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Investigation of drug release from suspension using FTIR-ATR technique: part I. Determination of effective diffusion coefficient of drugs

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Abstract

Fourier transform infrared attenuated total reflectance (FTIR-ATR) spectroscopy was used to study directly the release of drug particles (ketoconazole) in a liquid medium (paraffinum liquidum). In the case of the release experiment, the formulation is placed on the ATR crystal and the acceptor membrane on the top of the ointment. The decrease of the drug content in the sediment near the interface ATR crystal-formulation in the course of the release process was quantified by monitoring the changes of the IR spectrum in relevant spectral ranges using multivariate analysis. A mathematical model based on Fick's second law with appropriate initial and boundary conditions was applied in order to determine the diffusion coefficient of the drug in the liquid medium. Knowing this value, it is possible to calculate the effective diffusion coefficient of the drug in heterogeneous semisolid formulation (Vaseline) as a function of the volume fraction of the solid phase.

Keywords: Fourier transform infrared spectroscopy; Attenuated total reflectance; Drug release from suspension; Effective diffusion coefficient

1. Introduction

Nowadays, Fourier transform infrared (FTIR) spectroscopy with the attenuated total reflection (ATR) has emerged as one of the standard techniques used to monitor the permeation of drugs across membranes and to determine diffusion coefficients (Reinl et al., 1995; Tralhão et al., 1995; Pellet et al., 1997; Hanh et al., 2000). In such an experiment, a membrane is sandwiched between an impermeable ATR crystal and a reservoir of permeant. The membrane is initially devoid of permeant. As permeation through the membrane occurs, there will be a build up permeant at the interface between membrane and crystal, which can be examined online by the evanescent IR

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beam. The ATR technique was also applied for determining the diffusion coefficient of liquids in semisolid materials (Wuster et al., 1993).

The objective of the present papers is to elucidate the potential use of the ATR technique for investigating topics related to the drug release from semisolid formulations such as ointments and creams. In the literature there are no reports on such non-invasive measurements of drug release from semisolid formulations. It is known that the drug release from suspensions is a complex process (Addicks et al., 1990) involving the dissolution of the solid drug particles in the liquid phase of the vehicle, characterised by the dissolution coefficient, and the diffusion of the dissolved drug through the heterogeneous vehicle, described by an effective diffusion coefficient. Changing the portion of the liquid phase of the vehicle it is possible to vary the values of these two coefficients. The knowledge of both the dissolution coefficient as well as the effective diffusion coefficient of the drug in the vehicle would facilitate formulation design so that optimal system could be developed.

In contrast to permeation studies, in the release experiment the arrangement of donor and acceptor must be inverted: the formulation is placed on the ATR crystal and the membrane used as acceptor compartment on the top of the ointment (see Fig. 1). In this manner, the evanescent IR beam can monitor the changes of the drug content in the ointment near the surface of the crystal in the course of the release process. Certainly, the determination of the two characteristic parameters mentioned above requires two ATR experiments independent from each other. In Part I of this communication we will show that it is possible to derive the drug diffusion coefficient in a liquid medium and with it the effective diffusion coefficient in a heterogeneous semisolid formulation by utilising the FTIR-ATR technique in conjunction with an appropriate mathematical model. In Part II we will discuss the release experiment for determining the dissolution coefficient of the drug in the vehicle system. A dodecanol–collodion membrane was used as acceptor; ketoconazole was chosen as model drug and Vaseline as ointment base.

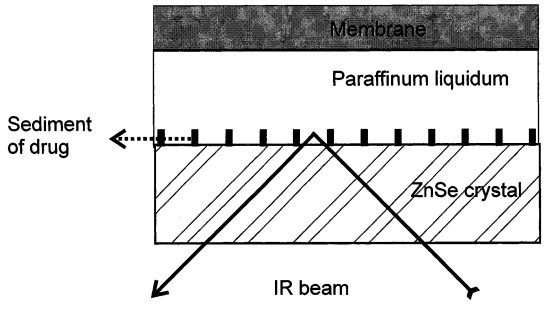

Fig. 1. Sample arrangement for the drug release experiment using ATR technique.

2. Materials and methods

2.1. Materials

The drug ketoconazole was purchased from Sigma–Aldrich Chemie (Deisenhofen, Germany), collodion solution (4% w/w in ether/ethanol) from Caelo (Hilden, Germany), 1-dodecanol from Merck–Schuchardt (Hohenbrunn, Germany) and paraffinum liquidum from Sigma–Aldrich. The preparation of the 4% (w/w) dodecanol–collodion (DDC) membrane (thickness approx. 25 μm) has been described elsewhere (Neubert et al., 1991). The mixture was prepared as 5% (w/w) ketoconazole in paraffinum liquidum.

2.2. FTIR-ATR spectroscopy

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, USA). This sampling compartment is a single reflection ATR accessory that uses a ZnSe crystal with an angle of incidence of 45° in a horizontal orientation. The diameter of the top of the ATR crystal amounts to 17 mm. Under these conditions and in the spectral range of interest 1100–1800 cm^{-1}, the theory of ATR (Jakobsen and Straud, 1993) predicts that the sampling depth in the membrane (refraction index ≈ 1.6) is in the range from 0.8 to 1.2 μm. A well-shaken amount of the mixture (20

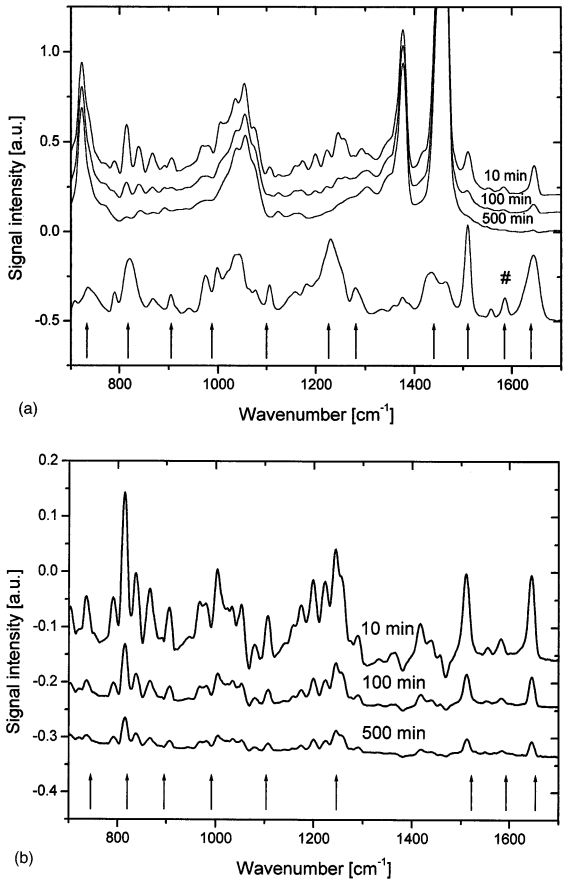

Fig. 2. Spectra in the spectral range 700–1700 cm^{-1} for the paraffinum liquidum/ketoconazole/membrane system recorded at various times of the release experiment. (a) FTIR-ATR spectra; for comparison the spectrum of ketoconazole (#) is also depicted. The arrows mark characteristic bands of ketoconazole. (b) Difference spectra $Sp(t) - Sp(t = 900\ min)$.

mg) was spread on the ATR crystal and then the sample was allowed for sedimentation over 24 h. The thickness of the sediment layer on the crystal amounts to be approximately 5 μm. Starting the experiment the DDC membrane (thickness 25 μm) was placed on top of the mixture, where a handling time of 5 min was required. Each IR spectrum was obtained by co-adding 100 scans (measuring time 90 s) with a resolution of 2 cm^{-1}. At the beginning of the experiment the spectra were recorded with a pause of 90 s between consecutive registrations and then in the further course with a break of 5 and 15 min, respectively. Altogether, 100 spectra were usually acquired. The manipulation and evaluation of the spectra were carried out using the Bruker OPUS software.

3. Results

FTIR-ATR spectra in the spectral range 700–1700 cm^{-1} for the paraffin liquidum/ketoconazole/membrane system at various times t of the release experiments are represented Fig. 2a. It is obvious that the intensity of characteristic IR bands of the drug decreases in the course of release. This behaviour is quite clearer from the difference spectra $Sp(t) - Sp(t = 900\ min)$ that are shown in Fig. 2b. For quantifying the decrease of drug we have used the multivariate analysis 'Quant 2' of the OPUS software package, where the vector normalisation in the spectral range mentioned above was applied. For the purpose of calibration the ATR spectra of sediments of various mixtures paraffinum liquidum/ ketoconazole (0, 2, 5, and 10% w/w) were used. In this manner, the decrease of the drug content near the interface ATR crystal–mixture as a function of time was determined (see Fig. 3).

The ATR signal intensity is a measure of the mass M within the sampling range of the IR beam. We assume $0 \leq x \leq 2x_s$ as sampling range, where x_s is the sampling depth (see Fig. 4). Thus, it follows that

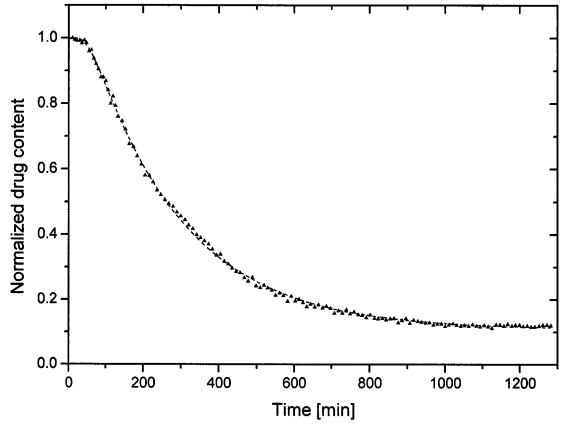

Fig. 3. Decrease of the normalised amount of ketoconazole as a function of time deduced by multivariate analysis of the ATR spectra.

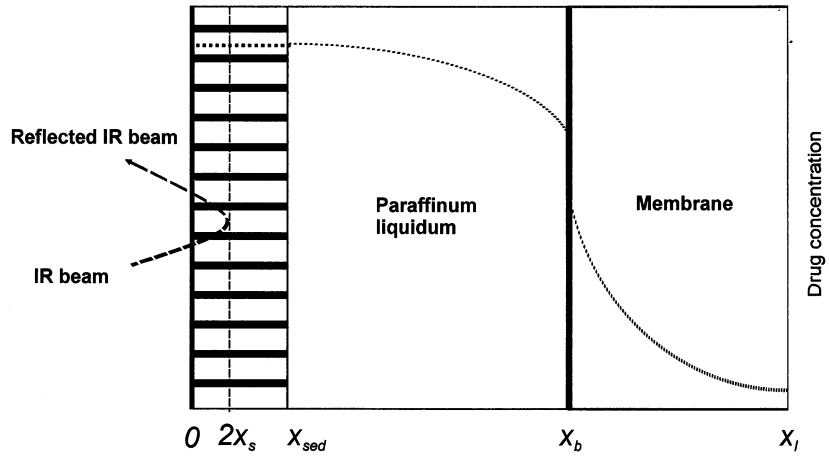

Fig. 4. Model of the drug concentration profile.

$$M = A \int_0^{2x_s} (c_{sat} + c_n)\, dx \tag{1}$$

where c_{sat} is the saturation concentration of the dissolved drug, c_n represents the solid drug particles, and A is the area of the ATR crystal. Due to the penetration of the drug into the membrane the value of c_n decreases whereas c_{sat} remains constant. Therefore, the difference spectrum is a measure of

$$\bar{c}(t) - \bar{c_n}(t = 900\ \text{min}) \tag{2}$$

where $\bar{c_n}(t)$ is the average value of $c_n(t)$ within the sampling range.

4. Mathematical model

In order to derive the diffusion coefficient of the drug from the experimental data, it is necessary to assume an appropriate model shown in Fig. 4. The drug diffusion in the liquid medium/membrane system obeys Fick's second law for the one-dimensional case (Crank, 1975), i.e.

$$\frac{\partial c}{\partial t} = D_{lm} \frac{\partial^2 c}{\partial x^2} \qquad x_{sed} < x < x_b \tag{3}$$

$$\frac{\partial c}{\partial t} = D_a \frac{\partial^2 c}{\partial x^2} \qquad x_b < x < x_l \tag{4}$$

where $c(x, t)$ is the concentration of the dissolved drug, D_{lm} is the diffusion coefficient of the drug in the liquid medium and D_a the diffusion coefficient in the acceptor. The Eqs. (3) and (4) were numerical solved for the following initial and boundary conditions:

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

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

$$\text{at} \quad t > 0 \qquad c = c_{sat} \quad \text{for} \quad 0 \le x \le x_{sed} \tag{4a}$$

$$c(\text{acceptor side}) = Qc(\text{liquid medium side}) \quad \text{for} \quad x = x_b \tag{4b}$$

$$D_a \frac{\partial c(\text{acceptor side})}{\partial x} = D_{lm} \frac{\partial c(\text{liquid medium side})}{\partial x} \quad \text{for} \quad x = x_b \tag{4c}$$

$$\frac{\partial c(x_l)}{\partial x} = 0 \tag{4d}$$

where c_{sat} is the saturation concentration and Q is the partition coefficient of the drug between liquid medium and acceptor. The numerical calculations of the partial differential equations were carried out by using SIMULINK and non-linear least-square data fitting by Gauss–Newton method of the software MATLAB (The Mathworks Inc., Natick, MA, USA).

5. Discussion

Taking the spectroscopic data as input data for the numerical calculations and the known diffusion coefficient D_a, the diffusion coefficient of ketoconazole in paraffinum liquidum was determined to be $D_{lm} = (5.9 \pm 0.6)\ 10^{-10}\ cm^2\ s^{-1}$. The diffusion coefficient of ketoconazole in the DDC membrane $D_a = (1.4 \pm 0.1)\ 10^{-10}\ cm^2\ s^{-1}$ was measured using the modified liberation model described elsewhere (Schendzielorz et al., 1999). The partition coefficient of ketoconazole between membrane and paraffinum liquidum amounts to be 7.2.

In heterogeneous media the diffusion coefficient is dependent on the volume fraction of the constituents. On the assumption that the solid constituents of the ointment base are of irregular size and shape and randomly distributed and that these particles are impermeable for the dissolved drug molecules, following Crank (1975), the effective diffusion coefficient of the drug in the vehicle is given by

$$\frac{1}{D_{eff}} = \frac{1}{D_{lm}}\left\{1 - \sqrt{\frac{3v_s}{2}} + \left(\sqrt{\frac{1}{1+\sqrt{2/3v_s}}}\right)\tan^{-1}\left(\sqrt{\frac{1}{1+\sqrt{2/3v_s}}}\right)\right\} \quad (5)$$

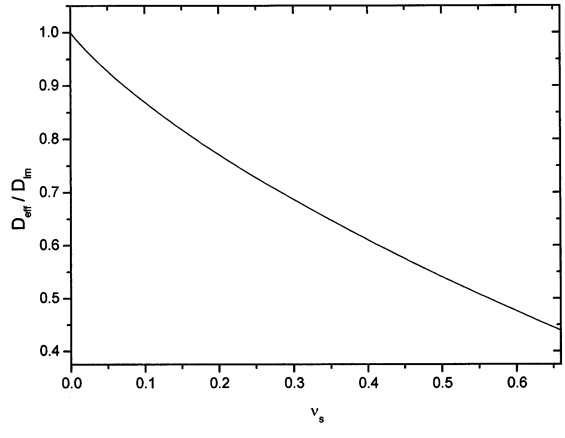

Fig. 5. Effective diffusion coefficient D_{eff}/D_{lm} of the drug in the heterogeneous semisolid formulation as a function of the volume fraction v_s of the solid constituent. For Vaseline (DAB 10) this volume fraction is about 0.4.

where v_s is the volume fraction of the solid constituent of the vehicle. Eq. (5) is valid for $0 \leq v_s \leq 2/3$. Fig. 5 shows how the ratio D_{eff}/D_{lm} varies with the volume fraction v_s.

6. Conclusion

We have successfully demonstrated that the FTIR-ATR technique is capable of providing data on the release process of drugs in semisolid formulations. Thus, it is possible to determine the diffusion coefficient of a drug in the liquid phase and with it the effective diffusion coefficient in the vehicle. The knowledge of the dependence of the effective diffusion coefficient of a drug within the heterogeneous semisolid formulation is of considerable interest for developing topical formulations.

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