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Research paper

Modeling of the drug delivery from a hydrophilic transdermal therapeutic system across polymer membrane

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Abstract

A mathematical simulation is presented which describes the in vitro drug delivery kinetics from hydrophilic adhesive water-soluble poly-*N*-vinylpyrrolidone (PVP) –polyethylene glycol (PEG) matrices of transdermal therapeutic systems (TTS) across skin-imitating hydrophobic Carbosil membranes. Propranolol is employed as the test drug. The contributions of the following physicochemical determinants to drug delivery rate control have been estimated: the drug diffusion coefficients both in the matrix and the membrane; the membrane - matrix drug partition coefficient: the drug concentration in the matrix and the membrane thickness. Drug transfer from the hydrophilic matrix across the membrane is shown to be controlled by the drug partitioning from the matrix into the membrane. The best correlation between simulation data and experimental results is obtained when the effect of membrane hydration is taken into consideration during in vitro drug release.

Keywords: Poly(vinyl pyrrolidone); Poly(ethylene glycol); Adhesive hydrogel matrix; Poly(dimethyl siloxane)–polycarbonate block copolymer; Skin-mimetic membrane; Propranolol; Drug diffusion; Partition; Transdermal drug delivery, Mathematical simulation

1. Introduction

The assessment of the release properties of transdermal therapeutic systems (TTS) represents an important test for TTS pharmaceutical performance. Regulatory authorities need a test analogous to the tablet dissolution test, where patches are placed in direct contact with an aqueous receptor medium or where a permeable membrane is inserted between the patch and receptor solution [1–3]. There are evident problems when the patch either releases drug very quickly, with a rate faster than the bio-membrane (skin) penetration, or undergoes dissolution in the receptor solution, or when water uptake by the patch affects the release kinetics during testing. The approach described in this work is useful for extracting the intrinsic release properties of highly hydrophilic or water soluble vehicles (transdermal, topical or buccal hydrogels) when the release is masked by the penetration limit of the membrane employed to shield the patch from the dissolution medium.

Recently, a hydrogel pressure-sensitive adhesive matrix based on a poly-complex between poly(*N*-vinylpyrrolydone) (PVP) and oligomeric poly(ethylene glycol) [PEG] has been designed for enhanced transdermal drug delivery [4–6]. To protect the hydrophilic matrix from dissolving in the receptor solution it has to be adhered to either human epidermis or a skin-imitating hydrophobic polymer membrane. Thus, it is essential to estimate the transport properties of both the matrix and the membrane (which ideally mimics the drug permeability of human epidermis).

Using 14 drugs covering a wide range of chemical structure, physicochemical properties and theraupetic classes, we have recently performed a comparative study of the barrier functions of human skin and polydimethylsiloxane–polycarbonate block copolymer membrane (Carbosil) [7,8]. Drug permeabilities across skin and the Carbosil membrane were examined as a function of permeant molecular weight, melting point, solubility, octanol/water partition coefficient and diffusivity. Drug delivery kinetics from the hydrogel matrix were found to be controlled by the permeation barriers: human skin epidermis (both in vitro and in vivo) [9,10] or

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the Carbosil membrane in vitro [7]. Both barriers possess similar diffusivities but Carbosil provides a higher drug solubility and, consequently, higher permeability compared to human skin epidermis [11]. However, by varying the composition of the block copolymer membrane, the diffusivity and solubility in the Carbosil membrane can be varied several-fold such that it gives not only a better representation of *stratum corneum* barrier properties [8], but the possibility of modeling transport phenomena [12] in both the membrane and the hydrophilic matrix.

The mathematical modeling employed in this work is not destined to serve in the place of our in vitro method of a hydrophilic patch quality control that has been recently described [7–9]. This test is based on using the skin-imitating hydrophobic Carbosil membrane which has been demonstrated to share with human skin epidermis a common permeability mechanism involving diffusion and partitioning processes in heterophase and heteropolar media. The mathematical modeling aims to explore the borders of the applicability window of the in vitro patch quality evaluating test for various drugs, donor vehicles and penetration barriers. Using conventional numerical simulation methods, this aim may be easily accomplished by varying the different rate-controlling factors imposed by device and membrane while keeping other diffusion and partition variables fixed.

This paper provides numerical simulation analysis of drug delivery kinetics (propranolol) from a hydrogel TTS matrix (PVP/PEG) across 'Carbosil' membrane in order to quantify the contributions of both the matrix and the membrane properties to drug delivery rate control.

2. Materials and methods

The transdermal matrices used were Propercuten-mite TTS, a propranolol-loaded adhesive hydrogel patch, based on a hydrophilic matrix composed of high molecular weight PVP (MW = 750 000–1 000 000) and oligomeric short-chain PEG (MW = 400). The drug and PVP were dissolved in a mixture of liquid PEG and ethanol (cosolvent). Then the solution was cast onto a poly(ethyleneterephthalate) film and dried at gradually elevated temperatures from 30 to 65°C. The drug content in the propercuten-mite TTS was 7.4% (250 mg/48 cm^2). The propranolol solubility limit in the matrix is 14 wt.% (established by endotherm curves with DSC). The equilibrium matrix hydration value varied from 8 to 11%. The TTS matrices are rectangular (6 × 8 cm), 0.7 mm in thickness and are combined with an occlusive 0.02 mm metallized polyethyleneterephthalate backing film. All samples contained 36 wt % of PEG-400.

Carbosil membranes of 0.04 mm in thickness were produced in 'Medpolymer', Moscow, Russia, from a block copolymer of polydimethylsiloxane (55%) with polycarbonate (45%).

In vivo propranolol transdermal drug delivery from the TTS matrices was studied in multicenter clinical trials approved by the Pharmacological Committee of the Public Health Ministry of the Russian Federation [13]. Propranolol concentration in human plasma after TTS application was determined by HPLC using fluorometric drug detection [14] with an acccuracy of 1.0 ng/ml. Human cadaver skin epidermis was obtained from males of 30–50 years old using conventional heat separation (30 s at 60°C) [15].

The determination of the in vitro propranolol delivery rates from the TTS matrix across Carbosil membranes was based on the USP rotating cylinder paddle-over-disk method using a LKB Tablet Dissolution System (paddle rotating speed 100 ± 1 min^{-1}). The measurement of drug appearance rate in the receptor phase (0.15 M NaCl) at 35°C was performed automatically with a UV- spectrophotometer Ultrospec-II (LKB) or manually with Shimadzu UV-160. The in vitro transdermal delivery rate of propranolol was determined using a Hitachi F-4000 spectrofluorimeter [5].

The estimation of propranolol diffusion coefficients in Carbosil membranes or human skin epidermis was conducted using Franz-type vertical diffusion cells at 35 ± 0.5°C. The donor (5 ml) and receptor (500 ml) chambers were mechanically stirred. Membrane-matrix drug partition coefficients were evaluated by placing the TTS adhesive matrix in contact with the Carbosil membrane at 25°C and allowed to equilibrate over 48 h. Over this period was ascertained by the determination of the drug remainder in the matrix.

Reproducibility of the in vitro propranolol delivery kinetics from the TTS patches across Carbosil membranes has been established with numerous tests, performed in the course of both the patch development and quality control. The batch-to-batch differences in delivery rates were within 7%, depending on the deviations in drug loading and membrane thickness. Numerical simulations of the in vitro drug transfer across Carbosil were carried out using a Turbo-Pascal program [16]. The relevant experimental data used for the simulations have been described and discussed in detail [6,7].

3. Theoretical development

We have considered a two-phase diffusion system which includes the gel polymer matrix (I) 0.7 mm in thickness with uniformly distributed drug molecules. An impermeable polymer film covers one surface of the matrix and its opposite side is combined with the drug permeable 0.04 mm Carbosil membrane (II). This skin-imitating protective membrane serves as a barrier to permeation for diffusing drug molecules and, at the same time, prevents the water soluble matrix from dissolving in the receptor aqueous solution (III).

Drug mass transfer within the matrix and the membrane results from diffusion (the drug diffusion coefficients in matrix and membrane are D_I and D_{II}, respectively). The

drug concentration in the receptor solution C_s^{III} is uniform due to efficient stirring and is considered negligible in comparison with drug concentration in matrix $C_s^{I} \gg C_s^{III} \approx 0$. In this, first, description we assume that the effect of water counterflow into the matrix across the membrane on drug delivery kinetics from the matrix is negligible. However this assumption has been shown [11] to be reasonable only for propranolol and other drugs of the first group listed in [6]. Matrix hydration kinetics need to be taken into account for the other drugs, where the rate of matrix hydration through epidermal water loss in vivo is similar to the rate of drug delivery [13]. Human stratum corneum permeability is usually the rate-limiting factor in transdermal drug delivery. However the Carbosil membrane transport for all the drugs examined is considerably higher than the rate of percutaneous drug absorption [8]. Although Carbosil membranes have higher permeabilities than human skin they can be used to provide an indication of the feasibility of delivering drugs transdermally [8]. The delivery rates can be linked with Guy and Hadgraft's [17–20] equations and appropriate software [21,22] to simulate in vivo blood levels

With this statement of the problem, the drug delivery kinetics from TTS matrices across the membrane can be described by diffusion Eqs. (1) and (2) with the following boundary conditions. For phase I (matrix with dissolved drug):

$$\frac{\partial C_S^I}{\partial t} = \frac{\partial}{\partial x}\left(D_I \frac{\partial C_S^I}{\partial x}\right) \quad (1)$$

where C_s^I and D_I are, respectively, the drug concentration and diffusion coefficient in matrix, t is time and x is diffusion coordinate.

The initial condition of drug distribution in matrix:

$$\text{if} \quad t = 0, \quad C_S^I = C_S^o \quad for \quad -L < x < 0$$

where C_S^o is the initial drug concentration in matrix with its thickness L.

The condition of the impermeable backing film is described:

$$\left(\partial C_S^I/\partial x\right) = 0 \qquad \text{for} \qquad x = -L$$

For phase II (the membrane, initially containing no drug):

$$\frac{\partial C_S^{II}}{\partial t} = \frac{\partial}{\partial x}\left(D_{II} \frac{\partial C_S^{II}}{\partial x}\right) \quad (2)$$

where C_s^{II} and D_{II} are, respectively, the drug concentration and diffusion coefficient in the membrane. The condition of initial drug absence in membrane:

$$\text{at} \quad t = 0, \quad C_S^{II} = 0 \quad \text{for} \quad x = l$$

where l is the membrane thickness. The boundary condition for negligible drug concentration in receptor solution of the diffusion cell:

$$\text{at} \quad t > 0 \quad C_S^{II} = 0 \quad \text{for} \quad x = l$$

At the membrane-matrix interphase boundary if $x = 0$:

$$C_S^{II} = KC_S^{II} \quad (3)$$

where K is the drug partition coefficient between the membrane and the matrix.

In the general case when diffusivity depended on concentration and/or time, D(c,t), it was not possible to obtain simple analytical solutions of Eqs. (1)–(3). Therefore, mathematical simulations using the finite difference method were produced. At fixed geometric sizes of TTS and membrane and at given initial drug concentration in matrix C_S^o, the drug delivery kinetics from TTS across skin-imitating polymeric membrane will be controlled by the parameters of the system D_I, D_{II} and K. Detailed analysis of the contributions of these determinants to the drug delivery kinetics is presented in the following sections of this paper.

4. Results and discussion

4.1. The effect of diffusivity in the membrane on the drug delivery rate from a matrix

Experimental data for the in vitro propranolol delivery kinetics from the TTS across a Carbosil membrane are shown in Fig. 1 together with the simulations based on diffusion coefficients in the membrane D_{II}. The closest correlation between the observed and predicted propranolol delivery profiles was noted for $D_{II} = 1.1 \times 10^{-8}$ cm^{2}s^{-1}, which is significantly lower than the propranolol diffusion coefficient in the membrane, obtained experimentally $D_{II} = (22.0 - 0.5) \times 10^{-8}$ cm^{2}s^{-1} [5,6]. Explanations for the difference are offered below. Lack of correlation between computed and experimental profiles, henceforth, shows that accounting for only one parameter (here it is drug diffusion coefficient in membrane) does not provide a satisfactory model of drug delivery kinetics. Therefore a more comprehensive approach is required.

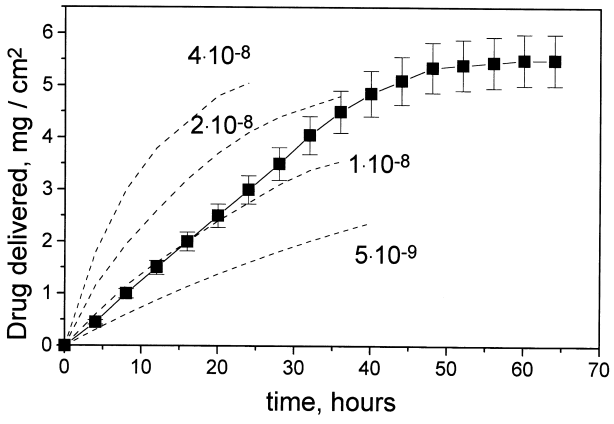

Fig. 1. Kinetics of propranolol delivery (mg·cm^{-2}) across a Carbosil membrane at different values of drug diffusion coefficient in membrane (D_{II}, cm^2·s^{-1}). $D_I = 4 \times 10^{-8}$ cm^{2}s^{-1}; $K = 0.22$; $L = 0.66$ mm; $l = 0.04$ mm. Dashed lines denote computed curves; points, experimental data.

4.2. The effect of drug diffusion coefficient in the matrix on the drug delivery kinetics

The contribution of the drug diffusion coefficient in the hydrophilic matrix to delivery kinetics across the membrane is presented in Fig. 2. Using a value for $D_{II} = 1.1 \times 10^{-8}$ cm^2s^{-1}, Fig. 2 shows that the drug delivery rate depends only slightly on the drug diffusion coefficient in the matrix. Drug delivery from the TTS matrix across the membrane is controlled mainly by the diffusion coefficient in the matrix. Hence, the rate-limiting factor in the drug delivery kinetics is not the drug diffusion in the matrix of considerable thickness, but the rate of drug transfer through the thin membrane.

The reason for the insignificant contribution of drug diffusion within the matrix to drug delivery kinetics lies in the hydrogel matrix structure the resultant high drug diffusivity. With a 4-fold decrease of D_I value in the range from 4×10^{-8}–1×10^{-8} cm^2s^{-1} the matrix contribution to drug delivery kinetics rises markedly, because in this range D_I and D_{II} values become comparable. The most satisfactory correlation between the computed and experimental kinetic profiles at the early stage of drug delivery is achieved if $D_I \cong 4 \times 10^{-8}$ cm^2s^{-1}. Drug diffusivity within adhesive matrices may be related to the tack of polymers and drug diffusion coefficients in diverse set of pressure-sensitive adhesives have been shown to be in the range $D_I = 5 \times 10^{-11}$–1×10^{-8} cm^2s^{-1} [23]. The determined value is therefore on the upper limit.

4.3. The influence of drug partition coefficient between the membrane and the matrix on drug delivery kinetics

Fig. 3 shows the profiles obtained when DI and DII are held constant at 1.1×10^{-7} and 4×10^{-8} cm^2s^{-1}, respectively, and K is varied. A small change in K is seen to have a very significant effect on drug delivery. When transport through a hydrophilic matrix is faster than that through the skin, K will have a significant impact.

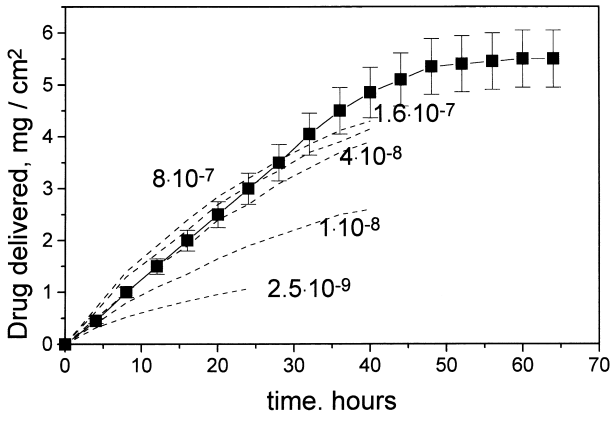

Fig. 2. Kinetics of propranolol delivery ($mg \cdot cm^{-2}$) at different values of drug diffusion coefficient in the matrix (D_I $cm^2 \cdot s^{-1}$). D_{II} in membrane = 1×10^{-8} cm^2s^{-1}, $K = 0.22$ (experimentally obtained value). Dash lines denote computed curves; points, experimental data.

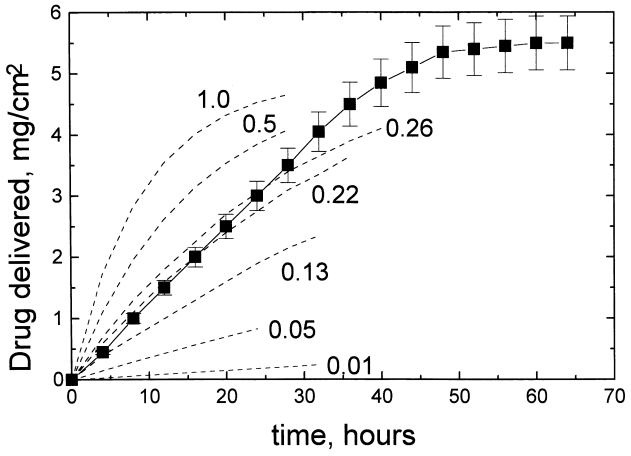

Fig. 3. Propranolol delivery ($mg \cdot cm^{-2}$) profiles at different membrane-matrix drug partition coefficients (K). D in matrix = 1.1×10^{-7}, D in membrane = 1×10^{-8} cm^2s^{-1}. Dashed lines denote computed curves; points, experimental data.

4.4. Drug release from water-soluble matrices and the contribution of penetration barriers to delivery

In these experiments drug transfer through Carbosil and skin has been demonstrated to be the rate-controlling step. A straightforward in vitro study of drug release kinetics from the hydrophilic matrix into an aqueous receptor solution is impossible because this matrix is water-soluble. Mathematical simulations allow us to consider hypothetical conditions when the membrane thickness l tends to 0. This would simulate direct release into an aqueous sink. The effect of the membrane thickness on propranolol delivery kinetics is plotted in Fig. 4. As expected, the best agreement between computed and observed curves occurs for $l = 0.04$ mm

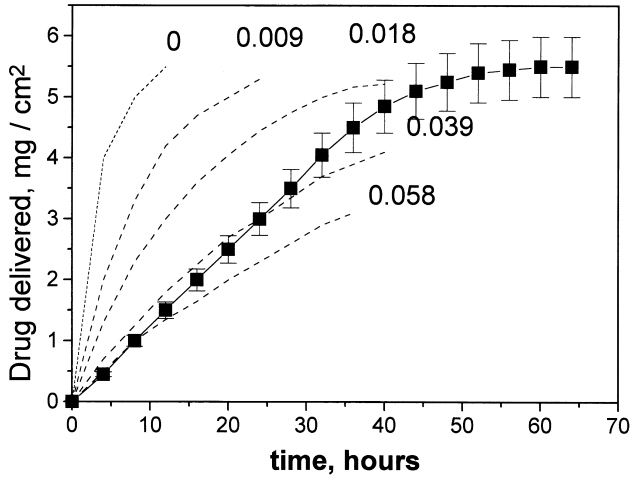

Fig. 4. Kinetics of propranolol delivery (mg cm^{-2}) across a Carbosil membrane at different values of membrane thickness (l, mm). Dashed lines denote computed curves; points, experimental data.

which corresponds to the real membrane thickness. In the special case of ($l = 0$) the observed kinetics represent only drug desorption from matix.

Without the membrane, drug release kinetics from the hydrophilic matrix are described by Eq. (1) with the following boundary condition:

$$\frac{\partial C_S^I}{\partial x} = 0$$

when $x = -L$ and $CS^I = 0$ at $x = 0$, from which it is possible to obtain a traditional analytical solution [25]

$$\frac{C_S^I}{C_S^o} = 1 - \frac{4}{\pi^2}\exp\left(-\pi^2 D_I t/4L^2\right) \quad (4)$$

Drug release kinetics from the hydrophilic TTS matrix are described by a typical exponential curve. During the initial period of drug release, when the TTS matrix may be described as a semi-infinite media and boundary conditions are practically constant in time (at low drug depletion degree), Eq. (5) has a solution similar to the Higuchi equation: drug release increases directly with square root of time [1]. Applying a simple algorithm, offered by Guy and Hadgraft [26], we are able to quantify the fractional contributions of the device (F_d), the membrane (F_m) and the skin (F_s) to drug delivery rate control. From Fig. 4, calculated at $l = 0$, the initial release rate of propranolol is 800 μg $cm^{-2}h^{-1}$. Drug delivery rates from this TTS, measured in vitro across the Carbosil membrane and human skin epidermis, average 99.5 and 26.0 μg $cm^{-2}h^{-1}$, respectively. In vivo delivery of propranolol across human forearm skin averages 22.7 μg $cm^{-2}h^{-1}$ [5,15,27]. Dividing the drug delivery rates by the value of drug release rate yields $F_d = 0.12$ in vitro across the Carbosil membrane, $F_d = 0.03$ both in vitro across human cadaver skin epidermis and in vivo across human forearm skin.

4.5. Effect of hydration on drug delivery kinetics.

The simple models described above, do not describe exactly the experimental profiles. The reason for this discrepancy may be due to the assumption that the parameters D_I, $D_{II} + K$ are constants and do not change with time. Drug transfer across the penetration barrier wholly controls the drug delivery rate from the hydrophilic TTS matrix. It may be possible to design a specific drug delivery system which allows the properties of the barrier to be altered in such a way to compensate the drug for concentration decrease in the matrix. This would be achieved by an increase of the drug diffusion coefficient in the barrier. There is an indication that this may be occurring in the experiments described above with Carbosil as the barrier membrane. Curve fitting of the data suggest that D_{II} is changing with time. The most satisfactory equation to describe the time dependency is

$$D_{II}(t)/D_o - 1 = \kappa t \quad (5)$$

where $D_o = 1.0 \times 10^{-8}$ cm^2s^{-1} and $\kappa = 0.07$ h^{-1} gives the best fit to the experimental kinetic profile in vitro (Fig. 5).

The implication is that there is a modification of membrane structure when the membrane is exposed to the receptor solution and the hydrophilic TTS matrix. Membrane plasticization may occur as a result of two possibilities: water transfer from receptor phase or drug and PEG molecules diffusing into the membrane from the matrix. Water transfer into the membrane from the receptor solution would be followed by membrane hydration with concomitant plasticization. Membrane hydration produces an increase in drug diffusivity [24] and may be the reason of the differences observed between the measured propranolol diffusion coefficient $D_{II} = (22.0 \pm 0.5) \times 10^{-8}$ cm^2s^{-1} and the computed value $D_{II} = 1.1 \times 10^{-8}$ cm^2s^{-1}. The value of D_{II} was measured over a period of time during which there was complete hydration of the membrane. In the computer analysis the conditions would not have allowed total membrane hydration, hence the lower D_{II}.

Similar time-dependent percutaneous penetration enhancement, induced by skin hydration, has been reported [28]. In vivo skin hydration results from occlusive TTS application. This effect may be important and should be considered if the in vivo TTS application period or in vitro test duration is greater than one day.

The steady-state water transfer from the receptor solution across a Carbosil membrane into the hydrophilic matrix averages 0.31 mg $cm^{-2}h^{-1}$, which is comparable to the in vivo rate of matrix hydration which is in the range 0.17–0.22 mg $cm^{-2}h^{-1}$ [7,11]. Water counterflow through a Carbosil membrane into a hydrophilic matrix during a long-term in vitro test is able to produce significant matrix hydration and can affect in vitro drug delivery kinetics. The delivery of propranolol, glyceryl trinitrate and isosorbide dinitrates across Carbosil membranes exceeds 50 μg $cm^{-2}h^{-1}$ [6] and for these TTS the water counterflow has no influence

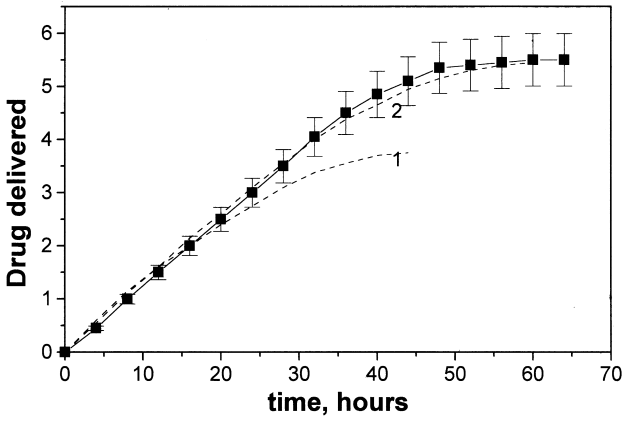

Fig. 5. Kinetics of propranolol delivery (mg cm^{-2}) across a Carbosil membrane. (1) Propranolol diffusion coefficient in membrane is time-independent ($D_{II} = 1.0 \times 10^{-8}$ cm^2s^{-1}. (2) D_{II} is linearly related to time by the equation $D_{II} = D_o + (0.07 \times 10^{-8}) \times t$, where $D_o = 1 \times 10^{-8}$ cm^2s^{-1}. Other constants are the same as in Fig. 2s and 3. Dashed lines, computed curves; points, experimental data.

on the drug delivery kinetics. However, the in vitro delivery rates of cytisine and clonidine are below 50 $\mu g\ cm^{-2}h^{-1}$. For these TTS in vitro water counterflow may be responsible for the change of drug delivery kinetics with time [11].

4.6. The rate-controlling contribution of the hydrophilic matrix to overall barrier-controlled drug delivery

The comparison of the relevant rate-controlling characteristics of the system (on the basis of data from Figs. 1–3) shows that the membrane-dependent parameters (D_{II} in membrane and K) contribute significantly to the amount delivered over the chosen range of variables. However, the contributions of the matrix characteristics (D_I and the drug concentration (CS^I) in matrix) are limited either by the drug solubility in the matrix or by the region in which diffusion in the matrix becomes dominant.

5. Conclusions

Using propranolol as a test drug, various rate-controlling factors were analyzed as physicochemical determinants of the drug delivery kinetics from hydrophilic TTS matrices across Carbosil membranes. The overall in vitro drug delivery kinetics from the hydrophilic matrix across skin and Carbosil membrane are barrier-controlled. When hydrophilic matrices are used it is difficult to design a 'dissolution' type test to describe the intrinsic release characteristics of the delivery system. The approach described in this paper describes how rate controlling membranes can be used. From experimental data diffusion parameters can be deconvolved to show the relative significance of K and D. Mathematical simulations can then be performed to show release characteristics as the barrier membrane thickness tends to zero. This is of use in quality assurance testing of this type of patch.

It is possible for water to permeate into and through the barrier membrane. The presence of water in the membrane, be it Carbosil or skin, can modify the barrier properties. This can be described by a time dependent diffusion coefficient and modelled appropriately.

If sufficient water can 'flow' through the membrane to alter the hydration state of the hydrophilic matrix, diffusional parameters in the delivery system may also be affected and should be taken into consideration. This may be a particular problem for occlusive patches applied to the skin over extended periods of time.

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