Ultra High Resolution Imaging for Permeability and Stability Measurements of Microcapsules for Controlled Drug Delivery

Stefan Henning[1], Daniel Edelhoff[1], Sabine Leick[2], Heinz Rehage[2], and Dieter Suter[1]
[1]*Exp. Physics III, TU Dortmund, Dortmund, Germany,* [2]*Physical Chemistry II, TU Dortmund, Dortmund, Germany*

Introduction: Microcapsules consisting of natural polysaccharide hydrogels such as alginates or pectinates have a large potential as carriers for liquid drugs [1,2]. If a controlled and site specific release of the encapsulated drugs in the colon is desired, they must be stored sufficiently long under variable environmental conditions. We optimize the capsules with respect to the retention time of the encapsulated drugs and the chemical stability under gastrointestinal conditions. To achieve this, we apply an external coating with the natural resin shellac [3]. Here, we show how the shellac coating reduces the permeability of the capsule membrane using MR microimaging for the visualization and quantization of the diffusion of MRI contrast agents. By combining these measurements with numerical simulations of the diffusion, we can obtain diffusion coefficients of different molecules in different membrane materials. The stability of the capsules under simulated gastric and intestinal conditions is also studied by the application of microscale FLASH imaging. With this technique we can measure if the capsules remain stable under gastric conditions and dissolve in intestinal media.

Materials and Methods: We use a 14 T NMR spectrometer equipped with a 1 T/m gradient unit to acquire images with a spatial resolution of the order of 10 µm. For each measurement of the permeability, a capsule with a diameter of approximately 1 mm was placed in a 5 mm outer diameter NMR tube containing a susceptibility plug (stabilization of capsule position) and an aqueous solution of the contrast agent (Cu^{2+} or Gd-DTPA). T_1-weighted images were acquired with a spin echo sequence as a function of time thus giving signal amplitudes depending on the contrast agent concentration in each voxel. In order to measure the capsule stabilities, differently prepared capsules were placed into solutions with a pH similar to gastric or intestinal conditions. Images of the capsules in the solution were acquired with a FLASH sequence again as a function of time. Acquisition of the images took about 1 minute for permeability and stability measurements leading to a time resolution of 1 minute.

Results and Discussion:

Permeability: Fig. 1 shows exemplary images of permeability measurements. In the first image, the signal arising from the liquid core of the capsule is very weak due to low contrast agent concentrations and therefore long relaxation times. As time increases, the contrast agent diffuses into the capsule and leads to stronger signals from the liquid capsule core. By measuring the concentration dependence of relaxation times and knowing the dependence of the signal amplitude on imaging parameters and relaxation times, we are able to calculate the concentration in each voxel. Fig. 2 shows the measured concentration inside the capsule depending on the time and the distance to the capsule center. In combination with a numerical solution of Fick's 2nd law (fig. 2 right hand side), we can determine diffusion coefficients for different contrast agents in different capsule membrane materials. Shellac coated capsules showed a significantly lower diffusion coefficient ($0.8 \cdot 10^{-10}$ m^2/s) than pure pectinate capsules ($1.8 \cdot 10^{-10}$ m^2/s) for both Cu^{2+} and Gd-DTPA as contrast agent.

Capsule Stability: Images of differently prepared capsules were obtained with a FLASH sequence. We observed that all coated capsules do not show structural changes in acidic media simulating the stomach (pH = 1.2) and small intestine (pH = 6.8), whereas they dissolve in basic media simulating the colon (pH = 7.4). Fig. 3 shows images of two capsules in colon simulating solution at different times in the dissolution process. They first swell due to the basic environment and break after some time. We could optimize the capsule production process regarding the dissolution time and achieved dissolution times of about 50 minutes.

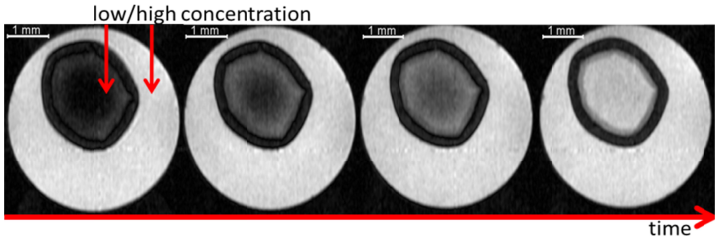

Figure 1: MR images of a contrast agent diffusing into a microcapsule leading to time dependent signal amplitudes within the capsule core.

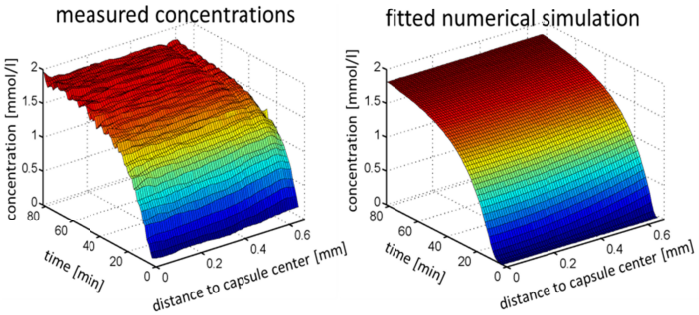

Figure 2: Calculated concentrations of contrast agent in the capsule depending on time and distance to the center of the capsule and numerical simulation of the concentration used for obtaining diffusion coefficients.

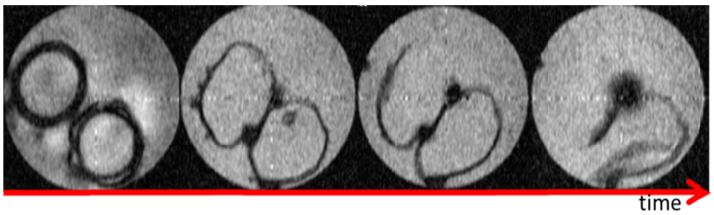

Figure 3: Time dependent MR images of microcapsules swelling and dissolving under simulated intestinal conditions.

Conclusion: NMR microscopy is an excellent tool for investigating the permeability and function of small drug carriers. We showed that diffusion coefficients of contrast agents in microcapsules can be obtained and that shellac coatings significantly decrease the permeability of pectinate microcapsules. Furthermore, we can also observe dissolution processes of the capsules which helps to characterize their functionality.

References:

[1] Leick et al. Phys Chem Chem Phys 2011;13:2765 [2] Champagne et al. Curr Opin Biotechnol 2007;18(2):184 [3] Henning et al. J Microencaps 2011 (in press)