is clear that only very small quantities of free nicotine are present within the gel. The imposition of the skin membrane adds a more complex barrier to the diffusional process and experiments confirmed that the passive diffusion of nicotine across skin into deionized water from agar/resin vehicles was negligible. These experiments were then extended by using phosphate buffer solutions as the receptor. However, in contrast to the behaviour observed with the Visking barrier (Fig. 1), the results showed that only very small quantities of nicotine (0.02 mg/h) were transported across full thickness skin over a 30-h period.

Table 1
Parameters obtained when release data were analysed on the basis of control by matrix diffusion through the gel (Eq. 1)

(a)

Concentrations (mg/ml)	Slope $\times 10^2$ (mg/cm^2/$t^{1/2}$)	Lag time (min)	Correlation factor
9.09	0.763 ± 0.02	50.09	0.988
15.28	1.548 ± 0.04	46.17	0.993
20.03	1.859 ± 0.06	5.66	0.995
40.11	3.536 ± 0.06	37.40	0.985

(b)

Grade of resin	Slope $\times 10^2$ (mg/cm^2/$t^{1/2}$)	Lag time (min)	Correlation factor
$\times 2$ 200-400	1.673 ± 0.003	10.42	0.994
$\times 8$ 200-400	1.564 ± 0.001	10.42	0.985
$\times 8$ 50-100	2.014 ± 0.009	27.51	0.996

(a) Release into phosphate buffer (pH 7.4) from the concentrations of nicotine shown in a hydrogel/Amberlite IRC-50 resin vehicles. (b) Release from a range of hydrogel/Dowex resin vehicles in each of which the nicotine concentration was 26.42 mg/ml into the same receptor.

4. Discussion

The experimental data measured here relate to the release, principally across Visking membranes, of nicotine which has been bound to beads of ion exchange resins which are then incorporated into a hydrogel to form vehicles for potential use in transdermal drug delivery devices. The results make it possible to understand the factors which control the passive release of the nicotine and to compare the processes occurring in this complex vehicle with those in which drug molecules are delivered, under different conditions, from ion exchange resins.

The immediate effect of binding the nicotine to any of the resins investigated is to greatly decrease its rate of delivery when compared to that from the simple hydrogel containing the same overall concentration (Fig. 1). Typically only some 5% of the nicotine content was released into deionized water after a 30-h period. However the supply of an ion suitable to exchange with the nicotine, through the substitution of a phosphate buffer receptor from which such ions could diffuse through the gel to the resin, dramatically increased the release of nicotine from the vehicles. Increases in the ionic strength of the receptor were found to produce corresponding increases in the release rates of nicotine from the vehicles, Fig. 2. Similar effects were found by Raghunathan et al. (1981) for the release of both phenylpropanolamine and chloropheniramine from a sulphonic acid resin. More recently, no significant difference was observed in the release rates of a range of drugs from sulphonic acid resins when the pH of the dissolution medium was varied but these rates were enhanced when its ionic strength was increased (Sandhavi et al., 1988). A range of experiments was carried out to try to establish exactly what processes controlled the rate of delivery of the nicotine from the vehicles.

Earlier work has shown that because cross-linking modifies the pore-size within a resin, and thus can hinder movement within the resin matrix, it can cause a slower release rate of an exchanged species from the resin as the degree of cross-linking is increased (Irwin et al., 1990). The rate of release has also been observed to significantly depend on the average size of the resin particles because of the greater diffusional path lengths in larger beads (Raghunathan et al., 1981; Schacht et al., 1982; Irwin et al., 1990). However the results from experiments in which these parameters were varied in the systems under study here indicate that neither of these two factors significantly alters the release rate of nicotine from the complex

vehicle. In this respect, it is important to realise that in the current experiments the release rates of the nicotine are not determined immediately it has left the resin. Rather they are measured after it has moved through the vehicle to the surface and has subsequently been transported across the Visking into the receptor.

There are similarities between the effects caused by the presence of the hydrogel surrounding the resin particles in these vehicles and those caused by the coatings sometimes used in other sustained release dosage forms employing ion exchange resins. Moldenhauer and Nairn (1990) observed that treating a theophylline-loaded Dowex ion exchange resin with a thin polymer coating appeared to remove any relationship between the drug release rate and the particle size of the resin. Woodworth et al. (1992), who studied the sustained release of hydralazine from a resin coated with a semi-permeable membrane suggested that the release characteristics were controlled more by the diffusion of the drug from the ion exchange resin. The influence of the hydrogel is also evident in effectively masking the differences that would be expected between the release because of the different chemical natures of the resins (Fig. 1). For example, Jayaswal and Bedi (1980) observed the rate of release of propranolol-HCl from Amberlite IRC-50 to be faster than that from the strong resin Amberlite IR-120. More recently Sprockel and Price (1989) found chlorpheniramine to be released more quickly from a carboxylic acid resin than from one containing a sulphonic acid. Both of these results are in contrast with the present observations with the agar/resin vehicles. Thus it is the diffusion processes, both of the sodium ions necessary to effect the ion exchange from the receptor buffer to the resin particles and subsequently of the liberated nicotine ions back to the vehicle surface that determine the observed release profile. The need for this double diffusion to take place before any nicotine enters the receptor results in substantial lag times and the subsequent release rates are governed by matrix diffusion control through the agar. Calculations, based on a simple model, predict lag times of the correct order and which vary with the ionic strength of the receptor buffer in a manner similar to those determined experimentally. So it is the hydrogel that ultimately controls the kinetics of release from these vehicles with some modification in the initial stages because of the need to release the drug from the ion exchange resins.

The results obtained with the human skin barrier show that the binding of the nicotine to the resin in these composite agar/resin vehicles make them unsuitable for use in passive transdermal devices. However, as will be described later (Conaghey et al., 1998) drugs can be released from ion-exchange resins under the influence of an electric current so that the storage capacity of the resins can be utilized in the design of more flexible iontophoretically-assisted transdermal drug delivery systems.

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