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EXPERIMENTAL AND THEORETICAL STUDIES ON THE DIFFUSION OF DRUGS IN POLYMER FILMS

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ABSTRACT

An interferometric technique was developed and used to determine the diffusion coefficient and the physico-chemical state of different drugs in a polyacrylate-copolymer as a carrier system. By applying Ficks' second law the release rate of the drug was calculated and compared to in vitro/ in vivo data. From the relativly good agreement of the prediction with the experimental results it can be concluded that the pure mobility of the drug in the polymer is the rate determining factor for the mass flux. The physical concept used in the Higuchi equation seems to be not applicable for the examined system with monodispersed drugs.

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INTRODUCTION

Using drugs incorporated in polymer systems as a transdermal delivery system for the controlled release, one has to get a closer insight into the diffusion-process in order to control and to design the polymer device in a proper way. One important factor is to know the distribution of the drug in the polymer matrix after the fabrication and the change of the concentration profile during the in vitro/ in vivo release of the drug. It is the purpose of this paper to show that by an interferometric method the amount of drug as a function of the distance in the polymer can be measured. By comparing these experimental data with the flux of the drug calculated by Ficks second law, the mechanism of the drug release can be described in proper terms.

MATERIAL AND METHODS

A. Drug-Polymer System

The drugs used in this investigation were scopolamine, haloperidol and brotizolam, a polyacrylate-copolymer (Supplier: Röhm/ Darmstadt) served as the polymer matrix. Boths components were dissolved in an organic solvent (e. g. acetone) and the highly viscous solution cast on an aluminium foil. After the drying process, a homogenous, colourless film resulted, with a constant thickness of about 150 µm. The percentage of the incorporated drug was varied in the range from 5 to 20% (w/w) depending on the type of drug, The in vitro release was determined by stick-

ing the aluminium containing side of a 3 cm^2 film on the bottom of a glasstube, the container was filled with 10 ml water or 0.1nHCl (T = 31°C) and the flux of the drug measured by the extinction at the appropriate wavelength as a function of time. For the measurements in the interferometer the polymer film was cut with a microtom into slices of 40 µm thickness rectangular to the plane of diffusion and placed in between the mirror-plates.

B. Interferometer

The interferometer we used for our experiments was a modified Fabry-Perot-Interferometer and was constructed by Prof. Fuhrmann/ University Kaiserslautern/ Germany. The principal set-upof the instrument is shown in fig. 1 Monochromatic light (λ = 0.63 µm) from a He-Ne-laser is focused and converted into parallel light and passes then through two silver coated glass-plates containing the polymer sample. The resulting picture of interference lines passes into a microscope, where it can be observed and photographed. A more detailed description of the conditions where the interference takes place is given in fig. 2. The sample is clamped within the two glass-plates, which enclose a very small angle ($\varepsilon \sim 7 \cdot 10^{-5}$°). A portion of the incident lightbeam passes directly through the sample, a further portion is splitted and reflected at the inner walls of the silver coated glass-plates. The two resulting beams interfere, a maximum of intensity is obtained if eq. 1 is fulfilled.

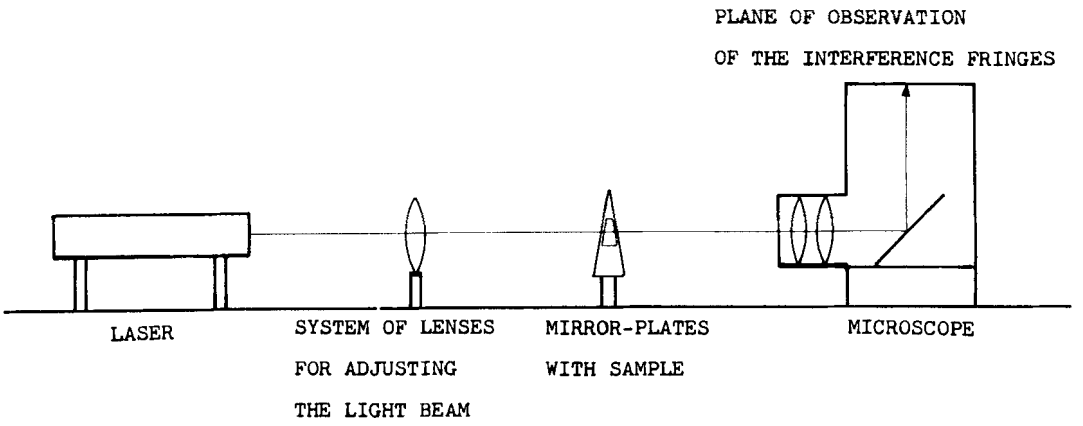


FIGURE 1

Principal set-up of the interferometer

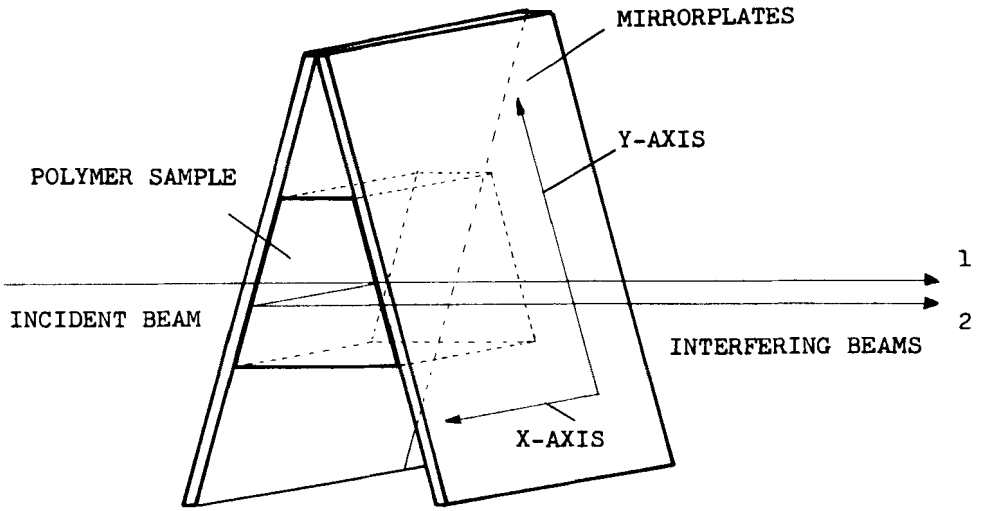


FIGURE 2

General illustration of the experimental conditions and the generation of the interference fringes

(eq. 1) $n \cdot a = K \cdot \lambda / 2$

n: refractive index of the medium between the glass-plates

a: thickness of the sample

λ: wavelength of the used light

K: integral number

The material to be examined has to be optically homogenous, in order to obtain proper interference fringes. From the interference picture, an example is given in fig. 3a, the refractive index n as a function of distance x in the polymer film can be determined. Based on the sound assumption that the refractive index n (x) in the drug loaded polymer film depends linearily on the concentration C (x) of the drug:

(eq. 2) $n(x) = a + b \cdot C(x)$

a and b: constants depending on the polymer/drug system

The curvature of the Kth interference line, as described by eq. 1, reflects the profile of the drug distribution in the polymer. An exact calculation, which is not discussed here in further detail, leads to the following simple expression:

(eq. 3) $$C(x) = C_{max.} \cdot \frac{\Delta Y(x)}{\Delta Yo}$$

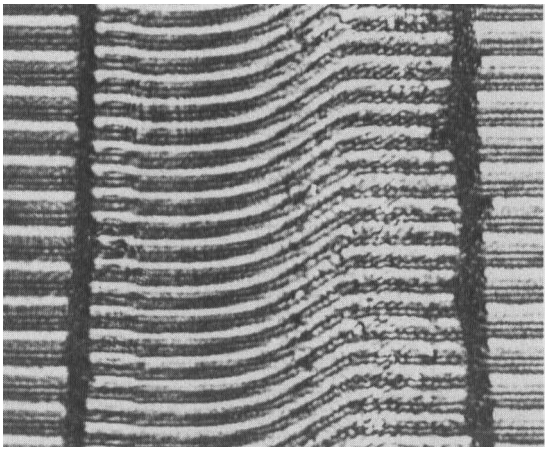


FIGURE 3a

Interference fringes obtained from a polymer-sample with a drug concentration profile

The used symbols are explained in fig. 3b. The concentration profile, knowing C_{max} the maximum drug concentration at the outer end of the film, is obtained in the proper unit by a simple measurement of length.

MATHEMATICAL MODELS AND EQUATIONS

For describing the diffusion process of the drug in terms of the concentration profile C (x,t) within the film, Ficks' second law has to be used:

(eq. 4) $$\frac{dC}{dt} = D\frac{d^2C}{dx^2}$$ (one dimensional case)

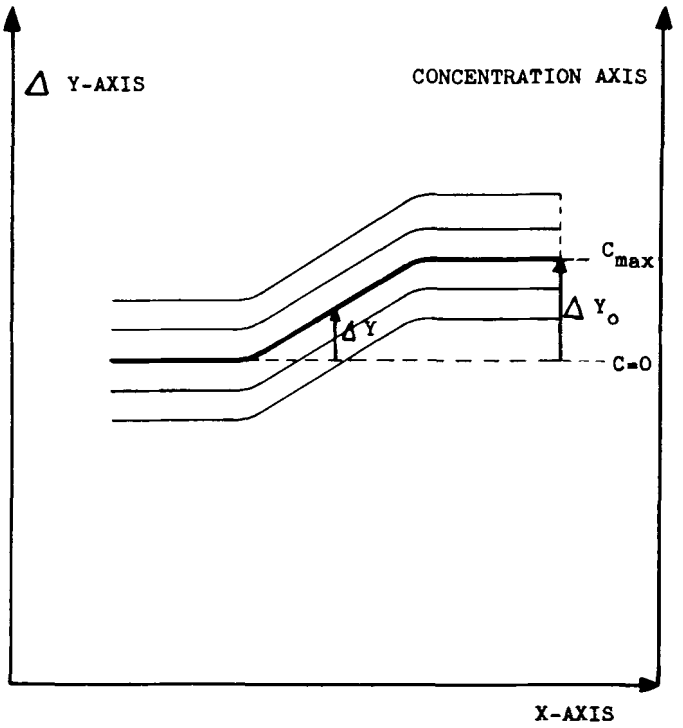


FIGURE 3b

Schematic drawing of fig. 3a with the explanation of the symbols used in the equations

C: concentration at the ordinate x and time t

D: diffusion-coefficient in cm^2/ day

The general solution of this differential eq. has the following from (1):

(eq. 5) $$C(x,t) = \sum_{n=1}^{\infty} b_n \cdot e^{-\left(\frac{n \cdot \pi}{L}\right)^2 \cdot D \cdot t} \sin\left(\frac{n \cdot \pi \cdot x}{L}\right)$$

L/2: length of the film in cm

b_n: Fourier coefficients

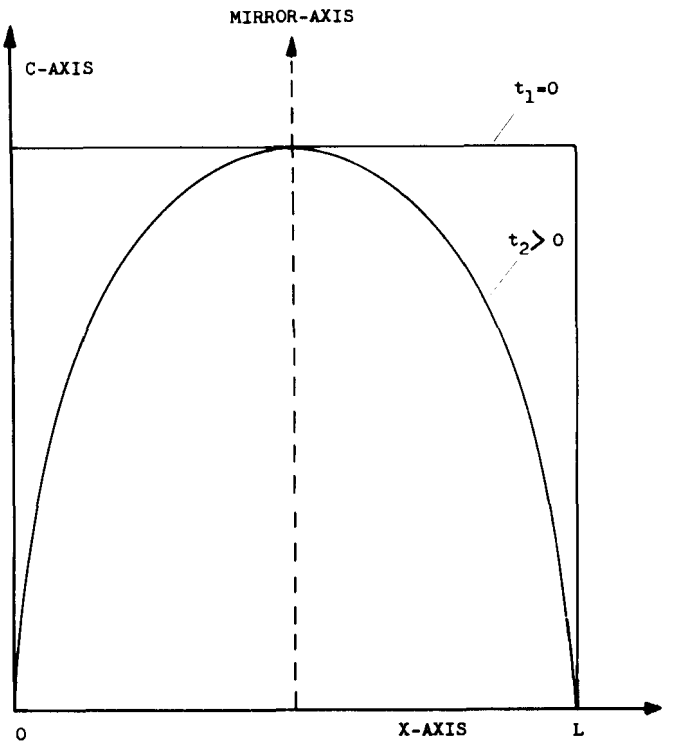


FIGURE 4

Schematic illustration of the concentration profile in a polymer film at two different times

Pure polyacrylate	Polyacrylate + 10% brotizolam t = 0 days	Polyacrylate + 10% brotizolam t = 2 days

The geometrical conditions are described in fig. 4, it should be pointed out that for mathematical purposes a symmetrical set-up is chosen. Because the diffusion process itself is symmetric the wanted concentration profile at different times can be evaluated by a simple shift in the x ordi-

nate. In order to apply eq. 5 the boundary conditions in the experiments have to be defined. For our purposes two situations are discussed: in the first case the concentration at the outer end of the film is always kept at zero. This experimental condition might prevail during the in vitro/ in vivo drug release. In mathematical terms

(eq. 6) $C(0,t) = 0$ and $C(L,t) = 0$

With this boundary condition the Fourier coefficient b_n in eq. 5 can be determined and one obtains the following expression.

(eq. 7) $$C(x,t)=2\cdot C_o \sum_{n=1}^{\infty}\left(\frac{1-\cos n\cdot\pi}{n\cdot\pi}\right)e^{-\left(\frac{n\cdot\pi}{L}\right)^2 D\cdot t}\cdot\sin\left(\frac{n\cdot\pi\cdot x}{L}\right)$$

C_o = initial concentration of the drug in the film with uniform distribution

In order to transform the concentration profile C (x,t) into the measurable quantity amount of drug released, eq.7 has to be integrated over the film length and this leads to the mass M (t) remaining in the polymer at time t

(eq. 8) $$M(t) = 8\cdot F\cdot C_o \sum_{n=1}^{\infty}\frac{L}{n^2\cdot\pi^2}\, e^{-\left(\frac{n\cdot\pi}{L}\right)^2\cdot D\cdot t}$$

n = odd numbers

F = area of the film through which the drug diffuses

In the second case the situation is treated where a drug containing film of length l_1 is placed together with an empty polymer film of length l_2. The boundary conditions are described in the following way.

(eq. 9) $C\ (0<x<l_2,0) = 0, \quad C\ (l_2<x<l_2+l_1,0) = C_o$

$$C\ (x,\infty) = C_o \cdot l_1 / (l_1 + l_2)$$

With the help of this expression eq. 5 can be solved, one obtains for the b_n-values

(eq. 10) $$b_n = \frac{2 \cdot C_o}{n \cdot \pi} (\cos n \cdot \pi \cdot K_1 - \cos n \cdot \pi \cdot K_2 + K_o - K_1) + C_o \cdot K_o$$

$$K_o = l_1 / (l_1 + l_2)$$

$$K_1 = l_2 / 2\ (l_1 + l_2)$$

$$K_2 = 2 \cdot l_1 + l_2 / 2\ (l_1 + l_2)$$

For completing the considerations the Higuchi eq. is cited. The reasoning for the deduction is given in the literature (2)

(eq. 11) $$Q\ (t) = \sqrt{D \cdot t \cdot (2A - C_s) \cdot C_s}$$

$Q\ (t)$ = amount of drug released after time t per cm^2

A = amount of drug in the polymer film per cm^3

C_s = solubility of the drug in the polymer per cm^3

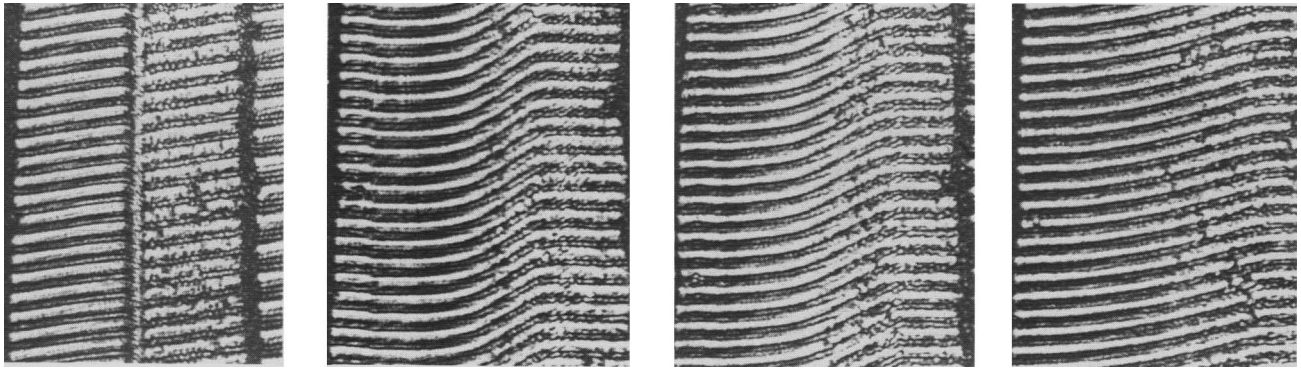
RESULTS AND DISCUSSION

As stated before, the polymer films have to be optically homogenous in order to get proper interference fringes. Vice versa the interferometric method allows to differ between a monodispersed and a partially agglomerated distribution of the incorporated drug in the polymer phase. As soon as the drug starts to build up spots of cristallized structure, the interference picture begins to disappear. An impression of the qualitative correlation between the different states is given in fig. 5. In fig. 5a the unloaded polyacrylate film (thickness ~150 μm) is shown, the same polymer material is than loaded with 10% (w/w) of brotizolam (fig. 5b). At the beginning the drug is homogenously distributed, the interference picture is properly formed, after two days the drug starts to cristallize from the right to the left (fig. 5c). This process and the physico-chemical state of the drug cannot be judged by a simple visual inspection. Because the crystallization causes an inhomogenous and random distribution of the drug in the polymer phase, this process will alter the release rate of the drug. The measurement of the interference pattern during the storage is therefore an important tool to control the distribution and to assure a constant release rate. It should be noted that a further prerequisite for the successful use of the method is a finite difference in the refractive index of the polymer and the drug, which is normally fulfilled.

FIGURE 5

Comparison of the interference fringes between the pure polymer and a drug loaded film in the monodispersed and partially cristallized state

If the polyacrylate film is applied on the skin or exposed to a water phase, the uptake of water in the polymer is about 15% (w/w) and nearly isochore ($\Delta V \sim 0$). The saturation with water is completed for a film of 150 µm thickness after two hours of exposure. For the diffusion of the drug in the polymer film the question arises whether the absorbed water is needed to start the diffusion process. In order to study this question a drug containing film was brought into contact with an empty polyacrylate film. A situation where the diffusion process is mathematically described by eq.10 and eq. 5 with a rectangular concentration profile at the beginning expressed by eq. 9. These bi-layered samples stored in between the glass plates at 31°C were interferometrically examined at certain time intervals. The change of the interference pattern as a function of the storage



Storage time 0 5 days 8 days 18 days

FIGURE 6

Interference pattern of a scopolamine containing film (20% w/w) as a function of time

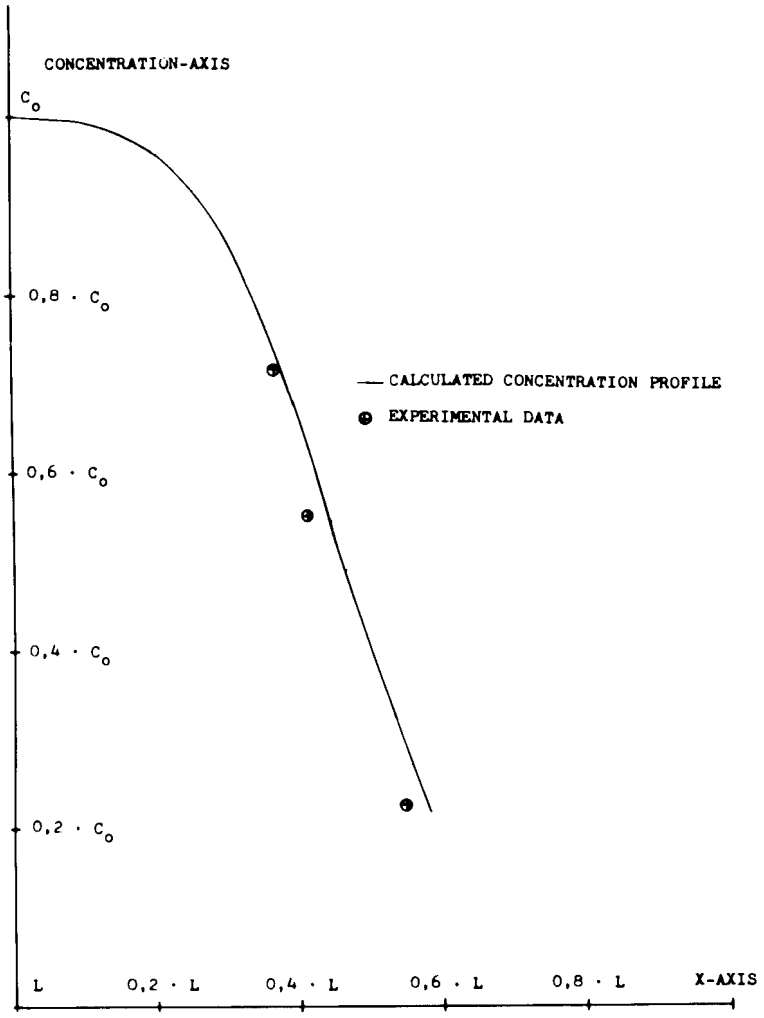


FIGURE 7

Calculated concentration profile for the in vitro diffusion of scopolamine,
D-value = $2.1 \cdot 10^{-6} cm^2/day$
film length L = $3.85 \cdot 10^{-2} \mu m$

time is shown in fig. 6. A clear cut is observed between the two films in contact at the beginning. Then the drug starts to diffuse into the empty film, resulting in a continous concentration profile which leads to the observed interference lines, every line fulfilling the condition $n \cdot a = \text{const.}$ (s. also eq. 1).

For evaluating the diffusion coefficient D from the interference lines, in the first step, the C (x,t) values were calculated with the aid of eq. 3. By using then the sum of the squared differences QS_u between the experimental and the calculated values

(eq.12) $$QS_u = \sum (C_{exp.} - C_{calc.})^2$$

as a criterium for a good fit, D in eq. 5 is changed by small increments until QS_u is minimized. The calculations were performed with a computer. The resulting profile for scopolamine (20% w/w) in polyacrylate after 8 days with a D-value of $2{,}1 \cdot 10^{-6}$ cm^2/ day and some experimental datapoints is shown in fig. 7. In the same way the D-values

Table 1

examined drug	molecular weight	C in % (w/w)	D-values ($T = 31^{\circ}C$) cm^2/ day	solubility in g/100 ml
scopolamine	303	20,0	$2{,}1 \cdot 10^{-6}$	10
haloperidol	376	5,0	$5{,}3 \cdot 10^{-7}$	$1{,}4 \cdot 10^{-3}$
brotizolam	370	7,0	$1{,}4 \cdot 10^{-6}$	$\sim 1 \cdot 10^{-3}$

were evaluated for the other two drugs, the data are shown in tab. 1.

Though the drugs differ very much with respect to their solubility in water, the diffusion coefficient of the molecules is of the same order of magnitude and seems to be nearly independent of this physico-chemical parameter.

Knowing the D-values, eq. 8 can be used to calculate the amount of drug released under sink-conditions from the polyacrylate film. The calculated and the experimental curves for the release of the drugs scopolamine and haloperidol under in vitro conditions using water and 0.1nHCl as a receptor medium (T = 31°C) are plotted in fig. 8 and 9, in the form: percentage of drug released as a function of time in days. In both cases the calculated curve leads to lower values than the experimentally observed under the chosen in vitro set-up. Nevertheless the magnitude of time is comparable with the values from the in vitro experiments.

In order to correlate the in vitro respectively the calculated release data with in vivo results, a scopolamine containing film (20% w/w) was worn 8 days on the upper arm and then interferometrically measured as described above. The observed concentration gradient under in vivo conditions is shown in fig. 10 and the obtained concentration values at certain distances from the surface are shown with the calculated distribution curve C (x, 8 days), applying eq. 7 in the fig. 11.

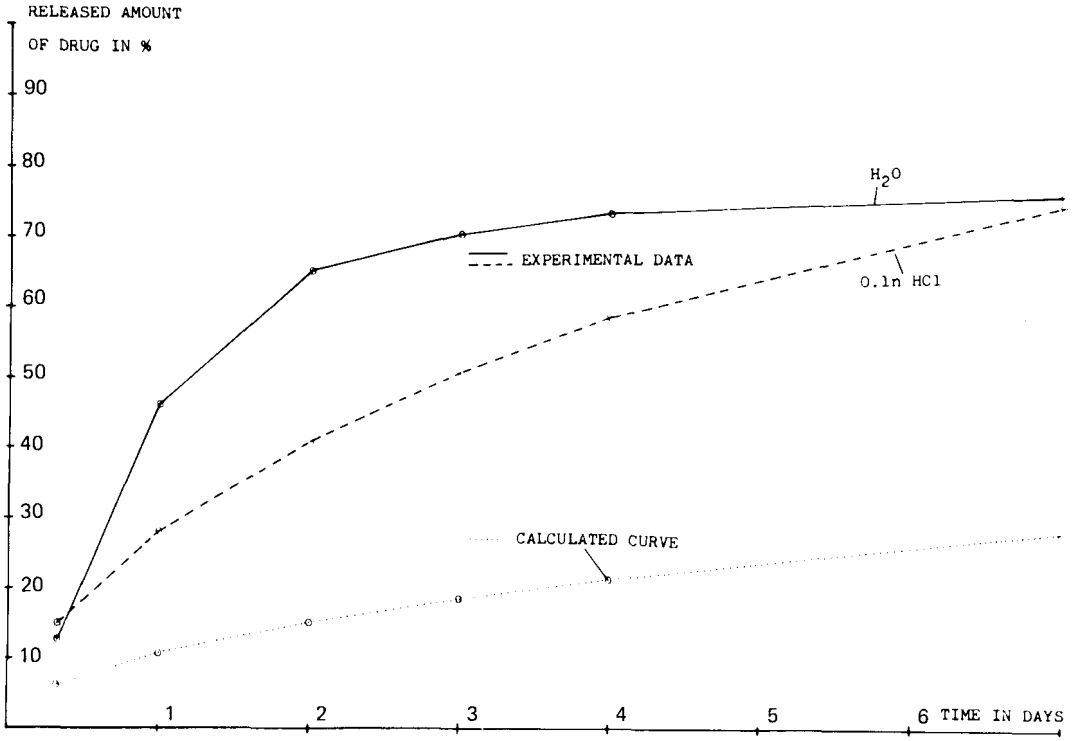


FIGURE 8

In vitro release rates of scopolamine in water and 0.1nHCl as a function of time, calculated release curve according to eq. 5, film length $L = 1.54 \cdot 10^{-2} \mu m$

The experimental data and the theoretical considerations so far obtained lead to several conclusions. The flux of the drug scopolamine in this polymer system is the rate determining step. If the mass-flux into the skin would be smaller there would not be any concentration gradient, only a decrease with a homogenous distribution at any time. The chosen in vitro-conditions consisting in the direct contact of water with the polymer film result in a release rate which seems to be higher than the in vivo release by a

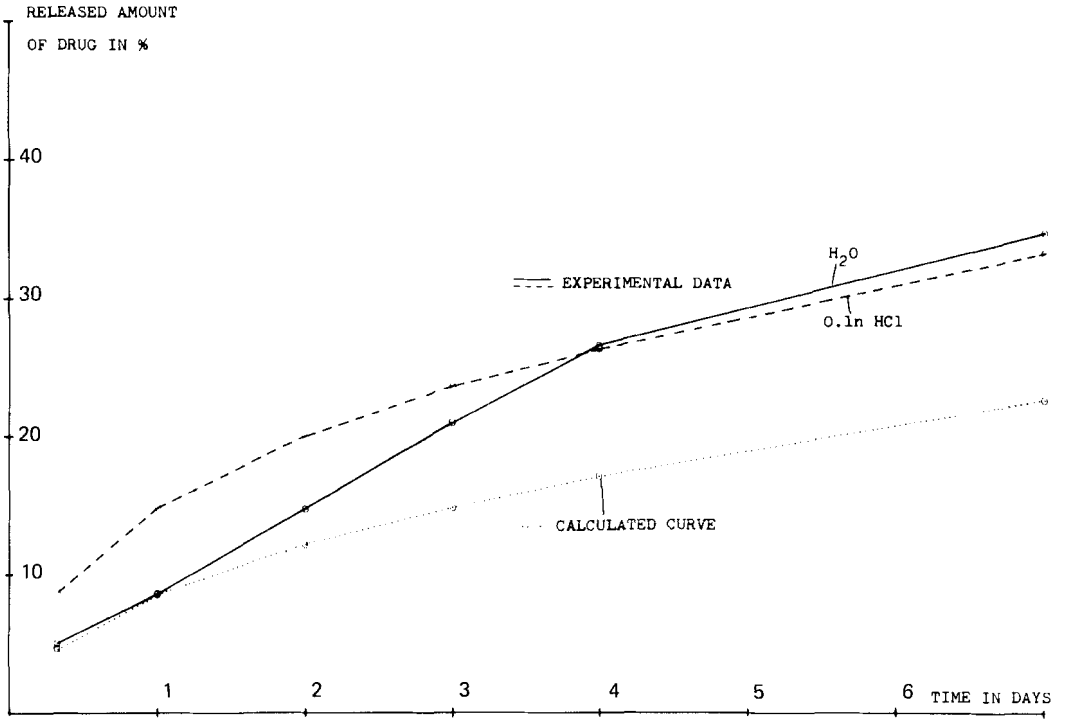


FIGURE 9

In vitro release rate of haloperidol in water and 0.1nHCl as a function of time, calculated release curve according to eq. 5, film length $L = 9.6 \cdot 10^{-3}\mu m$

factor of about 3 (s. fig. 8). The presence of water for polyacrylate as a drug reservoir does not seem to have a crucial effect on the flux-rate nor to be the fundamental requirement for the diffusion itself. For interpreting the diffusion of the drug out and in a polymer system in terms of the Higuchi-equation, the dissolution of the solid drug is the first step in the sequence of diffusion and only the dissolved drug is transported in water as the transport medium. Besides the above mentioned finding, the fact that

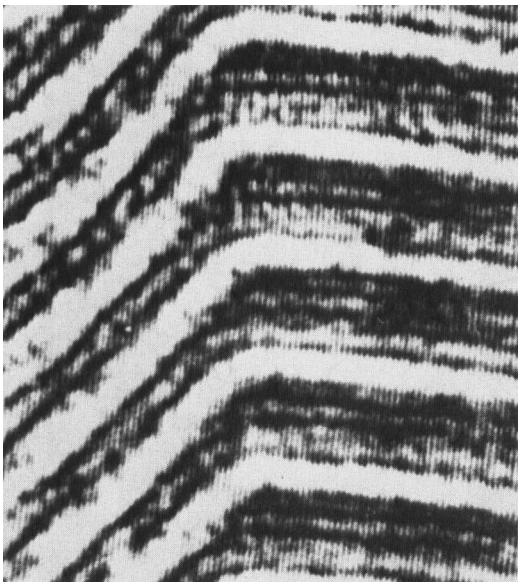


FIGURE 10
Interference pattern from a scopolamine containing film (20% w/w) worn 8 days on the upper arm

the release rate for the two drugs in the in vitro experiment is uneffected by using 0.1nHCl as a receptor medium indicates that this concept is not applicable. For the drug haloperidol the solubility C_s increases in the 0.1nHCl by a factor of 215 compared to neutral water. By applying eq. 11 the curve for the release rate pattern should be altered by a factor of 15, but no change is observed in the in vitro experiment. It can be concluded from this investigation that also for drugs with a low solubility in water and a high loading dose ($A>>C_s$, s.eq.

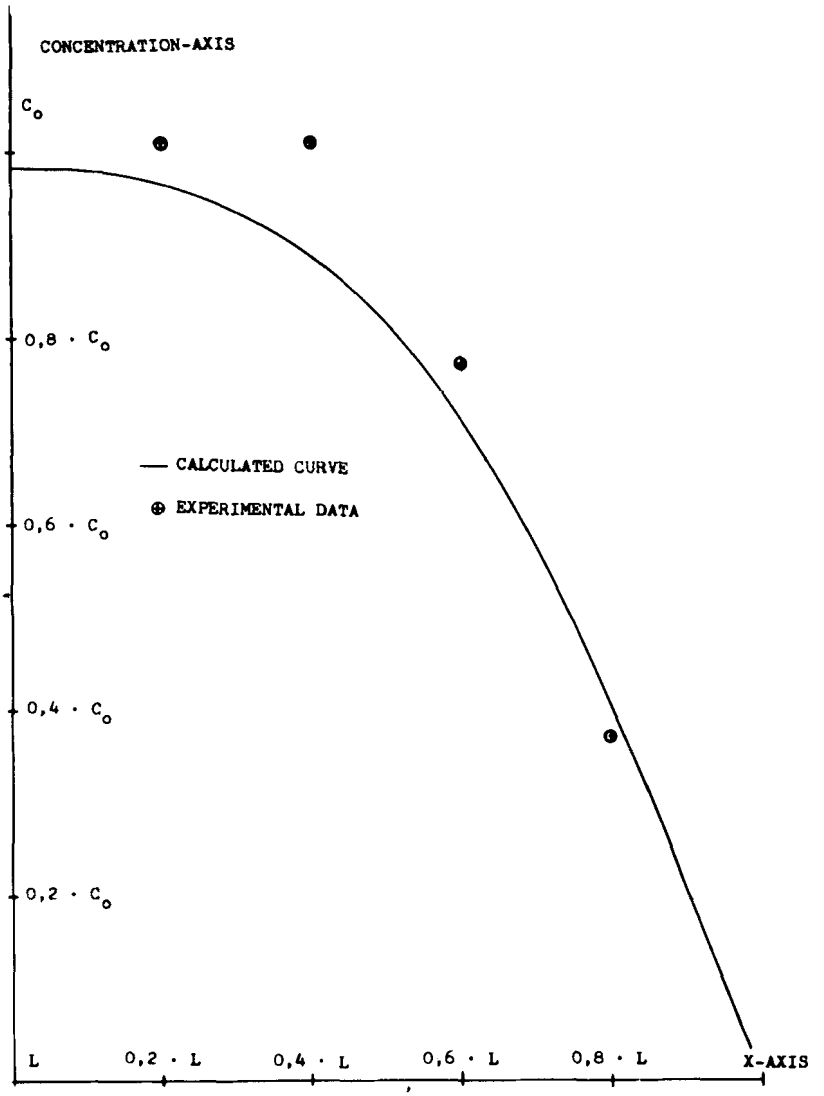


FIGURE 11
Comparison of the calculated concentration profile and the experimental data obtained from fig. 10

11) the flux of the drug in in vitro/ in vivo experiments can be described by Ficks' second law, with a D-value determined in the pure polymer phase by interferometric measurements. In order to change the mass flux of the drug the D-value has to be changed into a different order of magnitude. This can only be done by altering the polymer system by either modifying the chemical structure of the used macromolecules or by altering the physical properties of the polymer device.

References

1. H.G. Zachmann, Mathematik für Chemiker, Verlag Chemie GmbH, 1972
2. T. Higuchi, J. Pharm. Sci., 10, 874, 1961