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Drug delivery from a liquid crystalline base across Visking and human stratum corneum

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Abstract

The rates of in vitro release of two drug molecules, nicotine and salbutamol sulphate, from lyotropic liquid crystal gels across a non rate-limiting membrane and also across human stratum corneum have been determined. The effects of changing the water content of the gels and of their mode of preparation have also been studied. The drug-loaded vehicles were incorporated into electrically driven transdermal delivery systems and the rates of iontophoretically assisted drug transport from these determined as a function of the current densities across the membrane barriers.

Keywords: Transdermal; Iontophoresis; Liquid crystals; Diffusion; Drug delivery

1. Introduction

The value of continuous infusion therapy as a mode of drug administration lends impetus to the search for more flexible transdermal delivery systems. Liquid crystalline gels may be used as a reservoir from which drugs may be released by diffusion through the water channels of the gel matrix. For example Pluronic (polyoxyethylene–polyoxypropylene) F-127® gels are viscous isotropic liquid crystals and have been used in controlled drug delivery for both the topical and rectal routes (Miyazaki et al., 1986). Lyotropic liquid crystalline phases, such as those formed between monoolein and water, have been advocated as matrix systems for the controlled release of drugs. Engstrom et al. (1988) showed that the release of methylene blue from a cubic monoolein/water phase followed the typical square root of time dependence for a matrix system. Furthermore a capsule formulation filled with metoprolol dispersed in monolein formed a cubic liquid crystalline phase on penetration by an

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external water release medium. These monoglycerides, which are swelling amphiphiles, can incorporate considerable amounts of water causing the formation of various liquid crystalline phases (Collett et al., 1990). They also have the ability to incorporate solutes into their structures and the addition of a third component often results in a modification of the phase properties of the system and consequently of the drug release characteristics. More recently Burrows et al. (1994) investigated the in vitro release of model drugs with a wide range of aqueous solubilities from monolein/water liquid crystalline matrix systems. The release profiles could be fitted to both diffusion controlled or first-order kinetics. Monoglycerides are also physiologically compatible and this makes them potentially attractive as vehicles for the formulation of transdermal drug delivery systems. The work to be reported here investigates both passive and electrically assisted transport of model compounds from lytotropic liquid crystal gel-type transdermal formulations through non rate-limiting membranes and also through rate-limiting human stratum corneum. The drug vehicles were prepared from Myverol®. The initial in vitro experiments using Visking™ membranes as barriers to the receptor solutions were performed to investigate the effects of drug concentration and methods of preparation of the vehicle on the release rates of nicotine and salbutamol from different formulations of the Myverol gels. Apparent diffusion coefficients for both drugs were determined in each of the gel matrices. The work was then extended to transport across excised human stratum corneum and to study the effects of iontophoretic assistance on the drug transport processes across both membranes. The influences of vehicle composition, current density and the intermittent application of iontophoresis using direct currents were also determined.

2. Methods and materials

2.1. Release studies

The custom-built apparatus used for the determination of passive and electrically assisted release rates of the drugs has been previously described in detail (Bannon et al., 1987). It was a Franz (1975) type cell with a receptor volume of approximately 50 cm^3. The gel containing the drug, prepared and formed into a disc as described below, was placed on the membrane which covered the top of the cell and was held in place using parafilm. The receptor fluid was carefully stirred with a star-headed magnetic follower to give constant hydrodynamics and to ensure that a vortex did not form below the membrane. The Visking cellulose dialysis tubing (Visking 18/32) was obtained from the Visking Company, Chicago, IL. Earlier work has shown these membranes to have a dry thickness of 20 mm (Bannon, 1989) and with an average pore size of 2.4 nm (Corrigan et al., 1980). Before use the membranes were pretreated by immersion for several minutes in boiling deionized water that was changed frequently: this process removed any soluble materials such as sulphur compounds and glycerol (Molyneux and Frank, 1961). The seamless tubing was then cut into circular pieces which were secured over the diffusion area of the diffusion cell by Nescofilm (Nippon Shoji Kaisa, Japan).

The stratum corneum used was provided from samples of human cadaver skin taken within 48 h post mortem from the mid-abdominal region. The age and sex of the donor were recorded for each sample. The stratum corneum membranes were prepared according to the method of Kligman and Christophers (1963) and were stored in sealed packages at 273–275K until required. Before use the dried stratum corneum pieces were rehydrated for at least 1 h in phosphate buffer pH 7.4. The membranes were then positioned and secured across the diffusion area of the cells using teflon tape, Nescofilm and the custombuilt teflon holder.

2.2. Vehicles

Some comparative measurements were made using agar gels as the vehicle. Purified agar Code L28 was obtained from Oxoid and 4% (w/v) gels were prepared by adding 60 cm^3 of distilled water to 2.4 g of the agar. The mixture was then heated to boiling and the requisite quantity of drug was added. The resulting viscous gel was then poured

into a petri dish and after cooling discs with a cross-sectional area of 2.37 cm^2 and a volume of 2.32 cm^3 were cut out using a circular cutting tool.

Myverol 18-99 (m.p. 341K) and Myverol 18-92K (m.p. 308K) were supplied by Eastmann–Kodak. The principal difference between these products lies in the relative amounts of oleic and linoleic acids present as the glycerol esters. Both form liquid crystalline gels with water at or above room temperature and these were prepared by either of two methods. In the first, which was subsequently used for all the work reported here, the required quantity of drug was first weighed out and dissolved in a pre-determined quantity of water e.g. that required to give 30% w/v total gel composition. The requisite quantity of the Myverol was then gently melted in a heated water bath, removed from the heat and the drug solution added to it. The gel, which formed immediately was mixed thoroughly to ensure the homogeneous and complete incorporation of all the drug and water. In a second method, which was tested but proved to be less effective, the Myverol was again melted but in this case the solid drug was added directly to the melted Myverol and mixed thoroughly. At this stage in the preparation process the drug appeared to be dispersed rather than dissolved in the Myverol liquid. The requisite quantity of water was subsequently added to this mixture whereupon the gel formed immediately with no apparent undissolved drug particles present: the resulting gel was then thoroughly mixed. The gels prepared by both methods were allowed to equilibrate for several hours before use. Individual discs were then fabricated by moulding the gels into custom-made cylindrical teflon moulds which were 0.89 cm in depth with a diameter of 1.73 cm: the volume of the resulting discs was approximately 2.1 cm^3.

These gels were prepared at four different percentage (v/w) water concentrations i.e. 0.0, 23.0, 30.0 and 40.0%. Comparative studies of Myverol 18-99 gels at 30% water concentration prepared by both methods and of Myverol 18–92K gels at the same water concentration but prepared by the first method were also carried out.

2.3. Drug molecules

The compounds chosen to evaluate the liquid crystalline vehicles were salbutamol sulphate and nicotine. Extensive data exist for both the passive and iontophoretically-assisted delivery of these molecules from a 4% agar vehicle across both Visking and human stratum corneum. The salbutamol sulphate B.P. was supplied by K and K Greess UK. and was used as received. The nicotine (98–100% anhydrous) was obtained from Nicobrand, Coleraine Northern Ireland as a clear liquid that had been vacuum distilled: it was also used as received. The methods of HPLC analysis for both of these drugs have been previously described in detail (Bannon, 1989).

3. Results

3.1. Passive drug delivery across Visking

The rates of drug delivery into the receptor compartment were determined by withdrawing samples for analysis at appropriate time intervals. Plots of the quantities of drug released across Visking from 30% Myverol gels versus time were found to be non-linear for both nicotine and salbutamol: their slopes decreased with time. These data were found to be closely in agreement with matrix controlled release as represented by the equation developed by Higuchi (1960)

$$Q = 2C_0(Dt/\pi)^{1/2} \quad (1)$$

where Q is the quantity of drug released, C_0 its initial concentration in the reservoir and D its diffusion coefficient and this simplified form being valid when $< 30\%$ of the drug has been released. The linear relationship observed when the quantities of drugs released were plotted against the square root of time are shown for salbutamol sulphate in Fig. 1. The slopes are seen to increase with the drug loading and the x-axis intercepts, evident in all the studies, have previously been ascribed to a boundary layer contribution at early times (Bannon et al., 1987). The lag times for the release of nicotine were similar to those reported for its release from a 4% agar gel whereas those

for salbutamol sulphate were much shorter from the Myverol gels: there was also an inverse relationship between the recorded lag times and increasing water content in the Myverol 18-99 gels.

A further test of the appropriateness of the matrix-control equation is that a linear relationship should exist between the slope of the lines in Fig. 1 ($Q/t^{1/2}$), and the initial concentration, C_0, of the drug. This is shown to be true for both drugs in Fig. 2 and from the slopes of these plots the apparent diffusion coefficients of nicotine and salbutamol can be determined. The values obtained from the data shown are 3.04×10^{-7} and 9.70×10^{-7} cm^2 s^{-1} for nicotine and salbutamol, respectively, and these may be compared with the values 26.0×10^{-7} and 9.33×10^{-7} cm^2 s^{-1} obtained by Bannon (1989) for the diffusion of the same molecules from a 4% agar gel.

Fig. 3 shows the effect of changing the water content of the liquid crystalline base on the measured apparent diffusion coefficients of the drugs.

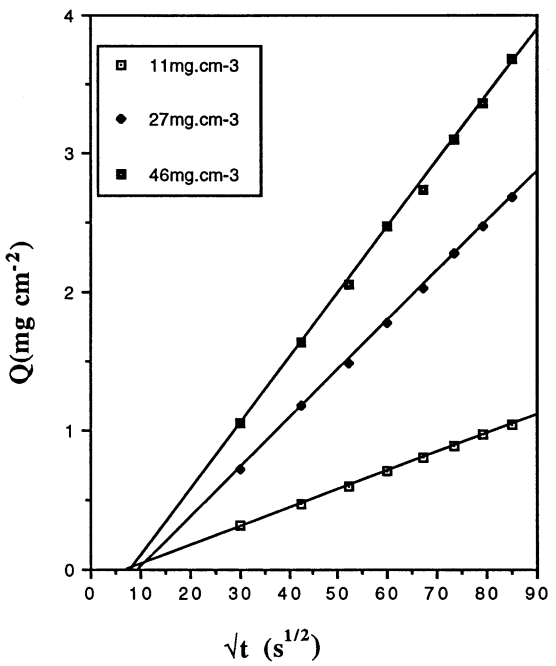

Fig. 1. The quantity of salbutamol sulphate, Q, transported per unit area across Visking membranes from 30% water Myverol 18-99 gels versus the square root of time. The key indicates the drug loadings in the gel.

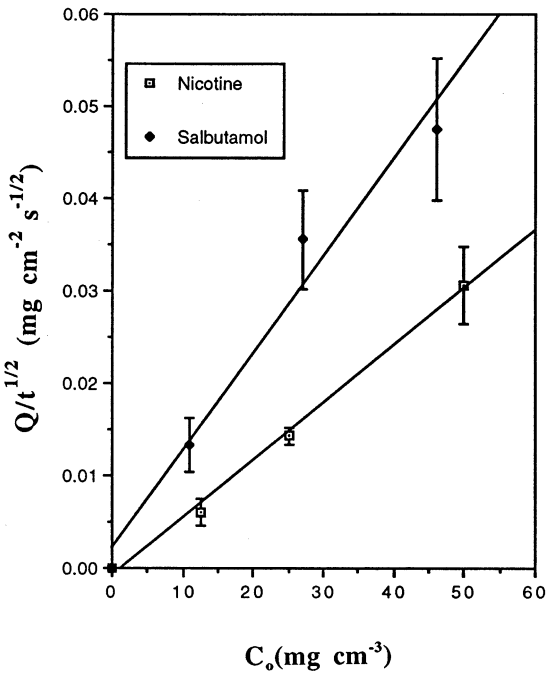

Fig. 2. The relationship between $Q/t^{1/2}$ and the initial concentrations of the drugs in the gels, C_0, for the transport of nicotine and salbutamol from 30% water Myverol 18-99 gels across Visking membranes.

Increasing the water content in the range 0–40% greatly increased the apparent diffusion coefficient of nicotine, whereas there was a decrease in the apparent diffusion coefficient of sabutamol sulphate. Myverol water partition coefficients, which were also determined during the course of this work, indicated that whereas nicotine showed a significant partitioning ($P_{\text{Myverol/water}} = 2.7$) into Myverol no partitioning of salbutamol from its sulphate salt was detected. This would explain why increasing the water content in the vehicle would lead to an increased flux for nicotine since it would decrease the concentration in the Myverol phase and hence increase its partitioning into the membrane. In the case of the salbutamol sulphate, which has no affinity for the Myverol phase, the increase in the water content of the vehicle would simply reduce the concentration of the drug and hence result in a reduced flux across the membrane.

The differences between the release characteristics of the Myverol 18-99 and 18-92K were investigated using both nicotine and salbutamol sulphate from the 30% water gel. Only small differences were found: the diffusion coefficients were lower for salbutamol but slightly higher for nicotine from the Myverol 18-92K gels.

Salbutamol sulphate, again in 30% water formulations, was used as the model drug to ascertain the effect of the method of preparation of the gel on the rate of drug release. For gels prepared by the second method, the measured apparent diffusion coefficients were reduced by approximately 15%. It is thought that the drug incorporated in this way may be entrapped between the surfactant bilayers and hence tend to diffuse more slowly through the more lipophilic regions of the Myverol to the aqueous channels from whence it is released across the membrane.

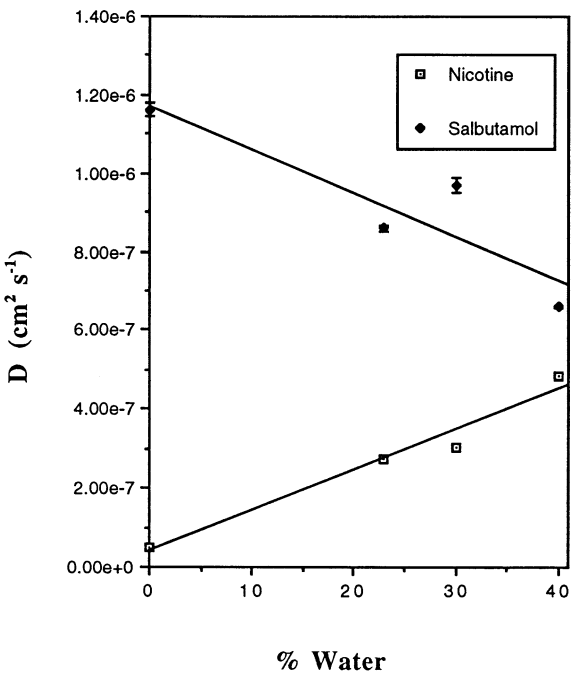

Fig. 3. The relationships between the measured apparent diffusion coefficients, D, and the percentage water contained in the Myverol 18-99 gels.

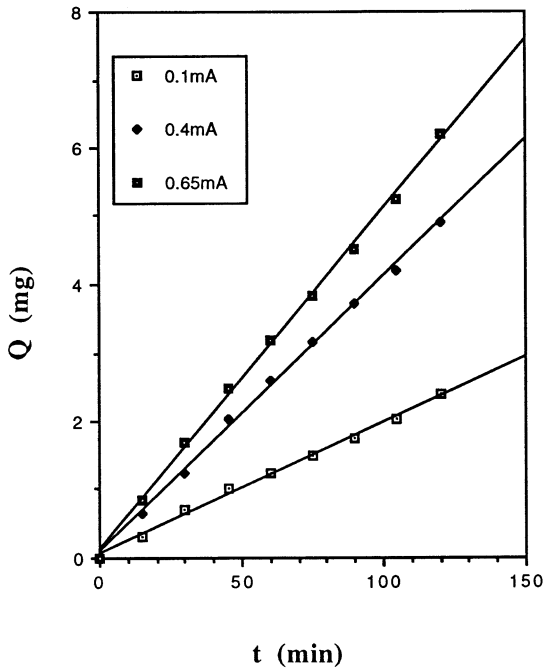

Fig. 4. Release profiles for the electrically-assisted transport of nicotine, initial concentration 12.5 mg cm^{-3}, at the currents shown from 30% water Myverol 18-99 gels.

3.2. Iontophoretic delivery across Visking

Electrical currents in the range 0.04–0.23 mA cm^{-2} were found to considerably enhance the transport of both nicotine and salbutamol over their corresponding passive release rates from the Myverol gels. The release profiles were, in general, found to be essentially linear with respect to time as shown for nicotine in Fig. 4. In addition, plots of the rate of drug transport versus the current through the device, shown in Fig. 5 for both nicotine and salbutamol, also indicate a linear relationship as had been observed previously for the iontophoretic release of these compounds from an agar gel. The quantity of drug transported iontophoretically may be written as

$$Q_i = f_i i_d t \quad (2)$$

where i_d is the current density (mA cm^{-2}), t is the elapsed time and f_i (mg s^{-1} mA^{-1}) is an iontophoretic constant that can be determined from the slopes of the delivery profiles. A simple empir-

ical model in which the total quantity of drug delivered during the electrically assisted delivery, Q_t, is taken as the sum of the passive (Eq. (1)) and iontophoretic (Eq. (2)) quantities

$$Q_t = Q_p + Q_i = 2C_0(Dt/\pi)^{1/2} + f_i i_d t \quad (3)$$

was found to give a good estimate of the observed rates of delivery. Effective transport numbers for the iontophoretic delivery were calculated by comparing the actual delivery with the quantity calculated using Faraday's Laws that would be delivered if the current was carried exclusively by the drug ions. These were found to vary within the range 0.6–0.75 for nicotine and 0.4–0.47 for salbutamol sulphate over the range of Myverol gels and current densities used and were in good agreement with numbers reported previously for transport of the same drugs from 4% Agar (Bannon, 1989).

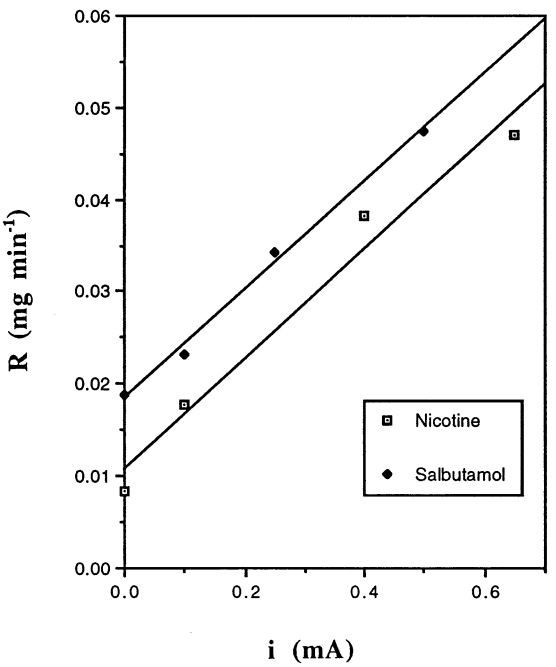

Fig. 5. The relationships between rates, R, of assisted transport of nicotine (12.5 mg cm^{-3}) and salbutamol sulphate (11 mg cm^{-3}) through Visking membranes from 30% water Myverol 18-99 gels and the iontophoretic currents used.

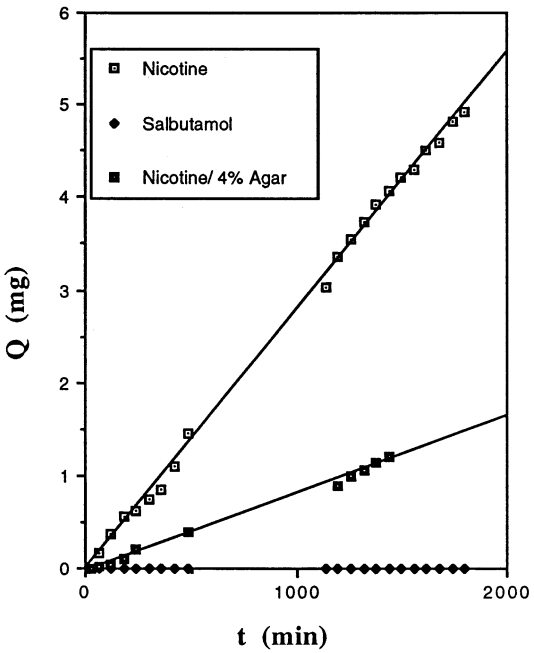

Fig. 6. Release profiles for passive transport across human stratum corneum. The data relating to 4% agar are taken from Bannon (1989) for comparison: the remaining data are for release from 30% water Myverol 18-99 gels at initial concentrations of 12.5 and 11.0 mg cm^{-3} for nicotine and salbutamol sulphate, respectively.

3.3. Passive transport through stratum corneum

Passive diffusion experiments were conducted for both nicotine and salbutamol sulphate through human stratum corneum from 30% water Myverol gels. No passive flux for the salbutamol could be measured since levels in the receptor compartment remained below the detection limit even after 30 h. This result is the same as that reported earlier for the transport of this drug from a 4% agar gel. In contrast, significant quantities of nicotine diffused rather rapidly through the skin. The profile, as shown in Fig. 6, was linear and the rates of delivery were typically 2–3 times those reported from 4% agar gel vehicles containing comparable concentrations of the drug. This suggests that the Myverol may act in some way as a penetration enhancer. There have been reports of monoglycerides being used as penetration enhancers in some formulations

(Mutsuo et al., 1990) with the effect being attributed to changes caused to the partitioning of the drug molecules into the skin.

3.4. Iontophoretic transport through stratum corneum

With iontophoretic current densities in the range 0.0–0.21 mA cm^{-2} significant enhancements were observed in the transport of nicotine and the transport of salbutamol sulphate was also observed to take place. Application of an intermittent d.c. voltage showed that these enhancements were reproducible for a given sample of stratum corneum and that on cessation of the current the rate of passive diffusion returned, though not instantaneously, to close to its original value: in the case of salbutamol sulphate this unassisted rate was essentially zero. Fig. 7 shows the relationships between the iontophoretic currents used and the observed rates of iontophoretic transport, for both drugs across stratum corneum. Analogous curves, measured by Bannon (1989), for the same processes when the drugs were transported from a 4% agar gel are shown for comparison. The rather limited data available suggest that the effect of increasing the current for delivery from the Myverol system is a linear but relatively small increase in the case of nicotine and a more marked and non-linear increase for the salbutamol sulphate. Indeed at currents in excess of 0.275 mA (current densities > 0.12 mA cm^{-2}) the rate of delivery of salbutamol already exceeds that of nicotine. This contrasts with their respective delivery rates from the 4% agar and clearly demonstrates the effect of the nature of the vehicle on iontophoretically-assisted drug delivery across the stratum corneum.

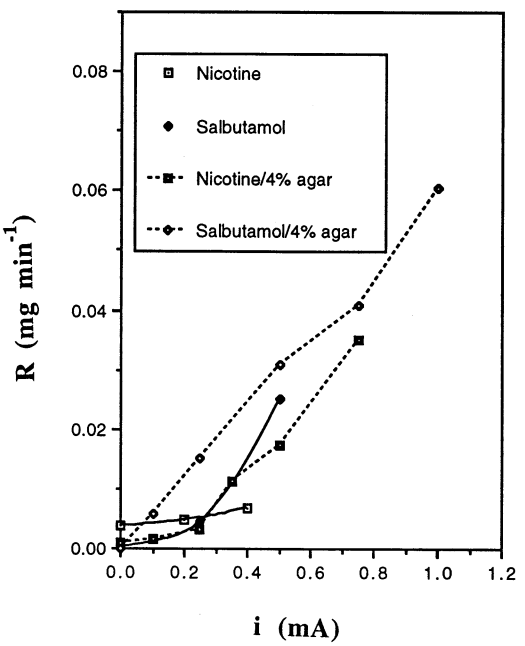

Fig. 7. The full lines show the relationships between the rates, R, of assisted transport of nicotine (12.5 mg cm^{-3}) and salbutamol sulphate (11 mg cm^{-3}) from 30% water Myverol 18-99 gels across human stratum corneum. The dotted lines are taken from Bannon (1989) and show the analogous data for the release of nicotine (11 mg cm^{-3}) and salbutamol sulphate (27.5 mg cm^{-3}) from a 4% agar gel.

4. Conclusions

The passive delivery of both nicotine and salbutamol sulphate from the various Myverol gel formulations used in this work was found to be matrix diffusion controlled. For transport across Visking the square root of time law was obeyed after initial lag times that are thought to be due to the hydrodynamic diffusion layer at the membrane-solution interface. The effect of increasing water contents in the gels gave contrasting results for the two drugs. The transport of nicotine increased with increasing water content whereas that of salbutamol sulphate was found to decrease. Partitioning of the drugs between the Myverol base and the aqueous layers is thought to be responsible for this behaviour. Overall, the delivery of nicotine from the Myverol gels was significantly reduced when compared with that from 4% agar: the delivery of salbutamol sulphate was similar from both types of vehicles.

The passive in vitro delivery of nicotine across human stratum corneum from the Myverol systems was significantly greater than that found in 4% agar systems thus suggesting a possible enhancing effect by some of the constituents of the Myverol. Significant increases in the transport of both drugs were effected by the passage of a

direct current through the vehicle and the rates of the assisted transport were found to depend on the magnitude of this current. Comparisons with earlier work on the same drugs demonstrate clearly that choice of vehicle can contribute significantly to the performance of these types of transdermal drug delivery systems.

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