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IN VITRO PASSIVE AND IONTOPHORETICALLY ASSISTED TRANSPORT OF SALBUTAMOL SULPHATE ACROSS SYNTHETIC MEMBRANES

A.M. Rodríguez Bayon[1], J. Corish[2] and O.I. Corrigan[3]

1. Departamento de Farmacia y Tecnologia Farmacéutica. Facultad de Farmacia. Universidad Complutense de Madrid. 28040-Madrid, Spain.
2. Department of Chemistry, Trinity College, University of Dublin, Dublin 2. Ireland.
3. Department of Pharmaceutics, Trinity College, University of Dublin, Dublin 2, Ireland.

ABSTRACT

The passive and electrically assisted transport of salbutamol sulphate through four synthetic membranes was investigated. Two of these were hydrophilic (Visking 18/32 and Celgard-3401®) and two hydrophobic (Celgard-2400® and Celgard-4500®). Significant differences in passive membrane transport were observed. The hydrophilic Celgard membrane gave similar passive transport rates to Visking 18/32. However, slower rates were observed with the hydrophobic membranes, the rate for Celgard-4500 being 4-5 fold smaller than Visking 18/32 and that for Celgard-2400 being negligible over a period of 6 hours. The passive release of salbutamol sulphate from the hydrogel across the hydrophilic membranes was matrix-controlled, whereas the membrane was the rate-limiting element for passive release through the hydrophobic membranes. Application of an electrical potential giving rise to iontophoretic currents in the range 0.100 to 0.500 mA led to an increase in drug transport rate and this

1. To whom correspondence should be addressed.

effect became larger as the current was increased. The quantity of drug transported in a given time period increased linearly with time for both kind of membranes. However the relative increase in transport induced by current was greatest with the hydrophobic membranes.

INTRODUCTION

The ability of an electrical potential to enhance salbutamol sulphate transport from a hydrogel across both Visking membranes and human skin has been previously reported[1]. While the rate of passive drug transport was greater through Visking, the relative enhancement on application of current was greater through *stratum corneum*. Similar differences between synthetic and natural membranes were observed with other drugs. To explore the reasons for these differences we have extended the work to other membranes including synthetic hydrophobic Celgard types.

In addition to their use as models for biological membranes synthetic membranes are frequently employed as rate-controlling elements in transdermal drug delivery systems. In these cases the rate is intended to be well below the maximum that human skin can accept. Thus, the device, and not the *stratum corneum*, will control the rate of drug diffusion through the epidermis and dermis.

Two main designs for these devices are in use, matrix controlled systems and transdermal patchs which incorporate a rate-limiting membrane[2-9]. *In vitro* transdermal studies using a range of synthetic membranes with different pore sizes, thicknesses, numbers of pores and physicochemical properties should be of assistance in understanding the *in vitro* release of drug both passively and with iontophoretic assistance. Iontophoresis can be described as the permeation of ionized molecules across biological membranes under the influence of electrical current[10]. It can be used for enhancing the rate of penetration of ions through the skin by the application of a voltage drop across the skin[11] and it is employed for the transdermal delivery of drugs for systemic therapy[12]. The increase in drug transport due to iontophoresis is well documented[13,14]. In the present work four different membranes with different pore sizes, thicknesses and chemical compositions are used to study the active and passive drug transport through them, as well as the quantitative effect of the size of the iontophoretic currents and to determine their possible application in transdermal drug delivery systems.

MATERIALS AND METHODS

Permeation Studies.

Transdermal hydrogel discs with a cross-sectional area of 2.16 cm^2 containing 11mg/ml of salbutamol sulphate were used as the donor phase.

These discs were placed on the surface of the membrane which was used in the diffusion cell previously described[15].

The cells were filled with pure water (Milli-Q) and were maintained at 37ºC using a water bath. This receptor phase was stirred constantly using a magnetic stirrer with star-head follower. An aliquot (1ml) of the receptor fluid was withdrawn periodically for analysis and replaced with the same volume of liquid.

The concentrations of Salbutamol sulphate in the samples taken from the receptor solution were determined by HPLC at 276 nm as previously described[1]. All passive transport experiments were run over 6 hours and, at least, in duplicate.

Electrically Assisted Transport (Iontophoresis).

The procedure was similar to that used to study passive transport but the migration of the ions was now assisted by an electrical current. The cells were placed in the water bath as above, with platinum electrodes placed behind the donor gel and also in the receptor compartment. The counter electrode was approximately 3 cm. below the membrane and a d.c. potential (Philips Harris supply) was applied between the pair of electrodes. Currents, in the range 0.1-0.5 mA were generated and current flows and voltages were monitored (3465 Digital Multimeter Hewlett-Packard). The voltage was adjusted as was necessary so that the current was maintained at a constant value throughout the experiment.

Membranes.

The membranes employed are classified as hydrophobic i.e., Celgard-2400® and Celgard-4500® and hydrophilic i.e., Celgard-3401® (Hoechst-Celanese Co.) and Visking 18/32 cellulose dyalisis tubing (Visking Co. Chicago Ill). Celgard-2400 and Celgard-4500 are porous hydrophobic polymer membranes. Celgard-4500 is a membrane laminate variant of the Celgard-2400 series exhibiting improved tear-resistance and increased thickness. Celgard-3401 is a hydrophilic variant of the 2000 series membranes and has low resistance to electrolytic conduction. It is treated with surfactants to allow wetting in aqueus solutions.

Celgard membranes are used in rate control applications and in transdermal drug delivery. The pores are rectangular slots and the pore width is considered to be the controlling factor. Each forms a tortuous

TABLE 1
Membrane Characteristics

	Visking	Celgard-3401	Celgard-2400	Celgard-4500
Chemical Name	Cellulose	Polypropilene	Polypropilene	Polypropilene
Thickness	20μm	25μm	25μm	175μm
Porosity	-	38%	38%	45%
Pore : dimension (wxl)	-	0.05x 0.125μm	0.05x 0.125μm	0.075x 0.25μm
Effective pore size	0.0024μm	-	0.05μm	-
Characteristics	Hydrophilic	Hydrophilic	Hydrophobic	Hydrophobic

interconnected channel through the membrane[16]. The characteristics of these membranes are summarised in Table 1.

Celgard membranes were used after immersion in pure water, at room temperature, in the dark, for at least 24 hours, the water being changed once or twice before commencing the experiment. Visking membranes were pretreated as described by Molyneux and Frank[17] by boiling several times in pure water.

RESULTS AND DISCUSSION

The effect of membrane type on the transport of salbutamol sulphate from a hydrogel to the receptor fluid under sink conditions is shown in Fig. 1. The two hydrophilic membranes, Visking and Celgard 3401 resulted in the most rapid drug transport. Release profiles for both were curved and practically superimposable. When the quantity released was plotted against the square root of time the profiles were linear. These results indicate that the two hydrophilic membranes offered little resistance to drug transport: the release was controlled by

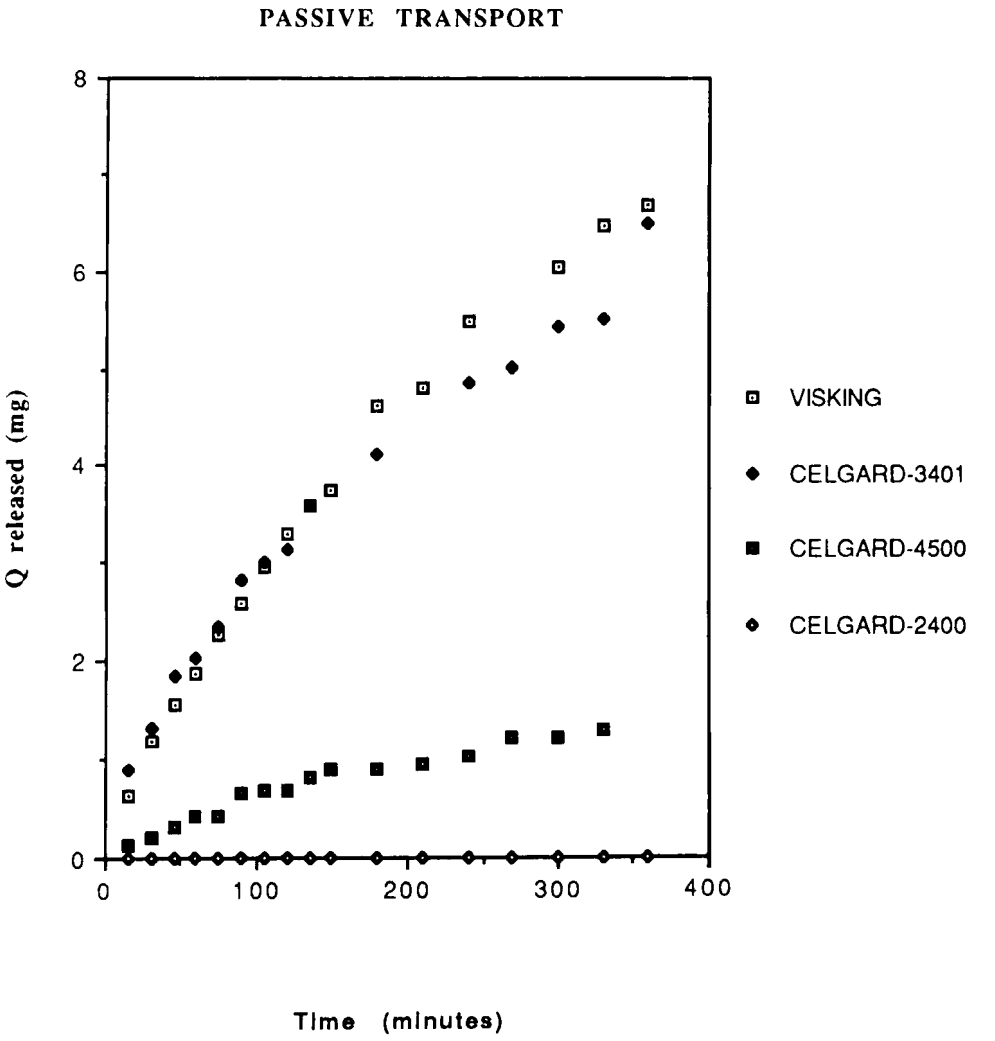

FIGURE 1

Effect of membrane type on the passive transport of Salbutamol from a hydrogel to the receptor fluid under sink conditions. Key: Visking ⊡ , Celgard-3401 ◆, Celgard-4500 ■, Celgard-2400 ◇.

diffusion from the hydrogel. The release profiles for passive diffusion of salbutamol across these hydrophilic membranes were found to be matrix controlled with the quantity released being proportional to the square root of time t , according to the Higuchi equation:

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

where q is the weight released, A is the surface area, C_O is the initial concentration of the solute in the gel and D is its diffusion coefficient.

In contrast to these results much lower release rates were observed with the hydrophobic membranes Celgard 2400 and 4500, the former showing negligible transport over a six hour period. This means that the hydrophobic membranes offer the major resistance to salbutamol transport. Despite the fact that Celgard 3401 and 2400 have similar porosity, pore size and thickness the hydrophobic nature of the latter results in neglegible drug transport over the duration of the experiment.

Previously we have reported neglegible transport of salbutamol across human *stratum corneum in vitro.* Thus of the four membranes studied the hydrophobic membrane with the smallest pores (Celgard 2400) behaves most like human skin.

Effect of current.

The application of an electrical potential across the membrane led to an increase in drug transport for all four membranes studied. The effects of the magnitude of the current for the two hydrophobic membranes, Celgard 4500 and 2400, are shown in Figs 2 and 3, respectively. The profiles become more linear with increased currents. The quantity transported in a given time increased with increasing current intensity in the range 0.10 to 0.50 mA. The rate of drug transport, R_i, estimated from the data by linear regression was found to depend on the magnitude of the applied current, i. Similar findings have been observed by several authors[18-22]. The slope of the linear dependence of R_i on the current, i, is given by equation (2) below, where f_i is a constant defined as the iontophoretic flux[18]:

$$R_i = f_i \, . \, I \qquad (2)$$

The iontophoretic fluxes for Visking and Celgard-3401 membranes were 0.7546×10^{-3} $mgs^{-1}mA^{-1}$ and 0.6745×10^{-3} $mgs^{-1}mA^{-1}$, respectively.

The magnitude of the enhancement in drug transport varied with the membrane employed. This is evident from Fig. 4 where the effects of a

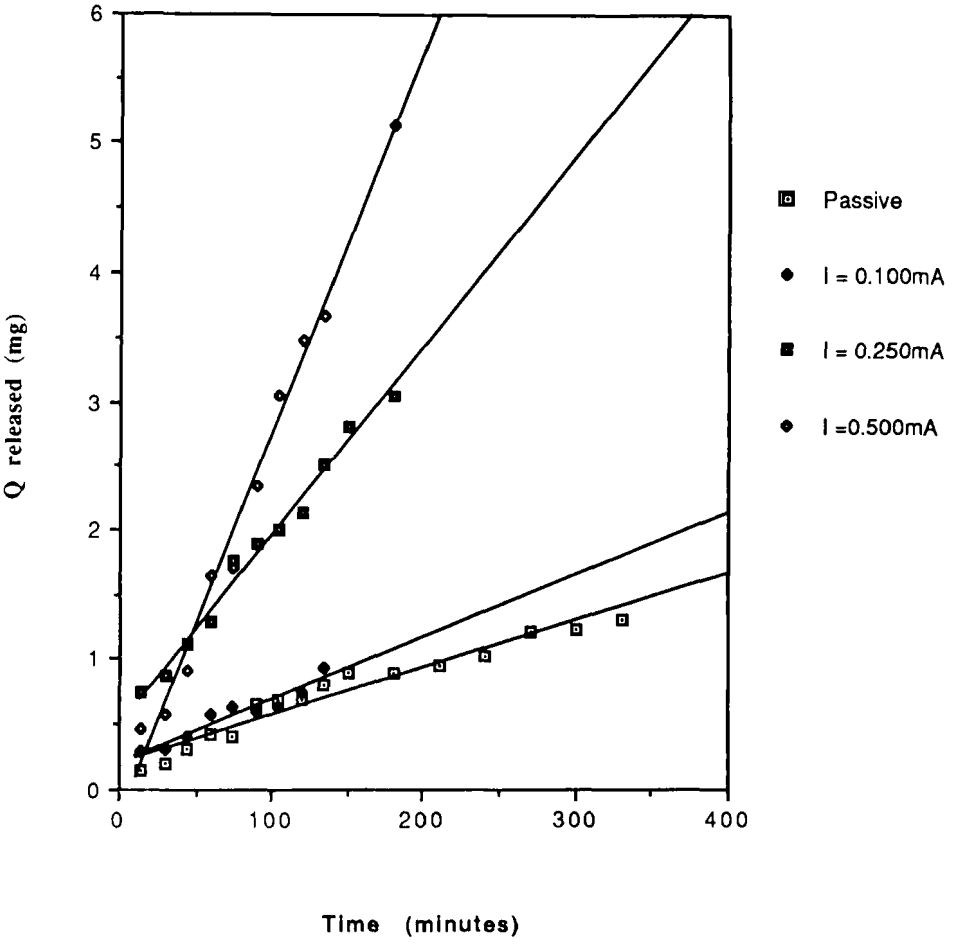

FIGURE 2

Effect of current on the transport of Salbutamol across Celgard-4500 membrane. Key: Current strength (mA) : 0.0 ⊡ , 0.1 ◆, 0.25 ■, 0.5 ◇.

current of 0.1mA across each membrane are compared. It is evident that whereas drug transport is still greatest through the hydrophilic membranes, the relative effect of current is greater with the hydrophobic membrane systems and consequently differences between the membranes became less. This result is more evident in Fig. 5 where the rates observed are plotted against the applied current for

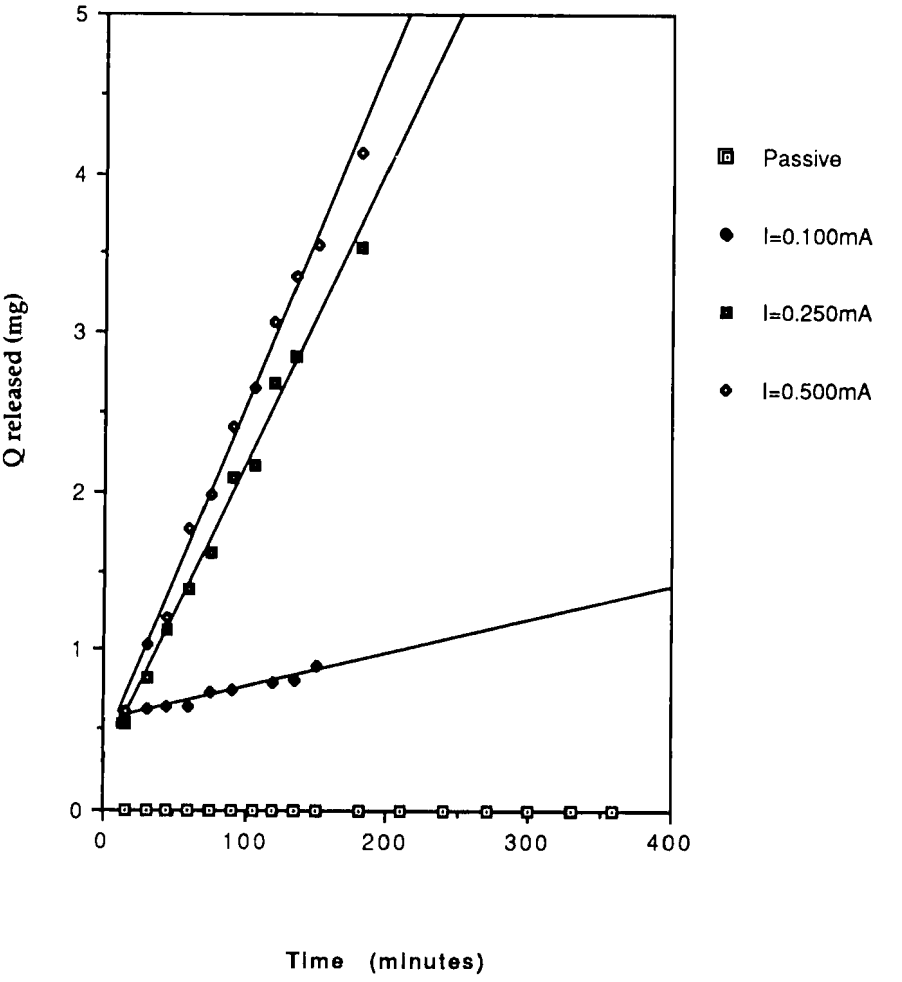

FIGURE 3

Effect of current on the transport of Salbutamol across Celgard-2400 membrane. Key: Current strenght (mA): 0.0 ⊡, 0.1 ♦, 0.25 ■, 0.5 ◇ .

each membrane type. The lines of best fit through the data fall into two groups with the hydrophobic membranes tending to have a larger slope and smaller intercept when compared to the hydrophilic membranes. The larger slope signifies more efficient use of the current in the drug transport process.

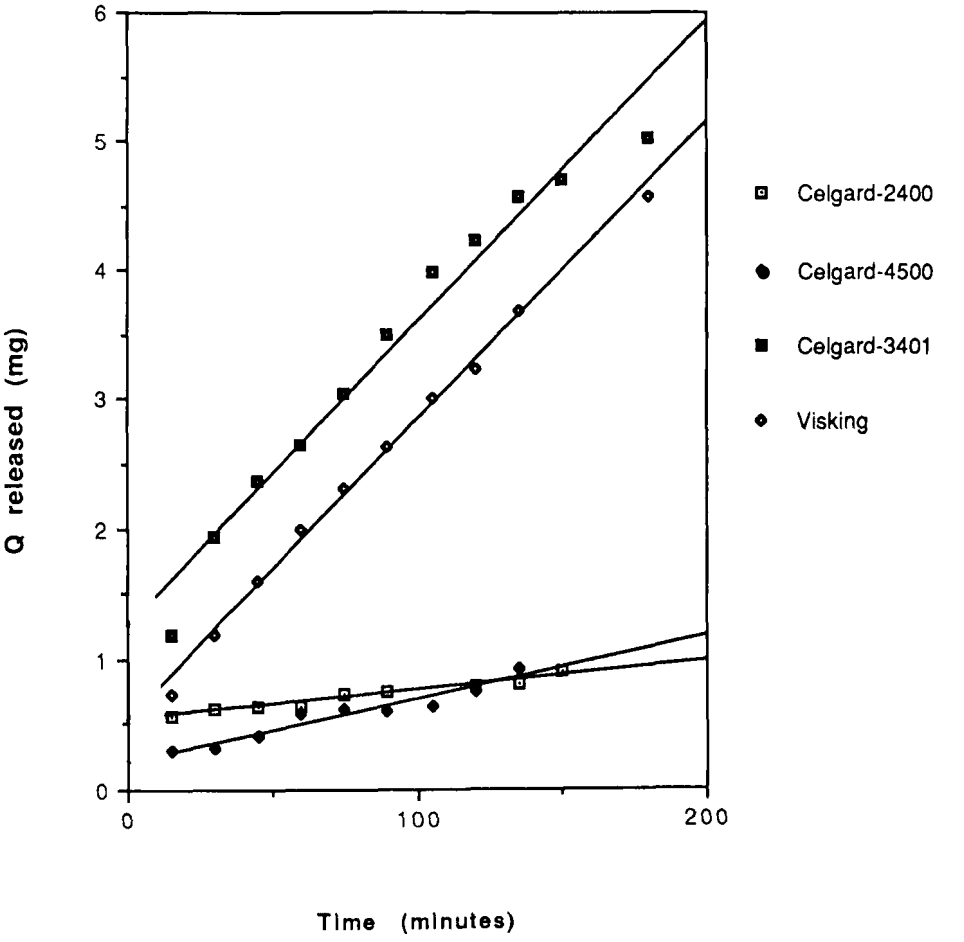

FIGURE 4

Comparison of the effect of current (0.100 mA) on the membrane transport of Salbutamol. Key: Visking ◇, Celgard-3401 ■, Celgard-4500 ◆ Celgard-2400 ⊡

The estimated transport numbers for the assisted transfer of salbutamol through Celgard-3401 and Visking 18/32 membranes were 0.2720 and 0.3043, respectively. The hydrophobic membranes Celgard 2400 and 4500 gave higher values of 0.3160 and 0.3685. Burnette and Ongpipattanakul[19] observed transport numbers of 0.26-0.30 for Cl^- using current densities in the range 0.078-0.23 $mAcm^{-2}$ through excised cadaver skin.

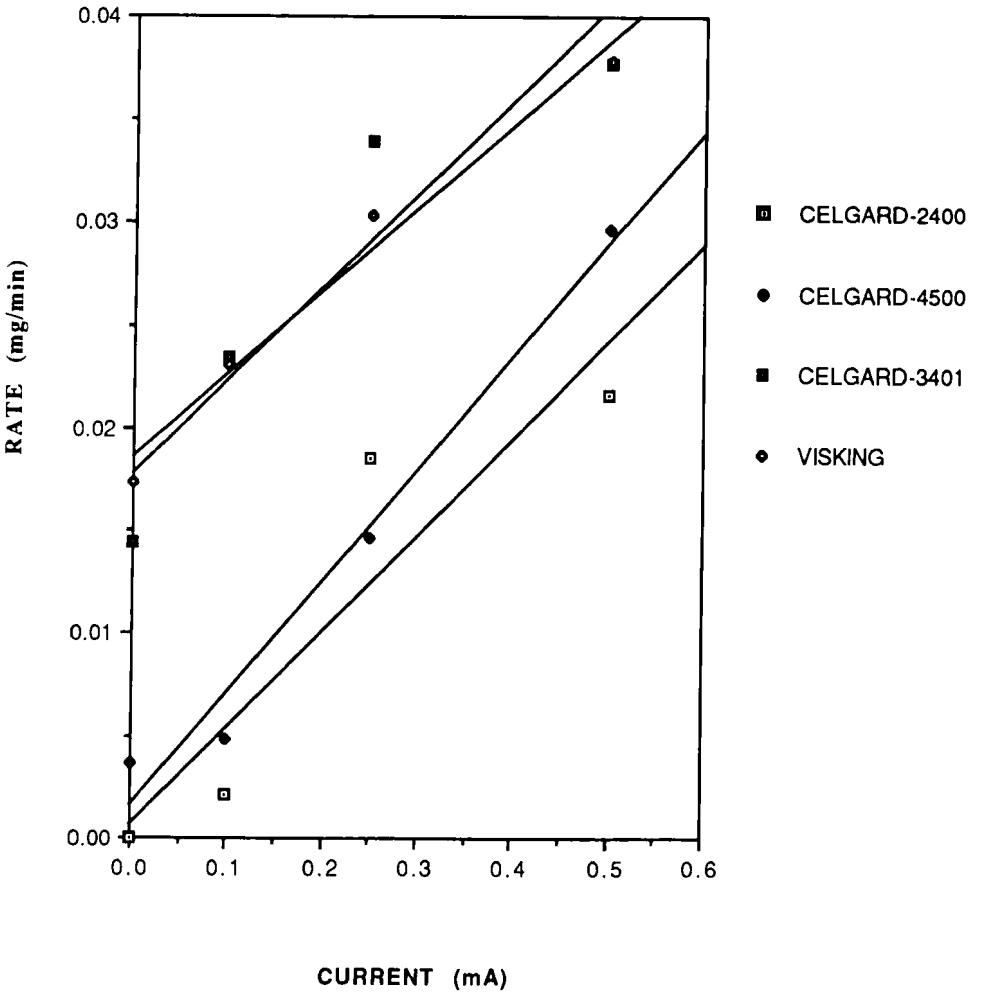

FIGURE 5

A plot of rate of transport Ri ($mg.min^{-1}$) against current I (mA) for the iontophoretically assisted transport of Salbutamol across different synthetic membranes. Key: Visking ◇ , Celgard-3401 ■, Celgard-4500 ◆, Celgard-2400 ⧈

The nature of the membranes was also reflected in their resistance to passage of the iontophoretic currents and in the times taken to attain the chosen current densities The experiments using Celgard-4500 required the longest period of time to reach the selected current but this may be partly due to the increased thickness of the membrane. In contrast the chosen current densities were quickly established with the hydrophilic membranes. With a constant current of 0.250 mA through Celgard-3401 the applied voltage decreased rapidly with time and was six times smaller than the initial voltage in a period of one hour. The corresponding decrease for a current of 0.5 mA was approximately three fold. The same period of time was observed by Maury et al.[23] using a current of 0.5mA through hairless mouse skin as membrane. Finally, longer periods of time and smaller decreases in voltage values were obtained for the least permeable hydrophobic membrane (Celgard-2400) when compared with the hydrophilic Celgard-3401.

CONCLUSIONS

Significant differences in passive transport of salbutamol were observed across hydrophilic (Visking 18/32 and Celgard-3401) and hydrophobic membranes (Celgard-2400 and Celgard-4500).

The rates across hydrophilic membranes were matrix-controlled, as determined by the release from the transdermal disc. However, the hydrophobic membranes were rate-controlling in the passive transport of salbutamol sulphate.

The use of iontophoretic currents in the range 0.10-0.50 mA resulted in enhanced transport of salbutamol and the rate of transport became proportional to the current density. The maximum relative enhancement was obtained with the least permeable membrane (Celgard-2400).

Furthermore, these studies demonstrated the hydrophobic membrane Celgard-2400 to be most like human *stratum corneum* since the passive transport of salbutamol through it was negligible over 6 hours, the duration of the study.

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REFERENCES

1. Y.B. BANNON, J.CORISH, O.I. CORRIGAN and J.G. MASTERSON, Drug Dev.Ind.Pharm., **14** , 2151, (1988).

2. Y.W. CHIEN , Drug Dev. Ind. Pharm., **9**, 497 (1983).

3. M. MIYAJIMA, T.OKANO, F. KOMADA, S.W. KIM, W.I. HIGUCHI, W.M. SHANNON and D.C. BAKER, Proceed. 13th Intern. Symp. Control. Rel. Bioact. Mater., p.91 (1986).

4. B.W. LIANG, Y.P. CHANG and Y. LU, Ap. G1 5ème Congrés International de Technol. Pharmaceutique. Paris, May (1989), Tomo III, p.322.

5. S.K. CHANDRASEKARAN, Drug Dev. Ind. Pharm., **9**, 627 (1983).

6. H. BREM, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., nºS-5, p.16 (1989).

7. I. NOZAWA, Y. SUZUKI, S. SATO, K. SUGIBAYASHI and Y. MORIMOTO, J. Controlled Release, **15**, 29 (1991).

8. W.R. PFISTER, R.P. SWEET, P.A. WALTERS and D.J. SANDVIG, Proceed. 13th Intern. Symp. Control. Rel. Bioact. Mater. , (1986), p.220.

9. A. KARIM, Drug Dev. Ind. Pharm. , **9**, 671 (1983).

10. C.R. BEHL, S. KUMAR, A. WASEEM MALICK, S. del TERZO, W.I. HIGUCHI and R.A. NASH, J. Pharm. Sci., **78**, 355 (1989).

11. V. SRINIVASAN, W.I. HIGUCHI, S.M. SIMS, A.H. GHANEM and C.R. BEHL, J.Pharm. Sci., **78**, 370 (1989).

12. A.K. BANGA and Y.W. CHIEN, J. Controlled Release, **7**, 1 (1988).

13. N.H. BELLANTONE, S. RIM, M.L. FRANCOEUR and B. RASAI, Int. J. Pharm. **30**, 63 (1986).

14. R.R. BURNETTE and T.M. BAGNIEFSKI, J. Pharm. Sci. , **77**, 492 (1988).

15. Y.B. BANNON, J. CORISH and O.I. CORRIGAN, Drug Dev. Ind. Pharm., **13**, 2617 (1987).

16. Product Information, Issued by Hoechst Celanese, Separations Products Division, (1988).

17. P. MOLYNEUX and H.P. FRANK, J. Amer. Chem. Soc., **83**, 3169 (1961).

18. J.P.PHIPS, R.V. PADMANABHAN and G.A. LATTIN, J. Pharm. Sci., **78**, 365, (1989).

19. R.R. BURNETTE and B. ONGPIPATTANAKUL, J. Pharm. Sci., **76**, 765, (1987).

20. R.R. BURNETTE and B. ONGPIPATTANAKUL, J. Pharm. Sci., 77, 132, (1988).

21. O. SIDDIQUI, M.S. ROBERTS and A.E. POLACK, J. Pharm. Pharmacol., 37, 732 (1985).

22. J.E. RIVIERE, B. SAGE and P.L. WILLIAMS, J. Pharm. Sci., 80, 615 (1991).

23. P. MAURY, B. BEVAN, E. TEILLAUD, C. HERRENKNECHT, F.FALSON-RIEG and G. COURRAZE, Ap G1. 5ème Congrés International de Technologie Pharmaceutique. Paris, June, (1989). Tomo III, p.304