

Diffusion of urea through membranes

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1. Introduction

Non-invasive real time monitoring of topical drug delivery is an important subject of dermatopharmaceutical research. It has been proved that Fourier transform infrared attenuated total reflection (FTIR-ATR) is a versatile technique to study drug diffusion through artificial membranes and biological systems [1]. Urea is widely used as moisturizer or ceratolyticum in pharmaceuticals, therefore, its diffusion behaviour in biological membranes is of great interest.

2. Materials

Urea was purchased from Merck (Darmstadt, Germany). Distilled water was used as acceptor. An aqueous urea solution 10% (w/w) was applied as donor. Two native membranes were utilized, namely human stratum corneum (thickness 24-36 μm) and a horny platelet (thickness 110-140 μm) cut from a bovine hoof. These membranes have been chosen because they have totally different physico-chemical properties. The bovine hoof membrane is a hydrophilic gel membrane [2], whereas stratum corneum is a lipophilic one [3].

3. Experimental

The diffusion experiments were carried out on a FTIR Spectrometer IFS 28 (Bruker Optics, Ettlingen, Germany) equipped with a HATR attachment (Thermo Spectra-Tech, Shelton, CT,

USA). The sampling compartment is a Fresnel ATR accessory consisting of a ZnSe crystal with an angle of incidence of 45° in horizontal orientation. The diameter of the top of the crystal is 20 mm. Fig. 1 shows schematically the specially designed diffusion cell that fits into this accessory, thereby, the acceptor solution is on the top of the ATR crystal [4]. Each spectrum was recorded at room temperature with 32 scans and a resolution of 2 cm⁻¹.

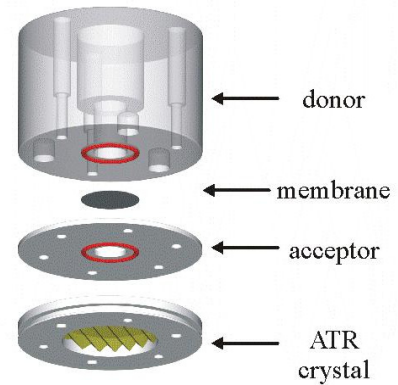


Fig. 1: FTIR-ATR diffusion cell

4. Mathematical model

Based on Fick's second law an appropriate mathematical model was developed for estimating the diffusion coefficients of the drug in the membranes. Using the symmetry of arrangement and the fact that the diffusion of the drug in the acceptor is much faster than the diffusion within the membrane, one obtains a linear one-dimensional equation with dynamic boundary conditions at the membrane-acceptor contact [4], [5].

Fick's second law:

$$\frac{\partial u}{\partial t} = D \frac{\partial^2 u}{\partial x^2} \quad 0 \leq x \leq L, t \geq 0$$

Dynamic boundary conditions:

$$u(t, x = 0) = u_D = \text{const.} \quad \text{and} \quad u(t, x = L) = v(t)$$

Initial conditions:

$$u(t = 0, x) \quad \text{and} \quad v(t = 0) = 0$$

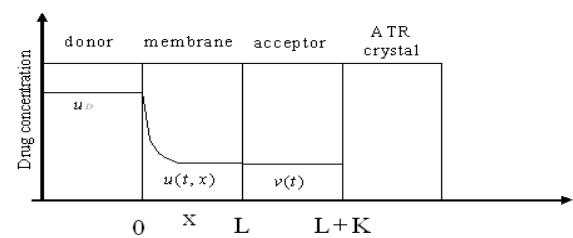


Fig. 2: Scene of the drug distribution where
 $u(t, x)$ - drug concentration in the membrane
 u_D - drug concentration in the donor
 $v(t)$ - drug concentration in the acceptor
 L - thickness of the membrane
 K - height of the acceptor compartment

Solutions:

$$u(t, x) = u_D \left[1 - \sum_{n=0}^{\infty} c_n e^{-\frac{\lambda_n^2 D t}{L^2}} \sin \lambda_n \frac{x}{L} \right]$$

with eigenvalues $n\pi \leq \lambda_n \leq \left(n + \frac{1}{2}\pi\right)$ defined by $\lambda_n \frac{K}{L} \sin \lambda_n - \cos \lambda_n = 0$ and

$$c_n = \frac{2}{\lambda_n \left(1 + \frac{K}{L} \sin^2 \lambda_n\right)}$$

5. Results

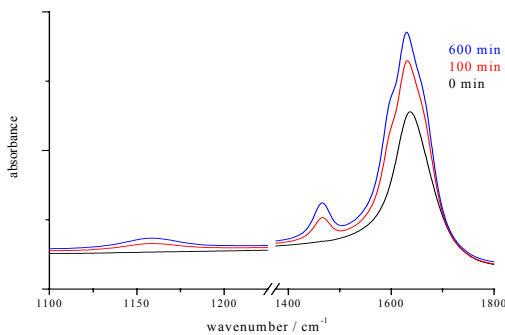


Fig. 3: FTIR-ATR spectra of the uptake of urea in the acceptor during the diffusion of urea through a bovine hoof membrane

Fig. 3 shows the FTIR-ATR spectra in the spectral range 1100-1800 cm^{-1} acquired at various times of the penetration process of urea through a bovine hoof membrane. It is obvious that several changes in the spectral features appear. The uptake of urea in the acceptor was quantified based on the

multivariate analysis Quant2 OPUS software in the spectral range from 1269 to 1581 cm^{-1} . For that purpose a calibration set of aqueous urea solutions in the concentration range from 0 to 10 wt% was used. The characteristic parameters of this procedure were the root mean square error of cross validation (RMSECV) of 0.0324 and the correlation coefficient (R^2) of 99.9.

The urea concentrations [% (w/w)] in the acceptor versus time for systems with different membranes are represented in Fig. 4.

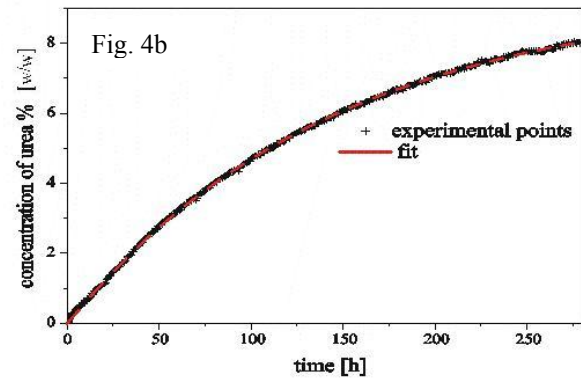
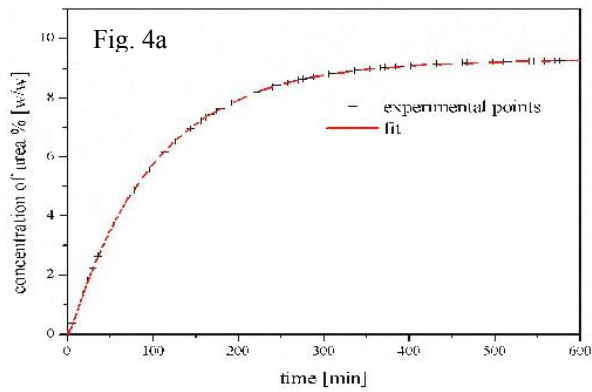


Fig. 4: Urea concentration in % [w/w] in the acceptor versus time for different systems of aqueous urea solution/membrane/water, which were determined by multivariate analysis; a: Bovine hoof membrane, b: human stratum corneum

From these data the diffusion coefficients of urea were determined using the mathematical model:

For bovine hoof membrane: $D = (3.12 \pm 0.30) 10^{-7} \text{ cm}^2\text{s}^{-1}$

For human stratum corneum: $D = (2.85 \pm 2.45) 10^{-10} \text{ cm}^2\text{s}^{-1}$

As expected the diffusion coefficient of the hydrophilic molecule urea is by a factor of 1000 larger in the hydrophilic membrane than in the lipophilic membrane.

5. Conclusion

The FTIR-ATR diffusion cell combines the advantages of the traditional Franz diffusion cell and the FTIR-ATR technique.

The advantages of this set-up are as follow:

- a) the acceptor and donor are well defined
- b) the membrane is not in contact with the ATR crystal
- c) physiological conditions can be simulated.

The FTIR ATR diffusion cell can be used to compare different pharmaceutical formulations in order to optimise them.

References

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