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Loading of Bacterial Cellulose Aerogels with Bioactive Compounds by Antisolvent Precipitation with Supercritical Carbon Dioxide

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Summary: Bacterial cellulose aerogels overcome the drawback of shrinking during preparation by drying with supercritical CO_2. Thus, the pore network of these gels is fully accessible. These materials can be fully rewetted to 100% of its initial water content, without collapsing of the structure due to surface tension of the rewetting solvent. This rehydration property and the high pore volume of these material rendered bacterial cellulose aerogels very interesting as controlled release matrices. Supercritical CO_2 drying, the method of choice for aerogel preparation, can simultaneously be used to precipitate solutes within the cellulose matrix and thus to load bacterial cellulose aerogels with active substances. This process, frequently termed supercritical antisolvent precipitation, is able to perform production of the actual aerogel and its loading in one single preparation step. In this work, the loading of a bacterial cellulose aerogel matrix with two model substances, namely dexpanthenol and L-ascorbic acid, and the release behavior from the matrix were studied. A mathematical release model was applied to model the interactions between the solutes and the cellulose matrix. The bacterial cellulose aerogels were easily equipped with the reagents by supercritical antisolvent precipitation. Loading isotherms as well as release kinetics indicated no specific interaction between matrix and loaded substances. Hence, loading and release can be controlled and predicted just by varying the thickness of the gel and the solute concentration in the loading bath.

Keywords: aerogels; bacterial cellulose; controlled release; supercritical antisolvent precipitation; supercritical drying

Introduction

Aerogels are highly porous, very lightweight materials that feature a multitude of interesting properties, such as large specific surface area, extremely low thermal conductivity and sound propagation or excellent shock adsorption. Due to the high porosity and the readily accessible inter-connected open-pore system, aerogels have been investigated as drug delivery systems.[1-3] Cellulosic aerogels as the "young" third generation – succeeding silica and synthetic polymer-based aerogels – are particularly intriguing materials as they feature material properties similar to their antecessors, with the additional advantages and characteristics of the renewable biopolymer cellulose.[4] Therefore, many current attempts are aiming at preparing aerogels from polysaccharides and also at utilizing these new materials as controlled-release systems.[5]

In general, cellulose aerogels of defined shape can be prepared by dissolving the

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cellulose pulp in an appropriate solvent, regeneration of cellulose II by replacing the solvent by an anti-solvent, and subsequent drying of the obtained lyogels, aiming at a far-reaching preservation of the initially formed cellulose aggregate structure which is a prerequisite to most aerogel applications. Different preparation routes towards cellulose aerogels have been published.[6–8] One promising technique is based on the Lyocell technology and comprises the following steps: (1) Dissolving of cellulose in N-methylmorpholine-N-oxide monohydrate ($NMMO \cdot H_2O$) at 110–120 °C and casting into defined geometries, (2) extracting the solidified castings with ethanol under regeneration of cellulose and removal of $NMMO \cdot H_2O$ and (3) drying of the obtained lyogels by supercritical carbon dioxide ($scCO_2$).[9] Aerogels obtained this way from solutions containing 3% cellulose were found to have densities of 0.046 to 0.069 $g\,cm^{-3}$ and specific surface areas of 190 to 310 $m^2\,g^{-1}$ depending on the type of commercial pulp used.[10] Distinctly lower densities are hard to obtain since cellulose aerogels prepared from solutions containing less than 3% cellulose increasingly lack mechanical stability and thus suffer extensive shrinking upon regeneration and $scCO_2$ drying.[9] For purposes of drug delivery, shrinking of the loaded aerogel upon drying would result in non-accessible pores for a subsequent release step. Also in the case of higher cellulose concentrations in the NMMO solutions, shrinking during regeneration and subsequent $scCO_2$ drying cannot be completely avoided, and thus the suitability of cellulose aerogels obtained by the Lyocell-route for controlled-release purposes appeared somewhat limited.

In addition to plant cellulose regenerated from solutions, also microbial (bacterial) cellulose can be efficiently used as starting material to prepare cellulosic aerogels,[11] especially when combined with the mild and advantageous $scCO_2$ drying.[4] Due to the outstanding properties of the resulting bacterial cellulose aerogels, in particular higher molecular weight and fiber strength of cellulose, these materials can be used to prepare materials with extremely low densities of up to 8 $mg\,cm^{-3}$ only and pore surface areas of more than 200 $m^2\,g^{-1}$. Due to the high crystallinity and molecular weight of bacterial cellulose, shrinking during $scCO_2$ drying becomes close to zero.[4] Biomedical devices from microbial cellulose gain attention because of an increased interest in tissue-engineered products for both wound care and the regeneration of damaged or diseased organs.[12–14] Due to its structure, microbial cellulose is a natural candidate for numerous medical and tissue-engineered applications. Additionally, it finds application in the food industry and many other industrial sectors.[15–17]

In the present work, we studied the potential of bacterial cellulose aerogels as controlled-release matrices. Aerogels can be loaded with active substances by adsorption of the particular compound from its supercritical solution[3] or by precipitation / adsorption from a solvent within the matrix.[5] Carbon dioxide can act as an antisolvent which induces precipitation of substances of low solubility in CO_2.[18] The main advantage of this technique is that supercritical drying and loading of the gel with the active compound can be performed at the same time, in one single step, for appropriate solute/solvent systems.

Controlled release can be of interest for several application fields reaching from medical to food technology. We studied CO_2-induced precipitation from ethanolic solutions within bacterial-cellulose matrices for two model substances with wide scopes of medical applicability, dexpanthenol (D-panthenol) and L-ascorbic acid (vitamin C).

Pantothenic acid is essential to normal epithelial function. It is a component of coenzyme A, which serves as a cofactor for a variety of enzyme-catalyzed reactions that are important in the metabolism of carbohydrates, fatty acids, proteins, gluconeogenesis, sterols, steroid hormones, and porphyrins.[19] Dexpanthenol is a precursor of panthothenic acid. It is essential for healthy skin function and a well-known ingredient of treatments against skin

irritation and lesion, burns, and sun burn. L-ascorbic acid is not only an essential nutrient (vitamin C), but also used as auxiliary medication in many diseases, e.g. of the influenza type. It is frequently used as natural antioxidant in food and cosmetics technology.

Several preparation techniques and thus release mechanisms exist for controlled release systems.[20] In the case of drug-loaded bacterial cellulose aerogels the compound is dispersed in a monolithic system and its release is primarily dependent on geometric factors. In our work we used the model of Korsmeyer et al. which considers solute diffusion into and drug diffusion out of the system simultaneously.[21] This model was found to be best suitable to describe the release behavior of the substances under study.

Material and Methods

Preparation of Bacterial Cellulose Gels

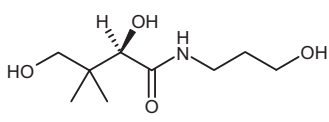
Cultivation of *Gluconacetobacter xylinum* was performed in aquarium-type glass tanks which were filled with steam-sterilized culture medium consisting of 20.0 g l^{-1} glucose, 5.0 g l^{-1} peptone, 5.0 g l^{-1} yeast extract, 1.15 g l^{-1} citric acid monohydrate and 6.8 g l^{-1} $Na_2HPO_4 \cdot 12\ H_2O$. Subsequently, the culture medium was inoculated with a suspension of *Gluconacetobacter xylinum*. After 30 days under static cultivation at 30 °C most of the glucose was consumed and the thickness of the bacteria cellulose layer amounted to about 3–4 cm. The harvested cellulose was cut into block-shaped pieces which were briefly boiled with water, treated three times with 0.1 M aqueous NaOH at 90 °C for 20 min each, and finally neutralized by rinsing with deionized water for 24 h. Prior to supercritical drying, the resulting bacterial cellulose aquogels were subject to a solvent exchange step which was performed by gently shaking in the twenty-fold volume of absolute ethanol (Sigma-Aldrich). After 6 and 12 h, the gels were transferred to a second and third bath, in which the same amount of fresh solvent was present. After another 6 h, the resulting alcogels were $scCO_2$ dried.

Supercritical Drying

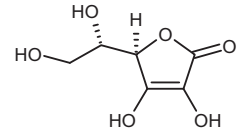
Supercritical drying was performed on a supercritical fluid formulation apparatus SF1 (Separex, France). Alcogels were placed on a stack which was loaded into the preheated 500 ml autoclave (40 °C). The autoclave was pressurized to 10 MPa. After reaching the final pressure, the outlet valve was opened and the autoclave was flushed with pure CO_2 for 1 hour at a flow rate of 2.5 kg h^{-1}. Ethanol was separated in a cyclone separator. After that drying period, the autoclave was depressurized slowly and the dry aerogels were removed.

Loading of Aerogels with Bioactive Compounds

Bacterial cellulose alcogels were placed into ethanolic solutions of dexpanthenol (compound A) or L-ascorbic acid (B, concentrations see below) instead of the third solvent exchange bath. The gels were kept in the bath for 24 hours at minimum, and the gels were dried according to the supercritical route described above.



A



B

Loading Isotherms

Solutions of different dexpanthenol and L-ascorbic acid concentrations, varying from 0.5 to 15 mg ml^{-1} (dexpanthenol) and 0.5 to 10 mg ml^{-1} (L-ascorbic acid) were prepared.

Each solution was charged with two alcogels. 24 hours later, the samples were removed and dried as described above. Following drying, the weight of each sample was recorded and 10 ml of distilled water were added. After quantitatively rewetting the porous matrix, the concentration of active compound in the release bath was determined photometrically at 223 nm (dexpanthenol) and 280 nm (L-ascorbic acid), respectively. The loading isotherm was obtained by plotting the amount of loaded dexpanthenol or L-ascorbic acid per sample weight against the corresponding concentration in the loading bath. All experiments were performed at room temperature.

Release Kinetics

Release kinetics were determined by charging 25 ml of distilled water with one loaded aerogel sample and measuring the UV absorption (223 nm for dexpanthenol and 280 nm for L-ascorbic acid) in dependence of time. For every time step a sample volume of 0.5 ml was withdrawn, measured and returned into the release bath. Release experiments took place in 50 ml tubes slowly shaken on an orbital shaker. When the gel was fully soaked the final concentration c_{inf} in the release bath was determined. Release kinetics was recorded for gels of different thickness. All experiments were performed at room temperature.

Results

Aerogels from Bacterial Cellulose

It has been recently found that bacterial cellulose gels can be dried via the supercritical pathway without significant alteration of their shape and dimension[4] whereas aerogels of comparable density obtained from plant cellulose via the Lyocell route undergo extensive shrinking under the same conditions.[9,10] The high dimensional stability of bacterial cellulose aerogels is mainly due to the bacterial cellulose's high average molecular weight and portion of crystalline areas. Due to this fact and because of the low solid content of bacterial cellulose gels, densities below $10\,mg\,cm^{-3}$ can be obtained. Remaining volume and density of the investigated bacterial cellulose aerogels are given in Figure 1. The specific surface area of bacterial cellulose aerogels was found to be about $200\,m^2\,g^{-1}$.[4]

The inset of Figure 1 shows two samples of bacterial cellulose: the alcogel before and the aerogel after supercritical drying. It is evident that almost no shrinking or other deformation occurred in the course of $scCO_2$ drying, which is in accordance with previously published data and indicates that the porous structure of the gels is largely maintained during this step.[4] Hence, it can be concluded that aerogels from bacterial cellulose outmatch those

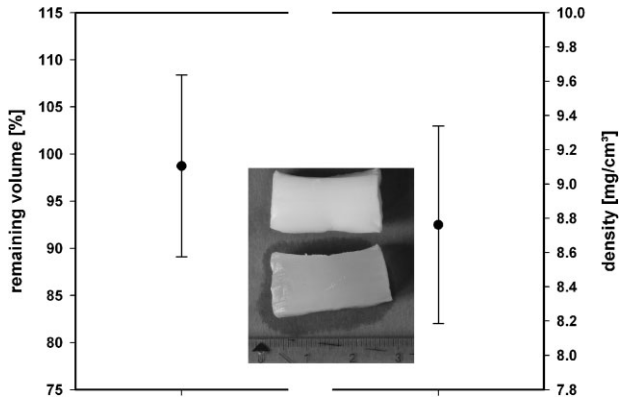


Figure 1.
Shrinking of bacterial cellulose alcogels (n = 10) upon $scCO_2$ drying (left) and resulting densities of the aerogels (right). Inset: Bacterial cellulose alcogel prior to (bottom) and after $scCO_2$ drying [n = 8].

from non derivatized plant cellulose in terms of dimensionally stability at the present state. The comparatively high standard deviation of the remaining volumes and densities (*cf.* Figure 1) are mainly due to uncertainties arising upon measuring the dimensions of the aerogels. Both, bacterial cellulose alcogels and aerogels are highly sensitive even to gentle pressure and thus difficult to handle.

As the porous system does not collapse upon drying, the full aerogel volume remains accessible to a rewetting solvent. During rewetting of highly porous and fragile materials, surface tension of the used solvent plays a decisive role for the dimensionally stability of the gel. It is known that forces alongside a capillary gradient adjacent to the solvent menisci can lead to capillary contraction and closure of the open pores resulting in inaccessible volume fractions of the gel.[22] However, in the case of bacterial cellulose aerogels even water does not significantly affect the pore structure which is most likely due to the high degree of polymerization and the comparatively high portion of crystalline domains typical for bacterial cellulose.

Figure 2 shows a bacterial cellulose alcogel prior to and after $scCO_2$ drying, and after rewetting with water. As mass and volume of the soaked samples equal those of the initial bacterial cellulose specimen before solvent exchange to ethanol, it can be concluded that $scCO_2$ dried bacterial cellulose aerogels can be fully rewetted without volume loss. Furthermore it implies that the full gel volume is accessible for the rewetting solvent which is a prerequisite to any material which is intended to be used as a controlled-release matrix. Incomplete rewettability and thus partial closure of the pore network upon rewetting would limit the release of an adsorbed bioactive compound and distort any release kinetics. Only if the full volume of the adsorbing matrix remains accessible, desorption of the active compound can be predicted using calculated release kinetics.

Both, the maintained full accessibility of the pore volume and the negligible shrinking upon rewetting render bacterial cellulose aerogels highly attractive for controlled release systems.

Loading of Aerogels with Bioactive Compounds

The principle of substances loading onto and releasing from bacterial cellulose aerogel matrices is shown in Figure 3. After solvent exchange from water to ethanol, the alcogels were placed into ethanolic solutions of L-ascorbic acid and dexpanthenol, respectively, and the solute starts to penetrate the gel pores driven by diffusion (step I in Figure 3).

Precipitation of CO_2-insoluble bioactive compounds inside the highly porous cellulose network (step II in Figure 3) can be realized using $scCO_2$ as an anti-solvent. According to Mukhopadhyay the solvent power of a mixture of solvent and supercritical CO_2 sharply decreases close to the critical pressure of the binary mixture at a given temperature and turns CO_2 to act as an anti-solvent.[23] For mixtures of CO_2 and

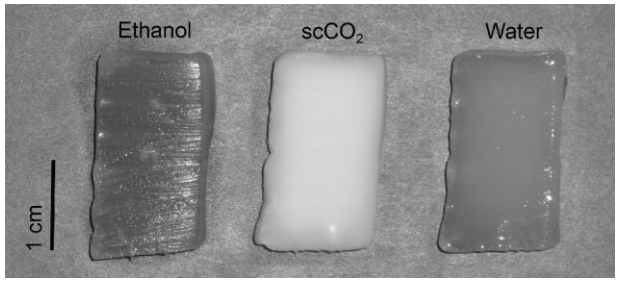


Figure 2.
$ScCO_2$ drying of a bacterial cellulose alcogel (left) and subsequent rewetting of the obtained aerogel (middle) with water (aquogel, right): The entire pore volume remains accessible for rewetting solvents after $scCO_2$ drying.

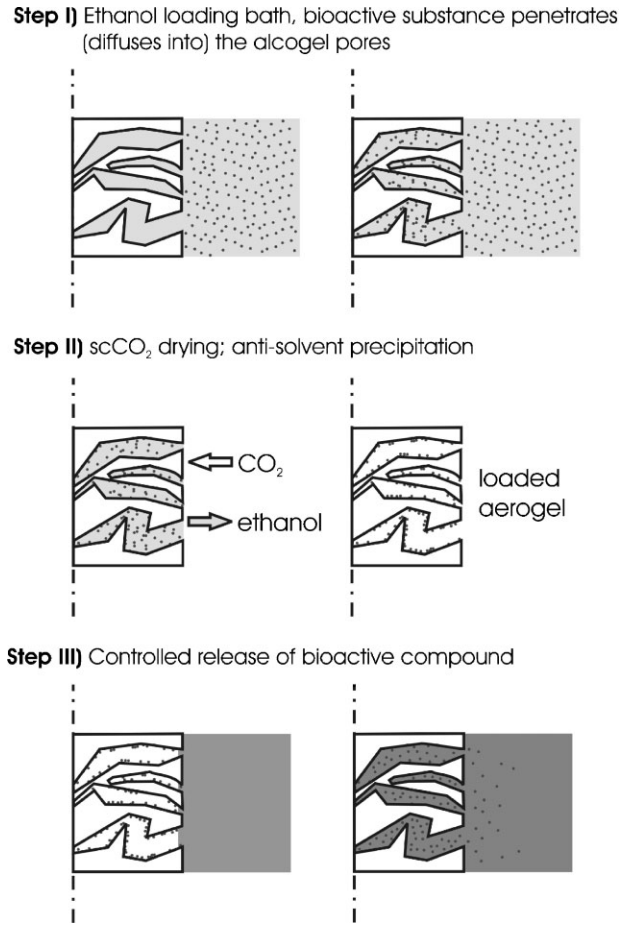


Figure 3.
Principle of loading (steps I + II) and releasing (step III) bioactive substances to and from a $scCO_2$ dried, highly porous bacterial cellulose aerogel matrix.

ethanol, the critical pressure is reached for 40 °C at 8 MPa[24] and further pressurization leads to solute precipitation inside the porous matrix. In the pressure range for precipitation, the interfacial tension between liquid and supercritical phase is reduced close to zero[25] which is a prerequisite for supercritical drying.[26] Thus, supercritical drying and supercritical anti-solvent precipitation require the same pressure and can be performed in parallel. This principle was used for loading bacterial cellulose alcogels with dexpanthenol or L-ascorbic acid and for subsequent preparation of $scCO_2$ dried aerogel matrices containing these bioactive compounds.

The correlation between solute weight fraction in the aerogel and solute concentration in the loading bath can be interpreted as sorption or loading isotherm. Figure 4 gives those isotherms for loading of dexpanthenol and L-ascorbic acid from ethanolic solutions onto bacterial cellulose. For both substances no saturation effects were observed. Even at very high solute concentrations close to the saturation limit of the solvent ethanol, the isotherms remained linear, which indicated that specific interactions between the solid matrix and the solute play a negligible role during loading, which is coherent, as loading is mostly achieved by filling the

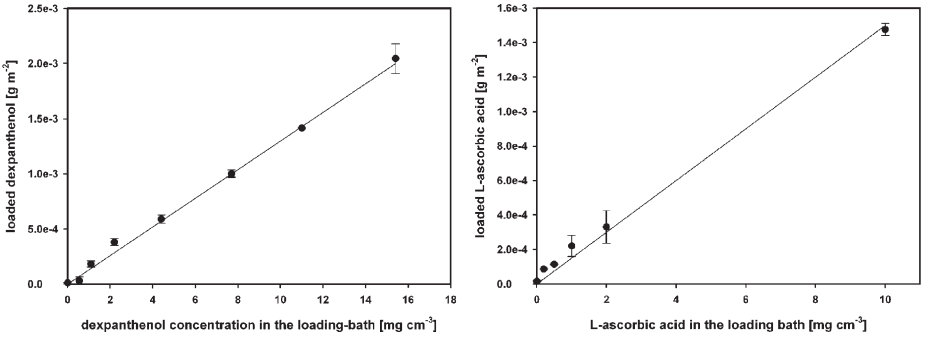


Figure 4.
Loading isotherms for dexpanthenol (left) and L-ascorbic acid (right) onto bacterial cellulose aerogels [n = 3].

pores with the solution and subsequent precipitation of the solute. This was further supported by the similar slopes of the loading isotherms.

Scanning electron microscopy (SEM) was applied to gain more information about microscopic changes of the solid matrix upon loading with dexpanthenol or L-ascorbic acid, and possible precipitation effects (e.g. formation of microcrystals or droplets) of the bioactive compounds (*cf.* Figure 5). Concerning the fibrous structure no significant differences between loaded and unloaded aerogels were found.

A strong tendency of bacterial cellulose to electrostatic charging has been reported recently.[4] This effect might explain the presence of some particles that could be seen in all SEM pictures and which are most likely dust particles adsorbed from the surrounding air.

Regarding the matrix properties upon loading, $scCO_2$ drying and rewetting it can be summarized that 1) the microstructure of the gels was not affected throughout the different process steps in terms of shrinking or swelling, and 2) the solute is assumed to be homogeneously distributed within the matrix as no accumulations (SEM) were visible. As the fundamental mechanism of loading is CO_2 induced precipitation, inhomogeneities of the solute distribution within the matrix may result from the CO_2 transport into the matrix upon pressurization. However, it is known that gas transport is comparatively fast and that supersaturation occurs also at pressures below the critical pressure of the binary mixture. Thus, the precipitation conditions are reached relatively fast.

A thin particle layer was observed at the surface of the loaded aerogels for L-ascorbic acid and high loading bath concentrations. Due to an increase of the volume of the liquid phase, a certain part of the pore solution is spilled out of the matrix and precipitation occurs at the surface of the gel. Nevertheless, as a first approximation it was concluded that the precipitate is homogeneously distributed within the aerogel and that drug release can be described by a lumped diffusion coefficient for each compound and is thus directly proportional to the thickness of the gel.

Release of the Adsorbed Active Substance

Figure 6 compares the dissolution kinetics in terms of the reduced compound concentration of the pure compounds with their release kinetics from the loaded bacterial cellulose aerogels. The reduced compound concentration is obtained by relating the compound concentration to the compound concentration in equilibrium. It is evident from the data that the dissolution (release) of the same compounds when loaded onto bacterial cellulose aerogels is significantly delayed. The graphs in Figure 6 are very similar to the typical exponential curves which result from a purely diffusion driven release kinetics which would be independent of the amount

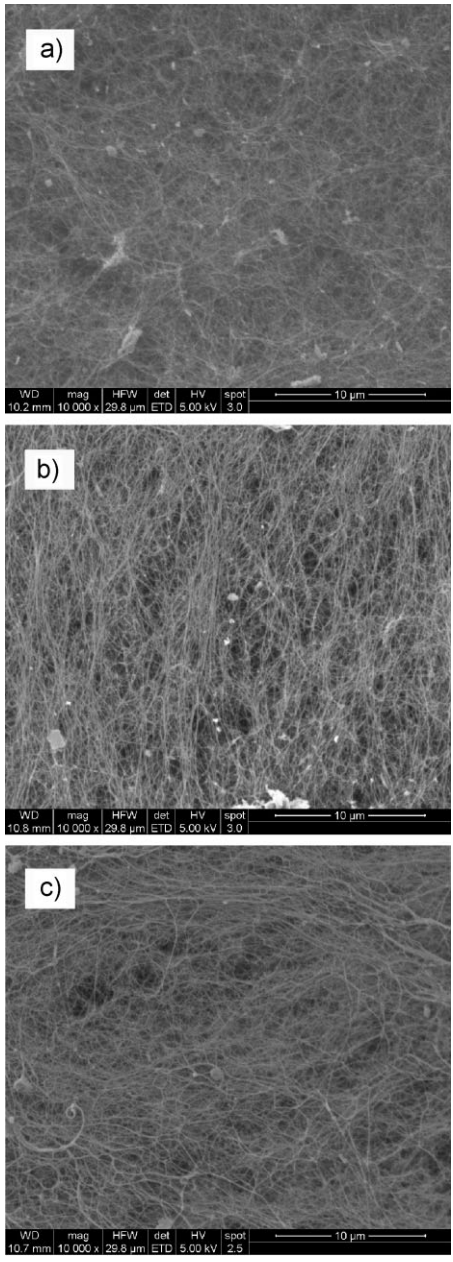


Figure 5.
SEM images of bacterial cellulose aerogels prior (a) and after loading with L-ascorbic acid (b) and dexpanthenol (c).

of loaded substance.[27] Thus, the release profiles are also similar for aerogel layers of comparable thickness. Differences in the release behavior (error bars in Figure 6) are mainly due to the fragile nature of bacterial cellulose aerogels which render each physical measurement a challenging task and thus that of geometrical shape, too.

The release kinetics can be adjusted to a large extent by varying the thickness of the gel layer (Figure 7). Therefore, bacterial cellulose aerogels seems to be a promising matrix material for controlled release applications. As the amount of loaded compound does not interfere its unloading by formation of stronger intermolecular forces to the cellulosic matrix, e.g., release kinetics as well as the resulting concentrations in the liquid phase can be varied independently.

The release profiles from gels of different thicknesses were compared with the model of Korsmeyer. Korsmeyer et al. proposed a mechanistically realistic mathematical model allowing for simultaneous consideration of the diffusion of water into an open-porous matrix and of a given organic compound out of it.[21] Polymer swelling has to be considered in most cases, too, but can be neglected for bacterial cellulose aerogels (*cf.* Figure 2).

Water diffusion can be described using Fick's second law for non-steady diffusion for the one-dimensional case

$$\frac{\partial c_{water}}{\partial t} = \frac{\partial}{\partial x}\left(D_{eff,water}\frac{\partial c_{water}}{\partial x}\right) \quad (1)$$

using a time and location independent effective diffusion coefficient $D_{eff,water}$ to describe diffusion of water inside the matrix. This coefficient can easily be estimated by suspending an aerogel sample into water and subsequently recording the mass of the rewetted aerogel with respect to its residence time t in the bath. According to this approach, a $D_{eff,water}$ of $5 \cdot 10^2\,cm^2\,min^{-1}$ was calculated. This value is assumed to be independent on the desorbing compound. The diffusion length x equals half the thickness of the gel and c_{water} is the reduced water concentration:

$$c_{water} = \frac{c_w}{c_{w,eq.}} \quad (2)$$

Here, c_w is the water concentration inside the matrix at a particular position,

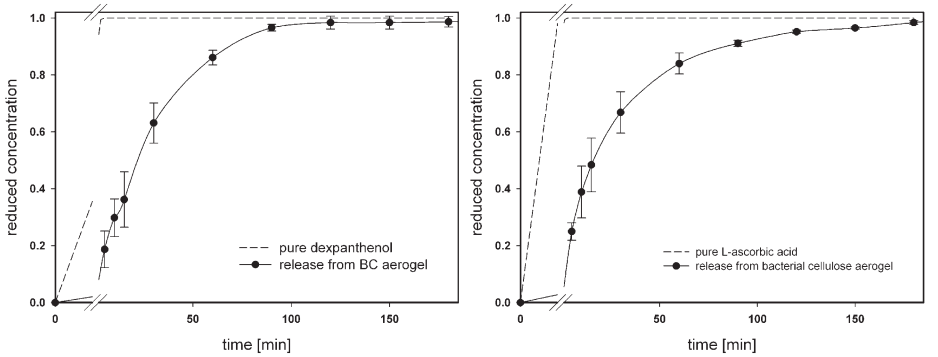


Figure 6.
Dissolution kinetics of pure dexpanthenol (left) and L-ascorbic acid (right) in water, compared to their release kinetics from loaded bacterial cellulose aerogels into water (25 °C) [n = 3].

and $c_{w,eq.}$ is the equilibrium water concentration of the system. The boundary and initial conditions which have to be considered for water diffusion are provided in equations 3–5.

$$c_{water}(x = l, t) = c_{water}(x, t = \inf) = 1 \quad (3)$$

$$c_{water}(x, t = 0) = 0 \quad (4)$$

For reasons of symmetry at the symmetry axis no flux occurs.[27]

$$\frac{\partial c_{water}}{\partial x}(x = 0) = 0 \quad (5)$$

After reaching a defined water content within an element of the matrix (0.5 in our case), diffusion of the loaded solute out of the matrix starts which can be described similar to water diffusion as:

$$\frac{\partial c_{drug}}{\partial t} = \frac{\partial}{\partial x}\left(D_{eff,drug}\frac{\partial c_{drug}}{\partial x}\right) \quad (6)$$

$D_{eff,drug}$ is the effective diffusion coefficient of the solute for the respective release system. Further parameters are the diffusion length x and the reduced solute concentration c_{drug} :

$$c_{drug} = \frac{c_d}{c_{d,eq.}} \quad (7)$$

Here c_d is the drug concentration in the matrix at a particular position, and $c_{d,eq.}$ is the equilibrium drug concentration in the system. For solute diffusion the following boundary conditions and initial conditions

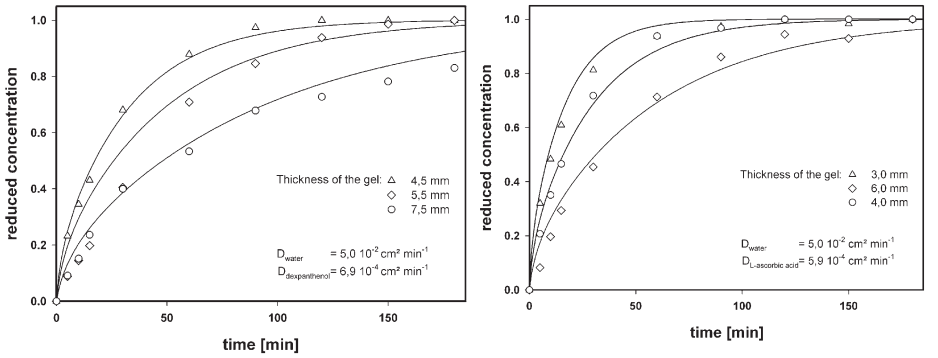


Figure 7.
Dexpanthenol (left) and L-ascorbic acid (right) release from loaded bacterial cellulose aerogel matrices of different layer thickness: Experimental values and mathematical model.

were considered (eq. 8–10):

$$c_{drug}(x = l, t) = c_{drug}(x, t = \inf) = 0 \quad (8)$$

$$c_{drug}(x, t = 0) = 1 \quad (9)$$

$$\frac{\partial c_{drug}}{\partial x}(x = 0) = 0 \quad (10)$$

The obtained set of partial differential equations was solved numerically according to the method of explicit finite-differences for discretization of the diffusion length.[27] The resulting ordinary differential equations were solved by the Runge Kutta method.

The initial drug concentration c_{drug} within the solid matrix can be correlated with the drug concentration in the loading bath via the loading isotherm which makes the proposed model suitable for performing release predictions from bacterial cellulose aerogels, just by adjusting only one parameter, namely $D_{eff,drug}$. Figure 7 shows the application of the model to the release of the two model compounds dexpanthenol and L-ascorbic acid from bacterial cellulose aerogels of different thicknesses.

The data obtained for the gel layer of 4.5 mm thickness was used to determine the diffusion coefficient of dexpanthenol ($D_{dexpanthenol}$) which exclusively determines the rate of the matrix unloading and dexpanthenol releasing step, respectively. The effective diffusion coefficient of dexpanthenol was found to be $6.9 \cdot 10^{-4}\,cm^2\,min^{-1}$. Applying the model using the calculated diffusion coefficient, release profiles for gels of 5.5 mm and 7.5 mm thickness were predicted and compared with the obtained experimental data. The good agreement between the theoretical values and experimental data was a solid proof for the suitability of the model used. Moreover, it was confirmed that no specific interaction between dexpanthenol and the cellulose matrix existed. By considering only diffusion of the solvent into and the solute out of the matrix, the release profiles were correctly predicted. For L-ascorbic acid, similar results were obtained (*cf.* Figure 7, right). In this case, the measured release kinetics for a gel layer of 3 mm thickness was used for determining $D_{L\text{-}ascorbic\ acid}$, which was found to be $5.94 \cdot 10^{-4}\,cm^2\,min^{-1}$. Also for L-ascorbic acid, the mathematical model was used for predicting the release profiles for gel layers of different thickness reasonably well.

A comparison of the calculated effective diffusion coefficients for the two model compounds revealed that L-ascorbic acid is slower released from the aerogel matrix than dexpanthenol.

Conclusion

In the present work, the usability of $scCO_2$ dried bacterial cellulose aerogels as controlled-release matrices was investigated, and their suitability for this purpose was unambiguously proven. The aerogels were loaded with bioactive compounds during the $scCO_2$ drying step according to the supercritical antisolvent precipitation concept. No capacity limitations were observed for the investigated compounds dexpanthenol and L-ascorbic acid, two substances chosen for their wide application scope and action profile. Loading of the gels was found to depend directly on the solute concentration in the loading bath. It is evident from the calculated loading isotherms that the loading rate is independent on the type of compound which is loaded onto the matrix for supercritical CO_2 antisolvent precipitation. Also there is no evidence from the release behavior of the investigated compounds for a specific interaction between the matrix and the loaded bioactive compounds. The release profile was found to be independent on the amount of loaded compound and highly dependent on the thickness of the aerogel layer.

A model considering both, simultaneous solvent diffusion into the gel pores and solute diffusion out of it was successfully applied to predict release kinetics for different aerogel thicknesses. By adjusting only one parameter, namely the effective diffusion coefficient of the solute, release kinetics can be predicted.

Unlike the loading process, release was found to be dependent on the type of loaded compound.

It was shown, that $scCO_2$ dried bacterial cellulose aerogels are suitable and easy to model controlled release matrices. Depending on the type of application, the matrices can be reloaded after releasing the bioactive compound. Due to the high dimensional stability of bacterial cellulose aerogels throughout the different process steps and the quantitative rewettability, bacterial cellulose as a comparatively cheap and biodegradable natural polymer is expected to get increasingly spotlighted by drug delivery application.

Studies of the loading and releasing behavior of other compounds will provide further insight into the potential of bacterial cellulose aerogels as controlled-release matrices. Exact modeling of the release process, such as by using a more refined model that considers specific interactions between matrix and bioactive compound, too, is subject to further investigations.

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