Quantification of skin penetration with contrast-enhanced MRI at 7T

Maximilian N. Voelker[1], Jan M. Burg[2], Peggy Schlupp[3], Ulf Maeder[2], Alexander M. Koenig[1], and Johannes T. Heverhagen[1]
[1]*Diagnostic Radiology, Philipps University, Marburg, Hessen, Germany,* [2]*Institute of Medical Physics and Radiation Protection, University of Applied Sciences Giessen-Friedberg, Giessen, Germany,* [3]*Institute of Biopharmaceutical Technology, University of Applied Sciences Giessen-Friedberg, Giessen, Germany*

Hypothesis:
Using a submicron emulsion as a carrier system, the penetration of MRI contrast agents into the skin can be measured directly by MRI. The efficiency and the dynamics of a Drug Carrier System on the penetration of a topically applied contrast agent can be quantified.

Methods:
Penetration studies according to OECD guidelines [1] were performed using skin samples taken from porcine ears. To enhance the transport of the contrast agent into the skin, a submicron emulsion containing different concentrations (0.1 and 0.5mmol/ml) of Gadolinium (Gadobutrol, Gadovist, Schering, Germany) was used. The experiments were performed using the Franz-Diffusion-Cell setup, a standard device for in vitro penetration studies. The penetration was done for 6h respectively 24h followed by deep-freezing of the skin samples.
In vitro MRI was performed on a 7T small animal scanner (Clinscan, Bruker, Ettlingen, Germany). A Bruker mouse head phased array coil (2x2) was used for imaging the skin samples. High resolution (55 x 55 x 400µm) T1-weighted TSE- sequences (TR: 600ms, TE: 11ms) were used for imaging the skin and assessing contrast agent penetration. TIR-sequences (TR: 5000ms, TE: 7ms, 200 x 200 x 500µm) with 6 Inversion times (31, 100, 250, 500, 750 and 1000ms) were used for measuring T1-Relaxation and contrast agent quantification. T1-Relaxivity of Gadobutrol was calculated from concentration dependent modified TIR-Sequences (TR: 7 - 16s, TE: 7ms, 8xTI: 31 - 7500ms). 9 different concentrations (0 - 10 µmol/ml) of the contrast agent were measured for precise assessment of T1-Relaxivity. One region of interest (ROI) was drawn for each of epidermis (0.1 – 0.2 mm deep), outer dermis (0.6 – 0.7 mm deep) and inner dermis (0.9 – 1.0 mm deep). T1 and contrast agent uptake were calculated in the different skin layers by using common linear model of Relaxivity (r): $r_1 = \left(1/T_1(c) - 1/T_1(0)\right)/c$ [2].

Results:
The T1-Relaxivity measurement of Gadobutrol shows very high linearity (R^2=0.996) and small standard error (R_1= 4.6 ± 0.1 l/mol*s; see fig. 1) allowing a precise assessment of contrast agent uptake in skin samples. Quantification of T1- shortening in skin samples shows a significant difference between different concentrations of contrast agent and penetration time (Fig.2). The uptake of Gadobutrol demonstrates a clear gradient from the outer to the inner skin layers allowing assessment of penetration depth over time (Fig. 2).

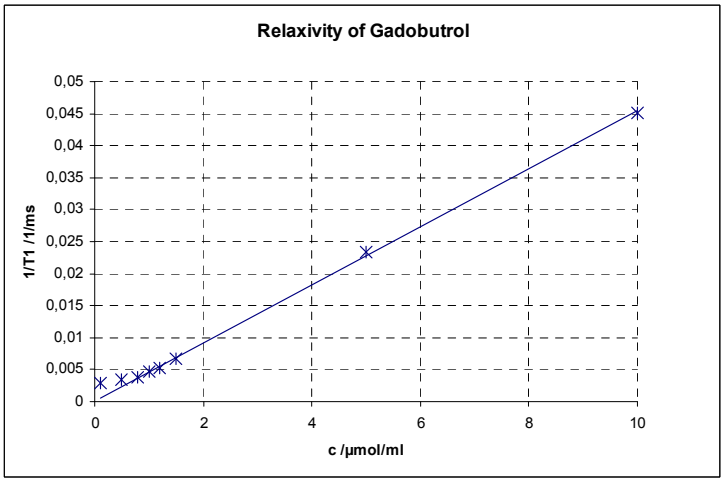

Fig.1: T1-Relaxivity of Gadobutrol for measurement setup. Measured T1- values over contrast agent concentration give the T1-Relaxivity as the slope of the linear regression

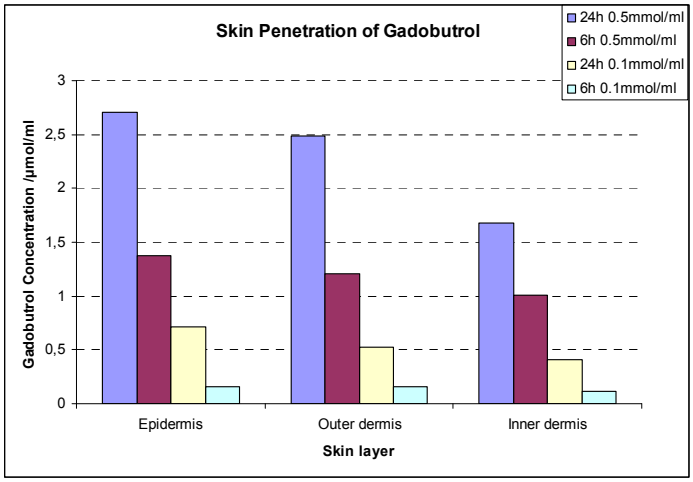

Fig.2: Skin penetration of Gadobutrol: Contrast agent concentrations are calculated for every skin layer at different penetration times and concentrations in applied emulsion.

Discussion:
Contrast enhanced MRI is a new tool for quantification of skin penetration by drug carrier systems like a submicron emulsion. The submicron emulsion is a suitable carrier system for facilitating the Gadobutrol transport into the skin. The influence of other drug carrier systems on the penetration performance of contrast agents and potential penetration enhancers, such as DMSO [3], should also be compared to the submicron emulsion.
The T1-Relaxivity is comparable to measurements in standard setup for 7T [2] and quantification can be done very precise by measuring the T1-Relaxivity of the contrast agent for measurement setup.
Compared with common optical and analytical assessment of skin penetration [3] contrast enhanced MRI has the advantages in unlimited imaging depth and easy and precise quantification but also a smaller resolution.

References:
[1] OECD Guideline 428 (2004) Guidance Document on Dermal Absorption. Skin Absorption: In Vitro Method. http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc20_rev_en.pdf.
[2] Noebauer-Huhmann I. (2010) Gadolinium-Based Magnetic Resonance Contrast Agents at 7 Tesla: In Vitro T1 Relaxivities in Human Blood Plasma, Investigative Radiology; 45, 9: 554-558.
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