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Research paper

Hydrophilic silica aerogels as dermal drug delivery systems – Dithranol as a model drug

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Abstract

A special class of porous silica materials, silica aerogels, was recently shown to be a potential candidate for oral drug delivery systems. It was demonstrated, that stability of drugs and their dissolution rate can essentially be improved through the adsorption on to these materials. In this work, drug loaded silica aerogels are firstly applied as dermal drug delivery systems. Dithranol is used as a representative drug since there is a need to enhance its dermal availability. The unstable and nearly water-insoluble drug exhibits a poor penetration. Release of dithranol from aerogels into various semi-solid formulations and its dissolution as well as the release and penetration into artificial membranes were investigated by Fourier-transform infrared attenuated total reflection (FTIR-ATR) spectroscopy. Two model membranes (one hydrophilic and one lipophilic) were applied. Several formulations were tested and the most promising one was used in order to study the penetration of dithranol into human stratum corneum (SC). Dithranol adsorbed on hydrophilic silica aerogels exhibited superior penetration behaviour compared to that of the standard ointment (dithranol in white soft paraffin).

Keywords: Hydrophilic silica aerogels; Dithranol; FTIR-ATR spectroscopy; Human stratum corneum; Model membranes; Release; Penetration

1. Introduction

In pharmaceutical technology, silica materials are widely used as additives, free flow agents and drug carriers. A special class of silica materials, silica aerogels, was recently shown to be a potential candidate for oral drug delivery systems [1,2]. Aerogels are low-density nanoporous solids with a fine, open-pore structure. They exhibit low densities (0.003–0.15 g/cm^3), high porosity and large surface areas (500–1000 m^2/g). These properties allow them to be used as host matrix for drugs. The chemistry of aerogel materials is rather flexible: their pore size and surface area can be tailored. Furthermore, different functional groups can be implemented in order to provide effective drug–aerogel interactions influencing the release kinetics and improving drug solubility and bioavailability. The chemical composition of aerogels is very close to that of another well-known silica material, Aerosil®, and xerogels; however, the structural and physical properties of these materials are quite different as can be seen in Table 1. Both xerogels and aerogels are produced via a sol–gel processes, although they undergo different drying procedures. If a wet silica gel is dried at normal pressure, it shrinks significantly providing a dense material with a relatively small pore size – a xerogel. In the case of supercritical drying the shrinkage is avoided and the three-dimensional structure is preserved in a resulting aerogel. If the hydrophilic aerogel has contact with water its pores are filled with water immediately and its structural integrity is lost (aerogel effect). If dried at normal pressure a wetted aerogel transfers into xerogel powder.

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Table 1
Properties of Aerosil® and other silica polymers

	Aerosil®	Silica xerogel	Silica aerogel
Nature of the gel	Xerogel	Xerogel	Aerogel
Contact with water	Transferred to lyogel	Transferred to lyogel	Shrinking and destroying of the structure
Bulk density		0.25–0.6 g/cm^3	0.003–0.35 g/cm^3
Inner surface	$\leqslant$200 m^2/g (Aerosil® 200, Degussa, Dusseldorf, Germany)	300–600 m^2/g	400–1000 m^2/g
Pores	Closed mesopores	Open mesopores	Open mesopores
Synthesis	Flame pyrolysis of $SiCl_4$	Sol–gel-process	Sol–gel-process

Previously, it was shown that several drugs can be successfully adsorbed on silica aerogels from supercritical solutions. The drying step, which is required if the loading is finished using liquid solutions, is avoided in this case since CO_2 is removed by a simple pressure reduction. The release rate of the drug from the drug–aerogel formulations is influenced by the hydrophobicity and pore size of the aerogels. In the case of hydrophilic aerogels an extremely fast release of drugs – even compared to nanocrystals – is achieved, which is especially advantageous for poorly water-soluble drugs [3]. This effect is based on the collapse of the structure of hydrophilic aerogels in aqueous solutions due to the surface tension inside the pores. Unlike this, using xerogels no collapse of the structure takes place as it occurs during the drying as described above. Hydrophobic aerogels exhibit slower release, which is governed by diffusion, because they are more stable in water [4].

Dithranol (1,8-dihydroxy-9(10*H*)-anthracenone, CAS-No. 1143-38-0) is a drug used in the treatment of psoriasis vulgaris; however, staining and skin irritation restrict the application. Two types of therapy management are widely used, long term administration and short contact therapy. The latter is preferred due to the reduced discolouration and inflammation of the skin. The semi-solid formulations are applied only for a few minutes to the affected areas and are removed afterwards. Another disadvantage of dithranol is its instability. In the presence of oxidative agents polymerisation to different, coloured polymers takes place [5]. In addition, it is well-known that only a few percent of dithranol is released from a white soft paraffin suspension, which is one of the common formulations used in dermatology, and that most of this fraction persists in the stratum corneum (SC) without reaching deeper epidermal regions [6,7]. In contrast, dithranol has an effect on mitochondrial function and structure and, hence, it is essential to obtain therapeutic drug concentrations in viable skin layers.

Therefore, the objective of this work was to prove the applicability of silica aerogels in dermal delivery. Suitable semi-solid formulations were evaluated concerning the release and penetration of dithranol through different membranes. Furthermore, the disadvantages of dithranol, such as staining and poor penetration, should be overcome by using silica aerogels as a host matrix for the drug.

The evaluation was done by Fourier-transform infrared (FTIR) attenuated total reflection (ATR) spectroscopy. This method has emerged as one of the standard techniques to study the uptake of drugs in both natural and artificial membranes, for analysing dermal or transdermal bioavailability or characterising the influence of penetration enhancers [8–10]. It is a non-destructive sampling technique that provides IR spectra of a material's surface and can be used to obtain on-line data in penetration experiments. ATR spectroscopy is based upon the fact that although complete internal reflection occurs at the interface between the sample and the internal reflection element (IRE), the ATR crystal, radiation does in fact penetrate a short distance (1–2 μm) into the sample. The sample interacts with this evanescent wave resulting in the absorption of radiation, which closely resembles its transmission spectrum [11]. FTIR-ATR spectroscopy is advantageous regarding the instability of dithranol because no further sample preparation and analytics are required like in the case of conventional systems for penetration studies (e.g. Franz diffusion cell).

At first several semi-solid formulations were evaluated based on the release and penetration of dithranol through artificial membranes. Because of the restricted availability of human SC, different model membranes were used to characterise the penetration of dithranol from several vehicles. Since the main barrier for drug penetration into the skin is the uppermost layer, the stratum corneum, the model membrane should have the similar properties. Lipophilic dodecanol collodion membranes were shown to be suitable and reliable models [6,12–16]. The incorporated lipoid consists of dodecanol and 10% octanol. Octanol is a well established medium for determine the partition coefficients. Moreover, according to Surber [17] log*P* [SC/water] correlates well with log*P* [octanol/water]. Since the common polyethylene glycol (PEG) ointment NRF 11.53 [18] interferes with dodecanol collodion membrane, cellulose–xanthogenate membrane (Nephrophan®) was applied for further investigations with this ointment. After these preliminary experiments, penetration studies using human SC and the most promising formulation were performed. Water saturated dodecanol–octanol was chosen as acceptor to avoid a second distribution step besides the distribution between vehicle and human SC.

2. Materials and methods

2.1. Materials

2.1.1. Aerogels

Silica aerogels were produced using a two-step sol–gel process as described in detail elsewhere [1].

In short, tetramethoxysilane (TMOS) was mixed with methanol, water and HCl in the ratio 1 mol TMOS:2.4 mol CH_3OH:1.3 mol H_2O:10^{-5} mol HCl. After 30 min of stirring, additional water and ammonia solution were added so that the following ratio was obtained: 1 mol TMOS:2.4 mol CH_3OH:4 mol H_2O:10^{-5} mol HCl:10^{-2} mol NH_4OH.

Then the mixture was diluted with acetonitrile to reach the desired target density and poured into the autoclave. After gelation the solvent and pore liquid were extracted by supercritical CO_2 for 24 h at 40 °C and 100 bar. The density of the resulting monolith silica aerogels was calculated by weighing a sample and determining its volume. Hydrophilic aerogels with two different densities (0.04 and 0.08 g/cm^3) were produced in this way.

To load the silica aerogel with dithranol, a weighed amount of the drug and an aerogel sample (0.5–1 g) were separately wrapped in filter paper and placed in the autoclave. Carbon dioxide was added until a desired pressure was reached. The system was stored under constant pressure and temperature for 72 h. Then CO_2 was vented and the loaded aerogel samples were weighed and milled in a pebble mill.

The quantitative analysis of the adsorbed dithranol was done by a multivariate analysis of the FTIR-ATR spectra of the milled powders.

2.1.2. Membranes

Three different types of membranes were used for the release and penetration studies: dodecanol collodion membrane, Nephrophan® membrane and human SC.

The lipophilic dodecanol collodion membranes were prepared according to [12] having a dodecanol content of 4%. The thickness of these membranes was about 13 μm.

The cellulose–xanthogenate membrane Nephrophan® (ORWO, Wolfen, Germany) had to be pre-treated by rinsing in a solution of 2% $NaHCO_3$ in 1 mM Na–EDTA at 60–70 °C for more than 3 h in order to remove glycerol from the pores. The membrane's thickness was 35–40 μm.

The skin was taken from plastic surgery (mamma reduction) and was purchased from the German Institute for Cell and Tissue Replacement (Berlin, Germany). After mechanical separation of the fat and parts of the dermis, it was stored at −82 °C. The SC was isolated according to Kligman [19], subsequently freeze-dried (Alpha 2–4, Christ, Osterode, Germany) and stored at −20 °C. Prior to the experiments, the SC samples were rehydrated in distilled water for 20 h at room temperature. For assembling the SC in the diffusion cell, it was firstly stabilised by being placed on a polycarbonate filter membrane (Avestin® pore size 5000 nm, thickness 11 μm, Avestin Europe GmbH, Mannheim, Germany). The thickness of the fully hydrated SC was about 17 to 27 μm.

2.1.3. Semi-solid formulations

White soft paraffin DAB 1999 was purchased from Caesar & Loretz, Hilden, Germany. Lipophilic ointment (Unguentum alcoholum lanae DAB 2000 (Synopharm, Barsbuettel, Germany) consisted of 93.5% wool alcohols, 0.5% cetostearyl alcohol and 6% white soft paraffin [20]. Hydrophilic ointment (Unguentum emulsificans DAB) was prepared with 45% liquid paraffin, 25% white soft paraffin (both Caesar & Loretz, Hilden, Germany) and 30% emulsifying cetostearyl alcohol Type A (Synopharm, Barsbuettel, Germany). Polyethylene glycol (PEG) ointment was used according to NRF 11.53 [18] containing a mixture of equal parts of PEG 400 Fluka Chemika, Buchs, Switzerland), 1500, 4000 (both BASF, Ludwigshafen, Germany), and propylene glycol as well as 1% salicylic acid (both Synopharm, Barsbuettel, Germany).

Furthermore, glycerol 98% (Roth, Karlsruhe, Germany), isopropyl myristate (IPM), medium-chain triglycerides (Miglyol® 812) (both Caesar & Loretz, Hilden, Germany), liquid paraffin (Caesar & Loretz, Hilden, Germany) and water were used to modify the vehicles.

The content of dithranol (Caesar & Loretz, Hilden, Germany) in the formulations varied between 0.5% and 1% (w/w). In the case of dithranol-loaded aerogels, they were incorporated to an amount of 5% (w/w), resulting in a drug content of 0.5% (w/w).

2.1.4. Acceptor media for the ATR-diffusion cell

The choice of the acceptor medium is based upon the kind of the membrane. The major partitioning process can be assumed to be between vehicle and membrane, if the acceptor does not form a discrete compartment.

In accordance with the hydrophilic nature of the Nephrophan® membrane, a hydrophilic acceptor was selected, therefore, a solution of 1% (w/w) salicylic acid in PEG 400 was applied. Salicylic acid protects dithranol against the oxidative polymerisation in pure polyethylene glycols.

For the experiments with human SC, a lipophilic acceptor was chosen. In the respective studies of Surber [17], log P [SC/water] correlates well with log P [IPM/water] and log P [octanol/water]. Because of its favourable spectral properties (e.g. less and constant IR bands during the whole experiment), a medium chain alcohol was preferred as acceptor. Due to further experiences a mixture of 10% (w/w) octanol (Gruessing, Filsum, Germany) and 90% (w/w) dodecanol (Oleo Chemicals Cognis, Dusseldorf, Germany) was chosen. In order to reduce the dehydration of the SC during the experiment, the mixture was saturated with distilled water.

2.2. Methods

Release and penetration experiments as well as the quantitative analysis of the drug loaded aerogels were done with the FTIR-spectrometer IFS 28 (Bruker optics, Ettlingen, Germany). For the penetration studies with human SC the FTIR-spectrometer Vertex 70 (Bruker optics, Ettlingen, Germany) was utilised. Both instruments were equipped with a horizontal ATR attachment (Thermo

Spectra Tech, Shelton, CT, USA) and a Fresnel ZnSe crystal (angle of incidence 45°, diameter 17 mm in the diffusion experiments and 1.3 mm for quantitative analysis). Each spectrum was collected with 32 scans, Blackman–Harris 3-term apodization and a resolution of 2 cm^{-1}.

To quantify the dithranol content after adsorption process, several physical mixtures of dithranol and silica aerogel (density 0.04 g/cm^3) in the range of 0–80% (w/w) dithranol were prepared, whereas the most samples reached between 0% and 15%. For this purpose adequate amounts of dithranol and silica aerogel were mixed by milling in a mortar for five minutes. Each sample was characterised triplicate by FTIR-ATR spectroscopy. The collected spectra were fitted by a multivariate analysis.

Different experimental set-ups were applied (see Fig. 1). In the first one (types a and b) the uptake of the drug in the acceptor (semi-solid formulation or membrane) was directly detected. Since it was not possible to calibrate the drug content in some of these acceptors and to ensure a constant intimate optical contact during the whole experimental time, the ATR diffusion cell was employed (type c). This improved set-up combines the Franz type diffusion cell with FTIR-ATR spectroscopy [21]. A liquid acceptor is sandwiched between the IRE and the membrane and guarantees the intimate optical contact. Furthermore it enables the calibration of the drug content in the acceptor medium. Fig. 2 exemplifies the FTIR-ATR spectra of such a penetration experiment using a water-saturated mixture of dodecanol–octanol as acceptor, human SC as a membrane and hydrophilic ointment with dithranol-aerogel as donor. For comparison the spectrum of crystalline dithranol is represented. The analysed region is labelled.

For data interpretation, the intensity of drug-associated IR bands was calculated and plotted versus time. If the ATR diffusion cell was applied, a calibration was performed in a separate experiment, correlating the intensity of the drug associated IR band and the drug concentration in the acceptor liquid (multivariate analysis, OPUS 5.5 software, Bruker optics, Ettlingen, Germany).

For all experiments, reference measurements with the pure semi-solid formulation were carried out.

Each experiment was done at least twice. Statistical analysis was only performed for experiments using the ATR diffusion cell ($n \geqslant 3$).

3. Results and discussion

3.1. Quantitative analysis of the dithranol content of the aerogels

There are different approaches to determine the drug content on loaded aerogels. In the common procedure, a loaded aerogel is dispersed in an organic solvent and the extracted drug is determined spectroscopically. Disadvantages include the incomplete release of the drug from the aerogel and especially for dithranol, its general instability in solutions. In this work, FTIR-ATR spectroscopy was applied as a non-destructive method, which requires a minimal quantity of the sample. The characteristic parameters of the multivariate analysis of the collected FTIR-ATR spectra were: rank 3, root mean square error of cross validation (RMSECV) 1.46 and correlation coefficient (R^2) 99.59 in the spectral range from 1315 to 1505 cm^{-1} using the silica vibration between 998 and 1250 cm^{-1} as an internal standard. Depending on different loading conditions, the dithranol content of the aerogels ranged between 6% and 10% (w/w). For further experiments, aerogels with a dithranol content of more than 8% (w/w) were applied.

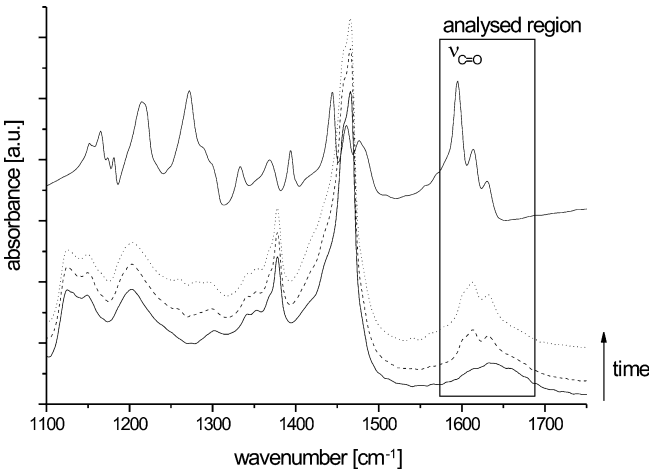

Fig. 2. FTIR-ATR spectrum of crystalline dithranol (grey) and FTIR-ATR spectra (black) of the acceptor of a penetration experiment (water-saturated dodecanol−octanol/dithranol-aerogel, hydrophilic ointment/SC) after 4 and 12 d and at its beginning (bottom spectrum). The evaluated region, which is associated with increasing dithranol content in the acceptor, is marked.

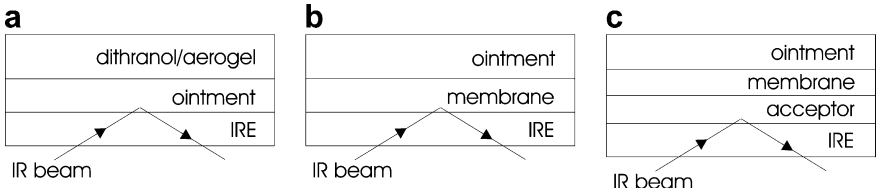

Fig. 1. Experimental set-ups for FTIR-ATR spectroscopy: (a) Release of the drug into the vehicle. (b) Penetration into dodecanol collodion membrane. (c) Penetration in Nephrophan® membrane or human stratum corneum.

3.2. Release of dithranol from the aerogel into the formulation

The prerequisite for drug release from a semi-solid formulation is the molecular dispersed state of the drug [22]. In the case of aerogel-containing vehicles, release of the drug from the aerogel has to be the preceding step.

Hence, release of dithranol from the aerogel into different vehicles was studied using the experimental set-up described in Fig. 1a.

As representative parameters of these experiments, area between the curves (ABC) and the time when 80% of the steady state band intensity were reached, t_{80}, are shown in Table 2. It should be remarked that all these data are semi-quantitative because a calibration was unavailable.

Using white soft paraffin no dithranol band appeared. Hence, other standardised semi-solid formulations of the German Pharmacopoeia were tested. Furthermore, they were modified by the addition of other ingredients such as water, liquid paraffin, IPM and glycerol in order to observe their influence on the release process.

Compared to the lipophilic ointment, release rate of dithranol from the aerogel in the vehicle was improved by several modifications. The effect increased due to addition of either water/paraffin (each 10%), 10% IPM or 50% water in the mentioned order. Because of the better solubility of dithranol in paraffin than in water, the extent of release was lower by addition of water than water/paraffin. Concurrently, water destroys the aerogel structure by aerogel effect and as a result, the dithranol is pushed into the formulation. However, the modifications of the lipophilic ointment had only marginal impact compared to the more hydrophilic formulations.

No influence of the additives on release of dithranol from the aerogels was found in the case of the hydrophilic ointment. The same experiment carried out with crystalline dithranol showed a slower and minor absorption of the drug into the hydrophilic ointment. The solubility of dithranol in this ointment was increased if dithranol loaded aerogels were applied. This might be due to the non-crystalline state of drugs adsorbed at aerogels and the aerogel effect itself.

Table 2
Parameters of release of dithranol from silica-aerogel into different semi-solid formulations, $n \geqslant 2$

Semi-solid formulation	ABC (min)	t_{80} (min)
Lipophilic ointment	130	271
Lipophilic ointment + 50% H_2O	77	180
Lipophilic ointment + 10% H_2O and 10% liquid paraffin	37	46.2
Lipophilic ointment + 10% IPM	65	98.3
Hydrophilic ointment	21	25.9
Hydrophilic ointment + 10% glycerol	33	31.1
Hydrophilic ointment + 10% IPM	62	72.3
Hydrophilic ointment, crystalline dithranol	147	291
Polyethylene glycol ointment	30	44.1

Because of the high solubility of dithranol in the polyethylene glycol ointment, the released amount of dithranol (reflected in the steady state level) was the largest among all the vehicles.

However, the highest release rate was observed for the hydrophilic ointment. Here, the time reaching t_{80} was the shortest. Considering the short contact regime in the administration of the formulation, it is essential that release, which is prerequisite for drug release, occurs as fast as possible and does not limit the penetration.

The influence of the density of the aerogel on release process was investigated for hydrophilic ointment. The aerogel with the highest density (0.08 g/cm^3) showed a slower rate compared to the aerogel with the lowest density (0.04 g/cm^3). In the case of aerogels with higher density, the effect of structure collapses is less pronounced since the network is stronger. Hence, aerogels with the density of 0.04 g/cm^3 were used for the following experiments.

3.3. Penetration into dodecanol collodion membranes

The investigation of drug penetration into dodecanol collodion membranes by FTIR-ATR spectroscopy is a well-established method [13–15]. According to these studies with conventional suspensions of drugs in white soft paraffin, the penetration of dithranol and dithranol-aerogels from several formulations was determined.

Vehicles based on the lipophilic ointment showed a slow and low penetration similar to a suspension of dithranol in white soft paraffin (Table 3). Moreover, neither the use of dithranol-aerogels nor the addition of water or other lipophilic ingredients was beneficial.

Furthermore, penetration from the hydrophilic ointment was studied. The highest penetrated amount was observed for the combination of hydrophilic ointment and dithranol-aerogel (Fig. 3). There was no difference in the time needed to reach steady state between crystalline dithranol and dithranol-aerogel, but the amount of dithranol in the steady state was higher if the adsorbed drug was utilised.

One reason is the state of the drug within the formulation. In the case of crystalline dithranol the drug is suspended in the vehicle, whereas dithranol adsorbed on the

Table 3
Parameters of penetration of dithranol in different vehicles in dodecanol collodion membrane, $n \geqslant 2$

Vehicle	ABC (min)	t_{80} (min)
White soft paraffin, dithranol	25.1	87.8
Lipophilic ointment, dithranol	No steady state within 400 min	
Lipophilic ointment,dithranol-aerogel	20.5	57.5
Hydrophilic ointment, dithranol	13.1	18.4
Hydrophilic ointment, dithranol-aerogel	10.2	14.8
Hydrophilic ointment + 10% IPM, dithranol-aerogel	10.3	13.2

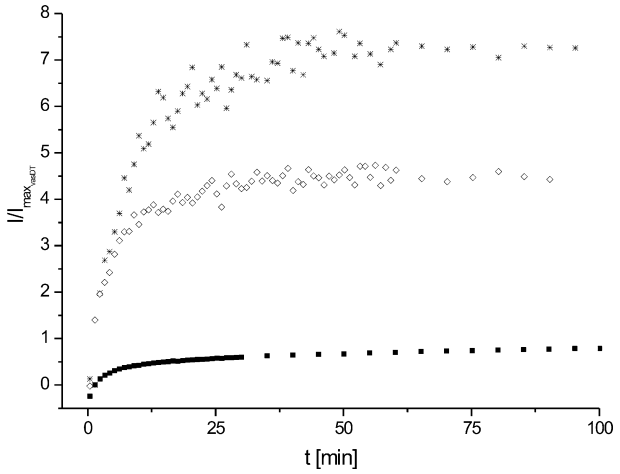

Fig. 3. Penetration of dithranol from different semi-solid formulations [dithranol, white soft paraffin (■), dithranol-aerogel hydrophilic ointment (*), dithranol-aerogel hydrophilic ointment with 10% IPM (◇)] into dodecanol collodion membranes; $I_{\text{dithranol, white soft paraffin}}$ ($\tilde{\nu} = 1603\ \text{cm}^{-1}$, $t = 600$ min) ≡ 1.

aerogel exhibits a non-crystalline structure as proved by X-ray experiments and electron microscopy [1]. Furthermore, vibrational spectroscopic analysis of the drug-loaded aerogels confirmed the non-crystalline state. Dermal absorption of drugs depends on their solubility within the vehicle as well as in the SC. Substances can only penetrate into a membrane – artificial or natural – in a dissolved state [22]. Thus, at least a partial dissolution of the drug in the vehicle is essential. Drugs in a non-crystalline state are better soluble than crystalline ones since no energy is needed to destroy the crystal lattice. Hence, the initial situation for the absorption of dithranol is advantageous if drug-loaded aerogels are used.

The aerogel effect might also be beneficial. In contact with liquids, especially water, the structure of the aerogel is destroyed by shrinkage and adsorbed molecules are abruptly released.

Following the addition of IPM and glycerol, respectively, to the hydrophilic ointment, no difference to the system dithranol-aerogel/hydrophilic ointment could be detected in the time reaching steady state.

For the experiments with polyethylene glycol ointment NRF 11.53 dodecanol collodion membranes were unemployable, due to collodion is dissolved by the polyethylene glycols; hence, the membranes were destroyed.

3.4. Penetration into Nephrophran® membrane

In order to include PEG ointment into the comparison of all the vehicles, Nephrophan® membrane, which is a hydrophilic, porous dialysis membrane, was chosen as additional model membrane.

In this case, an intimate optical contact between the membrane and the IRE, a basic condition for ATR spectroscopy, could not be realised. Hence, the experiments had to be done using the ATR diffusion cell. Polyethylene glycol 400 was used as liquid acceptor medium and 1% (w/w) salicylic acid was added for stabilising dithranol. In a separate calibration experiment, different well-defined solutions of dithranol in the mixture of PEG 400/salicylic acid (0–8% (m/V)) were prepared and spectroscopically examined to simulate the uptake of dithranol in the acceptor during the penetration process. The appropriate method of the multivariate analysis was used with minimum-maximum normalisation of the whole spectra and integration between 1590 and 1610 cm^{-1}. The characteristic parameters of this procedure were: rank 3, RMSECV 0.122 and R^2 99.78.

Similar to the prior distribution and penetration experiments with dodecanol collodion membranes, the penetration of dithranol from formulations like hydrophilic ointment, polyethylene glycol ointment and the standard suspension of dithranol in white soft paraffin were investigated. The results are presented in Fig. 4.

In accordance with the previous experiments, the modified hydrophilic ointment with dithranol-aerogel showed the best results.

The low dithranol concentration in the acceptor medium using polyethylene ointment is based upon the fact that the affinity of dithranol to the donor is nearly the same as to the acceptor. Therefore, the concentration gradient between the compartments, which is the main driving force for drug diffusion, is rather low.

3.5. Penetration into human SC

Finally, the penetration of dithranol into human SC was studied. Since the previous experiments showed promising results for the system dithranol-aerogel in hydrophilic ointment, this formulation was chosen. It was compared to the standard formulation dithranol in white soft paraffin.

Due to the inhomogeneous surface structure of the SC the optical contact to the IRE is reduced. Thus, an ATR diffusion cell had to be employed. Since the availability of human skin was restricted, a modified cell with a smaller penetration area (about half of that of the conventional cell) was used. The volume of the acceptor was also reduced, from about 90 μl to about 40 μl.

Firstly the same combination of PEG 400/salicylic acid as used in the Nephrophan® experiments was applied as acceptor liquid, but there was no dithranol detectable within three days. Another problem was the deliquescence of the acceptor: the SC desiccated during the experiment. As a result an acceptor medium consisting of a mixture of dodecanol and octanol, saturated with distilled water was chosen.

Similar to the preceding studies with the diffusion cell, a calibration of the dithranol concentration in the acceptor medium was performed. Different defined solutions of dithranol in the water-saturated dodecanol–octanol system were prepared (0–2 mg/ml). The appropriate method of the multivariate calibration helps to predict the dithranol con-

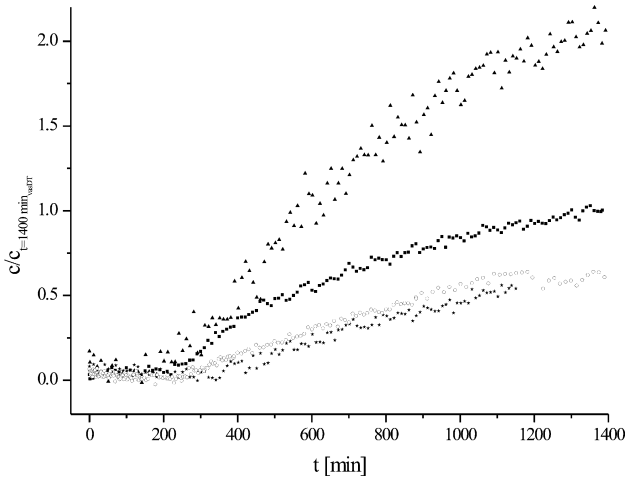

Fig. 4. Comparison of the penetration of dithranol through a Nephrophan® membrane using PEG 400/salicylic acid as acceptor, donors are dithranol, white soft paraffin (■), PEG ointment NRF 11.53 (*) and hydrophilic ointment with dithranol-aerogel (▲) and crystalline dithranol (○), respectively; $I_{\text{dithranol, white soft paraffine}}$ ($\tilde{\nu} = 1603\ \text{cm}^{-1}$, $t = 1400$ min) ≡ 1.

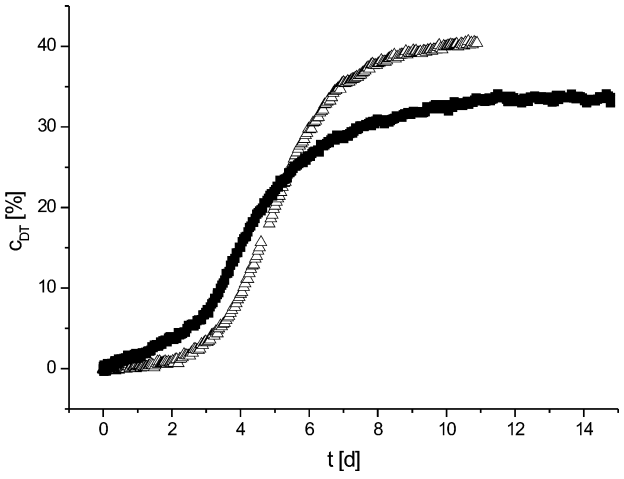

Fig. 5. Penetration of dithranol in white soft paraffin (■) and dithranol-aerogel, hydrophilic ointment (Δ) through human SC: concentration of dithranol in the acceptor medium as % of the applied dose versus time.

centration in the acceptor after transforming the ATR spectra to the first derivative in the range of 1590–1623 cm^{-1}. The characteristic parameters of this procedure were rank 2, RMSECV 0.108 and R^2 97.51.

Comparing typical parameters of the penetration process, the dithranol loaded aerogel in hydrophilic ointment was superior to the reference system dithranol in white soft paraffin. It showed a higher flux, a shorter lag time and the time taken to reach the steady state was shorter, too. Moreover, the dithranol concentration in the acceptor was higher, if the hydrophilic ointment was applied (see Table 4 and Fig. 5).

Diffusion through a membrane underlies the Fick's law. Parameters of this law include the diffusion coefficient, the concentration gradient of the diffusant along the membrane as well as the thickness of the membrane. The latter is directly proportional to the lag time. This could be a reason for the variation of lag time in the experimental series. The slope of the penetration curve is strongly associated to the diffusion coefficient and, therefore, the flux of the drug which is generally influenced by the formulation and the properties of the drug. Thus, dithranol-aerogel in hydrophilic ointment exhibits a higher flux than the crystalline drug in white soft paraffin (Table 4).

Table 4
Comparison of the parameters of the SC experiments, mean ± standard deviation

	Dithranol, white soft paraffin; $n = 4$	Dithranol-aerogel, hydrophilic ointment; $n = 4$
dc/dt [mg/ml/h]	0.210 ± 0.023	0.265 ± 0.035
Flux [g/m²/h]	0.49 ± 0.05	0.61 ± 0.08
Lag time [h]	47 ± 3.1	44 ± 22
$c_{\text{steady state}}$ [mg/ml]	25 ± 10	36 ± 19

Comparing different methods to characterise dithranol penetration, a lag-time was observed only for penetration experiments applying FTIR-ATR diffusion cell. In the case of Nephrophran® membrane it is at about 300 min for all formulations, demonstrating that the rate limiting step is not the membrane overcoming. The slope of the concentration–time curves characterises the release of dithranol in the acceptor. Both the concentration of dithranol in the acceptor at a defined time and the slope depend on the type of the vehicle. One can see that the formulation consisting of modified hydrophilic ointment/dithranol-aerogel shows the highest acceptor concentration. In contrast, penetration experiments with human SC showed different lag-times for both formulations as well as different fluxes. The penetration through the SC is rate controlling. Additionally, the release of dithranol from the vehicles influences the penetration.

The results of the release experiments applying a lipophilic model membrane suggested that a preferable dithranol release from the hydrophilic ointment takes place if dithranol-aerogel is used instead of the crystalline drug or the common dithranol/white soft paraffin. The subsequent studies with human SC, which has been shown to be the main barrier for dithranol [6,7], confirm these results.

4. Conclusion

This work demonstrated that drug loaded hydrophilic silica aerogels represent a new opportunity for dermal drug delivery. The loading procedure (adsorption from supercritical gases) allows for the homogeneous distribution of the drug inside the aerogel matrix on a molecular level, so that the drugs are present inside the highly porous matrix in a non-crystalline state. Using the model drug dithranol, it was shown that a drug-loaded aerogel can improve the release and penetration properties from semi-solid formulations as well as the stability (data not shown)

and staining. Based on the release studies of the drug from the aerogel into the formulation and the penetration experiments with artificial membranes, the most suitable semi-solid formulation for the dithranol-aerogel system was found to be a hydrophilic ointment. Penetration of dithranol from this vehicle into two different artificial membranes and the human SC was studied in comparison to a suspension of the crystalline drug. It was shown that a higher flux and a shorter lag time could be achieved if dithranol was adsorbed on silica aerogels. The enhanced penetration properties of novel formulations were reproducible for months after production.

Once again, FTIR-ATR spectroscopy was shown to be a versatile method for various studies relating to dermal drug delivery.

Overall, it is possible to improve the dermal availability of dithranol by applying drug-loaded aerogels. Furthermore, the chosen procedure-release studies, followed by penetration studies on model membranes and human SC is useful for optimising dermal formulations.

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References

[1] I. Smirnova, S. Suttiruengwong, W. Arlt, Feasibility study of hydrophilic and hydrophobic silica aerogels as drug delivery systems, J. Non-Cryst. Solids 350 (2004) 54–60.
[2] I. Smirnova, S. Suttiruengwong, M. Seiler, W. Arlt, Dissolution rate enhancement by adsorption of poorly soluble drugs on hydrophilic silica aerogels, Pharm. Dev. Technol. 9 (4) (2005) 443–452.
[3] I. Smirnova, M. Tuerk, R. Wischumerski, A.M. Wahl, Comparison of different methods for enhancing the dissolution rate of poorly soluble drugs: case of griseofulvin, Eng. Life Sci. 5 (3) (2005) 277–280.
[4] I. Smirnova, S. Suttiruengwong, W. Arlt, Aerogels: tailor-made carriers for immediate and prolonged drug release, KONA 23 (2005) 86–97.
[5] M. Lebwohl, S. Ali, Treatment of psoriasis. Part 1. Topical therapy and phototherapy, J. Am. Acad. Dermatol. 45 (4) (2001) 487–498.
[6] R. Neubert, W. Wohlrab, C. Bendas, Modelling drug penetration into human skin using a multilayer membranes system, Skin Pharmacol. 8 (3) (1995) 119–129.
[7] C. Bendas, Entwicklung eines In-vitro-Membranmodells zur Beurteilung der Arzneistoffverfügbarkeit aus topischen Arzneiformen, Dissertation, Halle, 1991.
[8] A. Naik, R.H. Guy, Infrared spectroscopic and differential scanning calorimetry investigations of the stratum corneum barrier function, in: R.P. Potts, R.H. Guy (Eds.), Mechanisms of Transdermal Drug Delivery, Drugs and the Pharmaceutical Sciences 83, Marcel Decker, New York, USA, 1997, pp. 87–162.
[9] M.A. Pellett, A.C. Watkinson, J. Hadgraft, K.R. Brain, Comparison of permeability data from traditional diffusion cell and ATR-FTIR spectroscopy. Part I. Synthetic membranes, Int. J. Pharm. 154 (1997) 205–215.
[10] M.A. Pellett, A.C. Watkinson, J. Hadgraft, K.R. Brain, Comparison of permeability data from traditional diffusion cell and ATR-FTIR spectroscopy. Part II. Determination of diffusional pathlengths in synthetic membranes and human stratum corneum, Int. J. Pharm. 154 (1997) 217–227.
[11] S. Wartewig, R.H.H. Neubert, Pharmaceutical applications of Mid-IR and Raman spectroscopy, Adv. Drug Deliv. Rev. 57 (2005) 1144–1170.
[12] R. Neubert, C. Bendas, W. Wohlrab, B. Gienau, W. Fürst, A multilayer membrane system for modelling drug penetration into skin, Int. J. Pharm. Sci. 75 (1991) 89–94.
[13] B.D. Hanh, R. Neubert, S. Wartewig, A. Christ, C. Hentzsch, Drug penetration as studied by non-invasive methods: FT-ATR, FTIR and UV photoacoustic spectroscopy, J. Pharm. Sci. 89 (2000) 1106–1113.
[14] B.D. Hanh, R. Neubert, S. Wartewig, Investigations of drug release from suspensions using FT-ATR technique: Part I. Determination of effective diffusion coefficient of drugs, Int. J. Pharm. 204 (2000) 145–150.
[15] B.D. Hanh, R. Neubert, S. Wartewig, Investigations of drug release from suspensions using FT-ATR technique: Part II. Determination of effective dissolution coefficient of drugs, Int. J. Pharm. 204 (2000) 151–158.
[16] T. Loftsson, F. Konrádsdóttir, M. Másson, Development and evaluation of an artificial membrane for determination of drug availability, Int. J. Pharm. 326 (2006) 60–68.
[17] C. Surber, C.P. Wilhelm, M. Hori, H.I. Maibach, R.H. Guy, Optimization of topical therapy: partitioning of drugs into stratum corneum, Pharm. Res. 7 (12) (1990) 1320–1324.
[18] Neues Rezeptur-Formularium (NRF), Govi-Verlag, Eschborn, Germany, 1995.
[19] A.M. Kligman, E. Christophers, Preparation of isolated sheets of human stratum corneum, Arch. Dermat. 88 (1963) 702–705.
[20] Deutsches Arzneibuch, Deutscher Apotheker Verlag, Stuttgart, Germany, 2000.
[21] M. Hartmann, B.H. Hanh, H. Podhaisky, J. Wensch, J. Bodzenta, S. Wartewig, R.H.H. Neubert, A new FTIR-ATR diffusion cell for drug diffusion studies, Analyst 129 (2004) 902–905.
[22] R. Niedner, J. Ziegenmeyer, Dermatika, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany, 1992.