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Investigation of drug release from suspension using FTIR-ATR technique: part II. Determination of dissolution coefficient of drugs

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Abstract

Fourier transform infrared attenuated total reflectance (FTIR-ATR) spectroscopy was applied to a release experiment in order to determine the dissolution coefficient of drug particles in heterogeneous semisolid formulations. The drug release experiment was carried out using ketoconazole suspended in Vaseline with various amounts of paraffinum liquidum as donor and an artificial dodecanol-collodion (DDC) membrane as acceptor compartment. Monitoring changes in IR bands due to ketoconazole the decrease of the drug content near the ATR crystal — ointment was followed as a function of time. A mathematical model based on Fick's second law with a source term was used to derive the apparent dissolution coefficient K_{dis} by numerical fitting the experimental data. It was found that K_{dis} is dependent on the fraction of paraffinum liquidum in the suspension. Taking into account all experimental parameters required, the transport process was simulated and discussed in terms of drug concentration — time and drug concentration — distance profiles. Calculating the area under the mass — time curve it was tried to predict the 'dermal bioavailability' in the acceptor (AUC_a). © 2000 Published by Elsevier Science B.V.

Keywords: Fourier transform infrared spectroscopy; Attenuated total reflectance; Drug release from suspension; Dissolution coefficient; Dermal bioavailability

1. Introduction

Fourier transform infrared (FTIR) spectroscopy with the attenuated total reflectance (ATR) is now a well-established technique in diffusion studies. Previously, we have reported that this method is also useful for investigating properties of drug release processes (Hanh et al., 2000). In part I of this communication, it was shown that it is possible to determine the effective diffusion coefficient of drugs in heterogeneous ointment base using FTIR-ATR.

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In the present paper we report the application of this spectroscopic technique to derive the dissolution coefficient of drugs in semisolid formulation. The drug release experiment was carried out using ketoconazole suspended in vaseline with various amounts of paraffinum liquidum as donor and an artificial dodecanol-collodion (DDC) membrane as acceptor. Furthermore, the drug transport within the system studied is simulated in terms of drug concentration — distance and drug concentration-time profiles. Finally, the 'dermal bioavailability' in the membrane can be predicted from the area under the mass — time curve (AUC_a).

2. Materials and methods

2.1. Materials

The substances collodion solution, dodecanol, ketoconazole, and paraffinum liquidum were the same as in part I. Vaseline was purchased from Woelm Pharma GmbH (Eschwege, Germany).

The initial radius r_0 of the ketoconazole particles was assumed as an average value $r_0 = (0.27 \pm 0.06)$ μm estimated by polarization microscopy (Optiphot-2, Nikon, Japan). The preparation of the 4% (w/w) DDC membrane has been described elsewhere (Neubert et al., 1991). The ointments were prepared as 2% (w/w) suspension in vaseline. The formulation with a mass corresponding to 2 mg/cm^2 was applied in the experiments.

2.2. FTIR-ATR spectroscopy

As in Part I., the IR spectra were acquired by using the Bruker spectrometer IFS 28 (Karlsruhe, Germany) equipped with a Spectra-Tech Single-Bounce HATR attachment (Shelton, CT). The suspension was carefully spread on the ATR crystal and then the DDC membrane was placed on top of the ointment. Prior to start the release experiment a handling time of 5 min was required. The same procedure as described in part I was applied for recording and evaluating the spectra.

3. Results

The difference FTIR-ATR spectra $Sp(t) - Sp(t = 900\ \text{min})$ in the spectral range 700–1700 cm^{-1} for the vaseline/ketoconazole/membrane system at various times t of the release experiment are represented Fig. 1. It is obvious that the intensity of characteristic IR bands of ketoconazol decreases in the course of the release. For quantifying the decrease of the drug concentration we have applied the multivariate analysis 'Quant 2' of the OPUS software package. The ATR spectra of the ointment with various amounts of ketoconazole (0, 2, 5, and 10% w/w) were used for the purpose of calibration. Thus, the decrease of the drug content near the interface ATR crystal — ointment with various amounts of paraffinum liquidum m_{pl} was determined as a function of time (see Fig. 2).

4. Mathematical model for the drug release experiment

In order to deduce the dissolution coefficient of the drug from the experimental data, it is necessary to assume an appropriate model (see Fig. 3). The transport of drug from the ointment (donor) to the membrane (acceptor) occurs sequentially, i.e.: (i) the solid drug particles dissolve in the liquid phase of the ointment; (ii) the dissolved drug molecules diffuse in the ointment; (iii) the drug crosses the interface between the donor and the acceptor, and finally (iv) the drug diffuses in the acceptor. In the case of our experiment, the ointment is a heterogeneous system consisting of vaseline, paraffinum liquidum and solid drug particles as source of the dissolved drug. Therefore, we have to consider the diffusion in a heterogeneous medium (Crank, 1975) with an internal source (Ayres et al., 1977). Accordingly, the concentration of dissolved drug, $c(x, t)$, is governed by the equations

$$\frac{\partial c}{\partial t} = D_{\text{eff}} \frac{\partial^2 c}{\partial x^2} + R \quad \text{for } 0 < x < x_b \tag{1}$$

$$\frac{\partial c}{\partial t} = D_a \frac{\partial^2 c}{\partial x^2} \quad \text{for } x_b < x < x_l \tag{2}$$

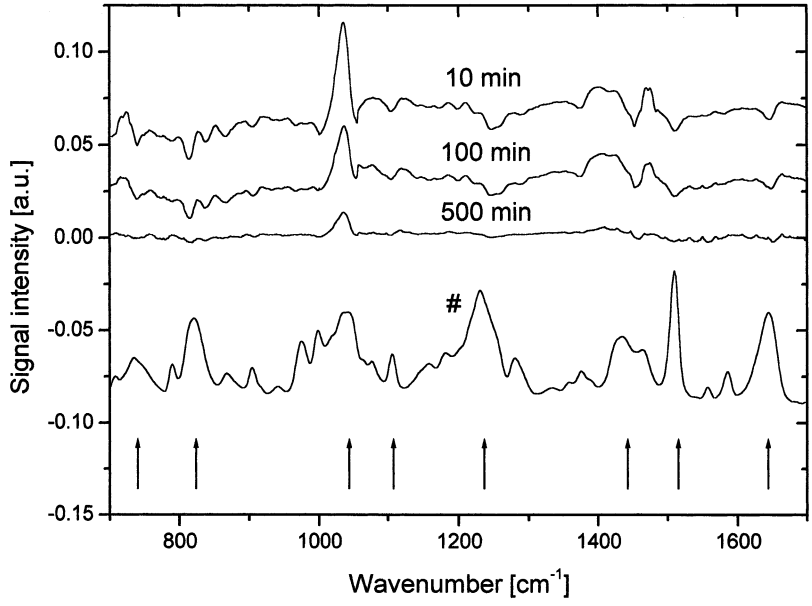

Fig. 1. Difference FTIR-ATR spectra Sp(*t*)–Sp($t = 900$ min) in the spectral range 700–1700 cm^{-1} for the Vaseline/ketoconazole/membrane system at various times t of the release experiment. For comparison the spectrum of ketoconazole (#) is also shown.

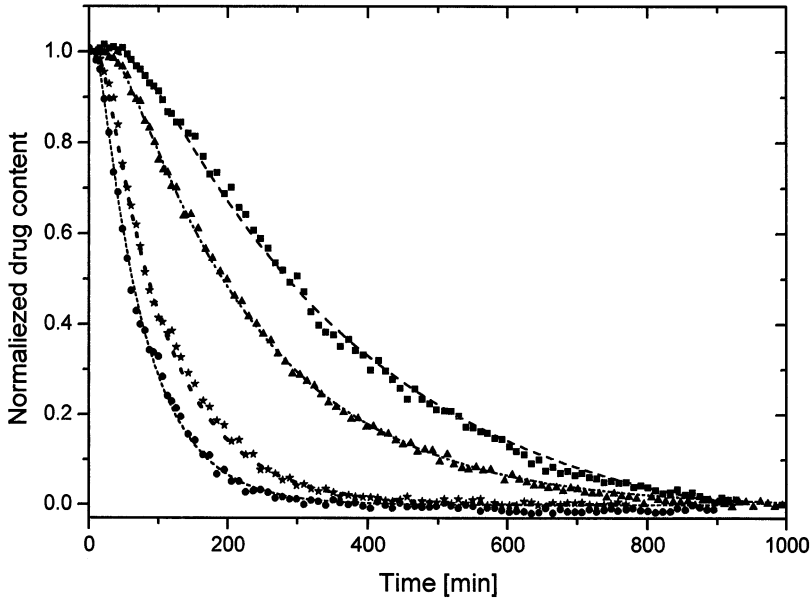

Fig. 2. Normalized amount of ketoconazole for the Vaseline/paraffinum liquidum/ketoconazole/membrane system versus time deduced by multivariate analysis of the ATR spectra. Fraction of paraffinum liquidum $m_{pl} = 0\%$ (■); 5% (▲); 10% (★); 20% (●).

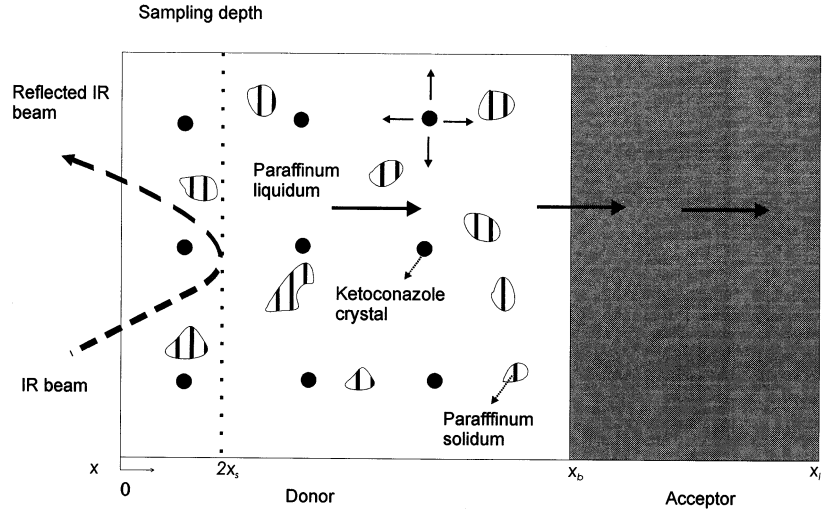

Fig. 3. Schematic model of the drug release experiment.

with the initial and boundary conditions:

$$\text{at } t=0 \quad c=c_{\text{sat}} \quad \text{for } 0\le x\le x_{\text{b}} \tag{3a}$$

$$c=0 \quad \text{for } x_{\text{b}}<x\le x_{\text{l}} \tag{3b}$$

$$\text{at } t>0\text{: } c \text{ (acceptor side)} = Qc \text{ (donor side) for } x=x_{\text{b}} \tag{4a}$$

$$D_{\text{a}}\frac{\partial c(\text{acceptor side})}{\partial x}=D_{\text{eff}}\frac{\partial c(\text{donor side})}{\partial x} \tag{4b}$$

$$\text{for } x=x_{\text{b}}$$

$$\frac{\partial c}{\partial x}=0 \text{ at } x=0 \text{ and } x = x_{\text{l}} \text{ (impermeable boundary)} \tag{4c}$$

where Q is the partition coefficient between donor and acceptor. The effective diffusion coefficient of the drug in the ointment D_{eff} is available from the release experiment with paraffinum liquidum (see part I). The diffusion coefficient of the drug in the acceptor D_{a} can be derive form the lag-time determined by the standard liberation method (Schendzielorz et al., 1999).

The source term R is defined by

$$R=\frac{3K_{\text{dis}}v_{\text{d}\,0}^{2/3}}{r}\cdot\frac{c}{c_{\text{sat}}}(c_{\text{sat}}-c)\times\left\{1-\frac{1}{\rho}\cdot\frac{K_{\text{dis}}}{rv_{\text{d}\,0}^{1/3}}\cdot\frac{c}{c_{\text{sat}}}\int_0^t[c_{\text{sat}}-c(x,\tau)]\text{d}\,\tau\right\} \tag{5}$$

where K_{dis} is the apparent dissolution coefficient of the drug, r the radius of the drug particle, v_{d} the volume fraction of the drug particles, $v_{\text{d}\,0}$ the initial volume fraction of the drug particles, ρ the density of drug particles, and c_{sat} is the saturation concentration. Suppose that the drug particles can be approximated by spheres of radius r, the decrease of the drug radius due to dissolution is simply given by

$$\frac{r}{r_0}=\sqrt[3]{\frac{c_0-\int_0^t R\,\text{d}\,t}{c_0}} \tag{6}$$

where c_0 is the initial total concentration of drug (sum of dissolved and non-dissolved) and r_0 is the initial radius of the drug particles.

In the ATR experiment, the signal intensity recorded is a measure of the mass M within the sampling range of the IR beam, which is given by

$$M=A\int_0^{2x_{\text{s}}}(c+c_{\text{n}})\text{d}\,x \tag{7}$$

where c_n is the 'concentration' of the non-dissolved drug and A is the area of the ATR crystal.

The partial differential equation system was numerically solved by applying the program SIMULINK (Simulink, 1999) and the non-linear least-square data fitting by Gauss–Newton method of the software MATLAB (The Mathworks Inc., Natick, MA).

5. Discussion

Based upon this mathematical model and the spectroscopic data obtained, we have determined the apparent dissolution coefficient K_{dis} of ketoconazole in the ointment base with various contents of paraffinum liquidum. It turns out that K_{dis} is dependent on the fraction of paraffinum liquidum in the suspension. Fig. 4 shows this finding. To explain this behaviour one has to take into consideration that the dissolution process is influenced by the disposable surface of the drug particle. In the case of a high fraction of paraffinum solidum as in ointments, this area can be considerably smaller than the real surface of the particle. Therefore, the dissolution rate seems to be reduced and this effect is described by an apparent dissolution coefficient.

Knowing all parameters for the drug release in suspension, it is possible to simulate the drug transport by utilizing equations (1)–(4). In order to adapt our model to in vivo transport we assume a perfect sink condition at the acceptor boundary, i.e.

$$c = 0 \text{ at } x = x_1 \quad (8)$$

Further, we presume that the diffusion coefficient of the drug in the liquid phase of vaseline is the same as that one in paraffinum liquidum.

The results of this simulation for 2% ketoconazole suspended in vaseline with 15% w/w paraffinum liquidum are illustrated in Figs. 5–8. So, Fig. 5 shows the normalized drug concentration versus the distance in the vehicle and membrane at various times. The normalized drug concentration as a function of time at various positions within the membrane is plotted in Fig. 6. Furthermore, the time dependence of the total amount of drug in the membrane is depicted in Fig. 7. Finally, the area under this curve (AUC_a), the so-called 'dermal bioavailability', for various amounts of paraffinum liquidum m_{pl} is represented in Fig. 8. As it can be seen that with increasing amount of paraffinum liquidum the AUC_a reaches a maximum value at m_{pl} approximately 12% w/w, for higher values of m_{pl} a slight fall occurs. This behaviour is governed by several factors, namely the effective diffusion coefficient, the apparent dissolution coefficient and the saturation concentration of the drug in the liquid phase of the formulation. These three parameters

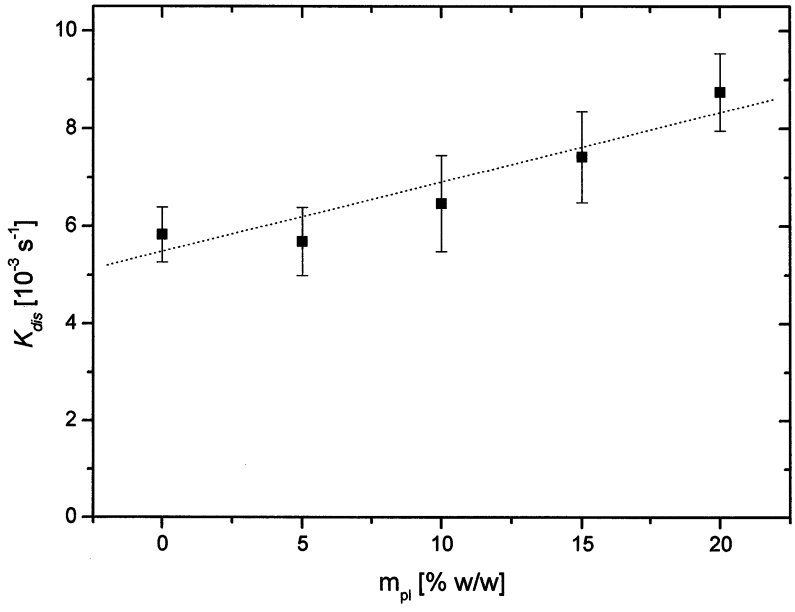

Fig. 4. Dependence of the dissolution coefficient of ketoconazole, (K_{dis}) on the amount of paraffinum liquidum, m_{pl}, added to vaseline.

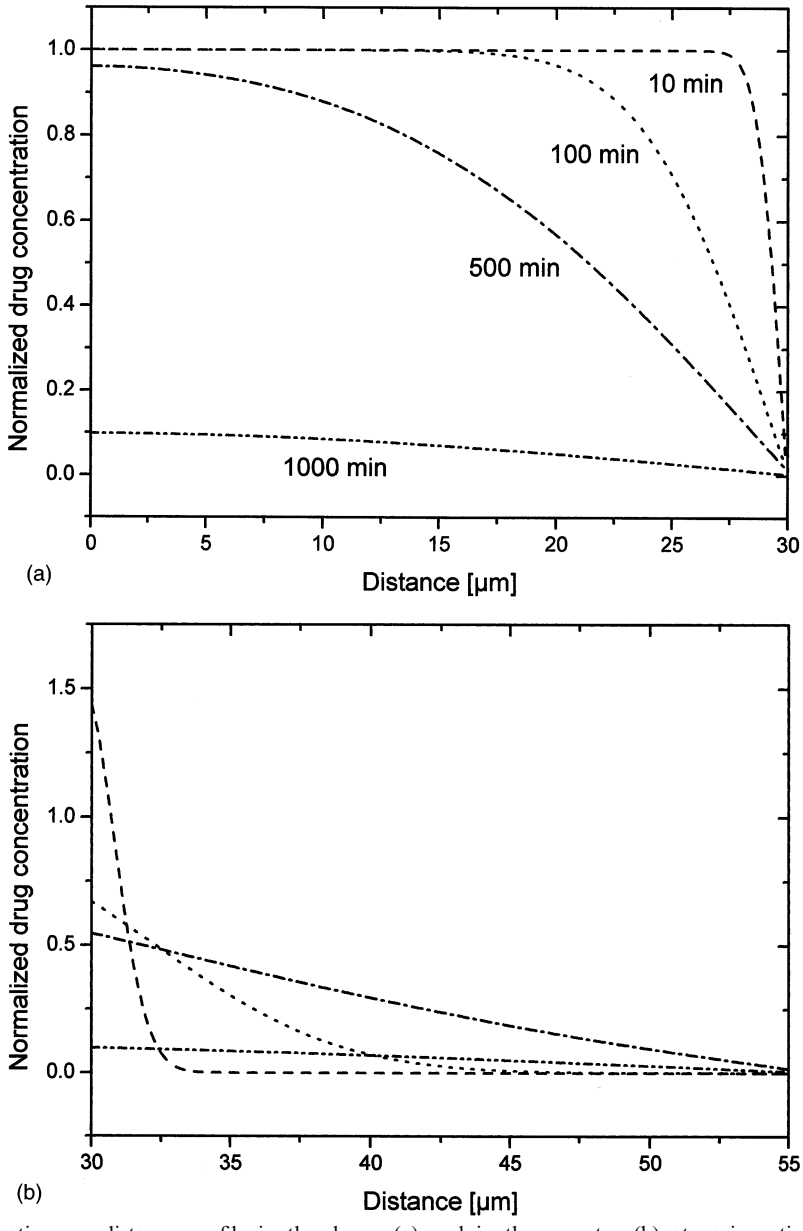

Fig. 5. Drug concentration — distance profile in the donor (a) and in the acceptor (b) at various times simulated for 2% ketoconazole in vaseline with 15% paraffinum liquidum.

increase with adding of paraffinum liquidum to Vaseline. The higher values of the effective diffusion coefficient and of the apparent dissolution coefficient accelerate the drug transport process in the vehicle. The higher solubility of the drug causes on the one hand a growing of the dissolution rate, which accelerate the transport process as well. On the other hand, the partition coefficient of the drug between donor and acceptor decreases, which delays the transport through the interface between donor and acceptor. All together, an optimal composition

of the semisolid formulation exists for the 'dermal bioavailability'. The results obtained underline findings in the literature (Bendas et al., 1995) that an optimal solubility of the drug in ointments is required for maximum 'dermal bioavailability'.

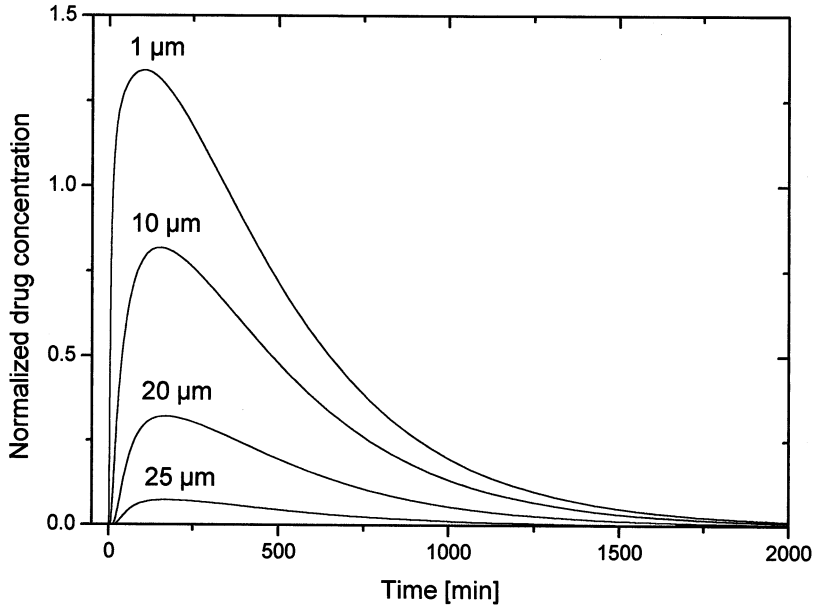

Fig. 6. Drug concentration — time profile at various position in the membrane simulated for 2% ketoconazole in vaseline with 15% paraffinum liquidum.

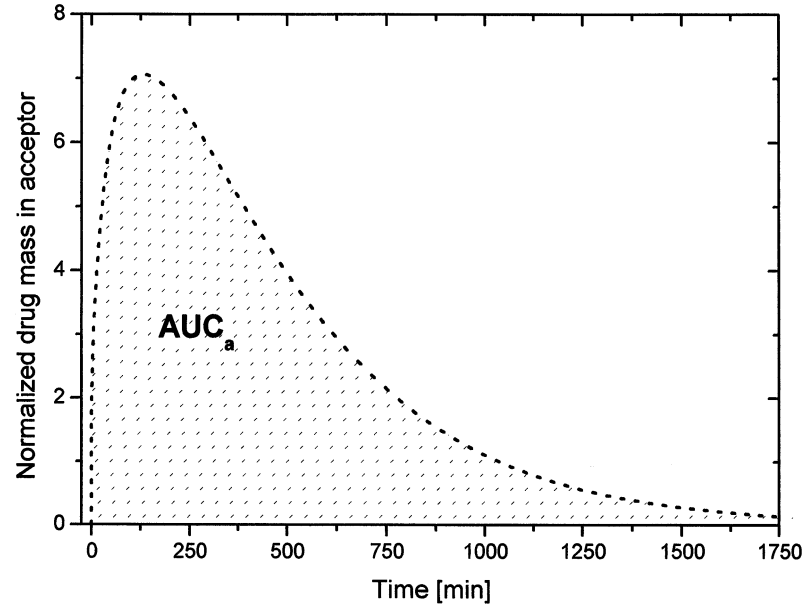

Fig. 7. Total amount of drug in the acceptor (membrane) versus time simulated for 2% ketoconazole in vaseline with 15% paraffinum liquidum. AUC_a is the area under the curve, the so-called 'dermal bioavailability'.

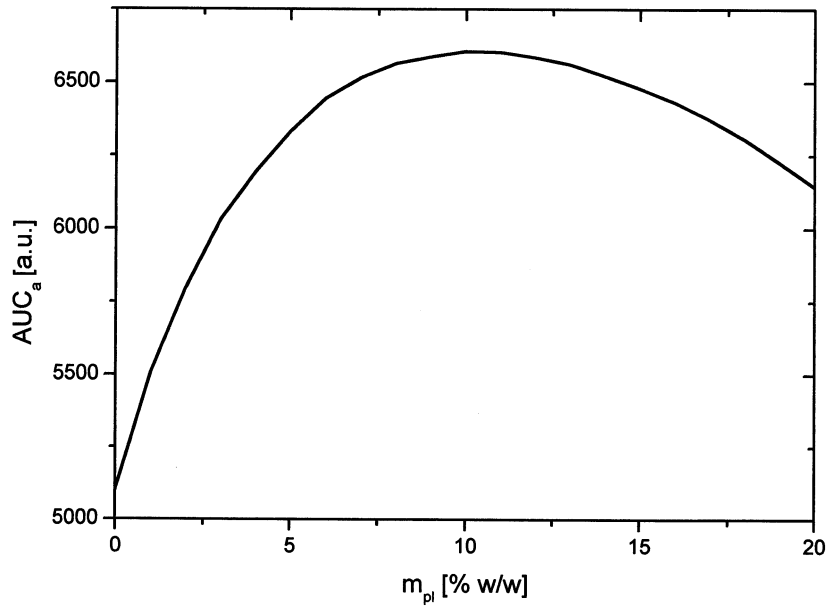

Fig. 8. AUC_a in dependence on the fraction of paraffinum liquidum, m_{pl}.

6. Conclusion

We have shown that applying the FTIR-ATR spectroscopy to a drug release process in a semisolid formulation can provide the dissolution coefficient of the drug. Based on a mathematical model and the knowledge of all parameters of the donor — acceptor system, it is possible to simulate the transport process in terms of the drug concentration — distance and the concentration-time profiles as well as AUC_a in the acceptor. The results reveal how adding of liquid constituent to the semisolid formulation can influence the 'dermal bioavailability' of the drug.

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