Visualization of Drug Dissolution using ^{19}F-MRS and -MRI

Janet Friedrich[1], Julia Schröder[1], Sarah Kindgen[2], Stefan Fischer[1], Mark Schuppert[1], Karsten Gogoll[2], Peter Langguth[2], and Laura Maria Schreiber[1]
[1]*Department of Radiology, Johannes Gutenberg University Medical Center, Mainz, Germany*, [2]*Institute of Pharmaceutical Technology and Biopharmacy, Johannes Gutenberg University, Mainz, Germany*

Introduction

Oral applications represent one of the most important ways for administration of active pharmaceutical ingredients. Tablets and capsules are most widely used. A lot of techniques have been developed to investigate the dissolution and release mechanisms of these dosage forms (e.g. ultrasonic and magnetic marker monitoring). Up to now, ^{1}H MRI using super paramagnetic and paramagnetic substances is the only method that is capable of combining noninvasive, radiation free examination while accounting for ingestion and aliment composition as well as for complementary anatomical information. A main disadvantage of the indirect contrast agents is the low contrast enhancement in comparison to surrounding tissue and intra luminal content. The aim of the current work is the development of a new MRI technique that allows for the investigation of dissolution and the release behavior of different drug forms. The present work includes the exploration of two fluor containing substances and the development of an optimized MR coil.

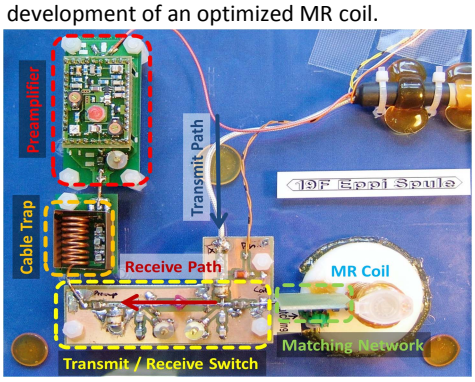

FIG. 1: Outline of the home-made ^{19}F-solenoid-coil.

Material and Methods

All measurements were performed on an 1.5T MRI system (Siemens, Magnetom Avanto, Erlangen, Germany). Perfluoro crown ether emulsion (PFCE-emulsion) and fluor tablets (Fluoretten 0.5 mg, Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany) were investigated using a purpose-built, home-made transmit/receive ^{19}F-solenoid-coil (c.f. FIG 1). It was optimized for a 1.5-mL-microcentrifuge-tube and had a diameter of 13mm and a length of 40mm. The signal of 10 fluor tablets was observed for 15 minutes during the dissolving process in 1 mL water. One minute after adding the water a spectrum was acquired every two minutes. Perfluoro crown ether was encapsulated with alginate. The small pellets had a diameter of 4 mm. T_1 and T_2 relaxation times were determined utilizing an inversion recovery sequence and a spinecho sequence, respectively. A gradient echo sequence was used to image the substance (FA/TE/TR: 15°/10 ms/100 ms; averages: 10; Matrix: 128 x 128).

Results

The ^{19}F-solenoid-coil and the transmit/receive paths are shown in in FIG. 1. It had a quality ratio of $Q_{unloaded}/Q_{loaded}$ of 290/176 = 1.65 when loaded with a 1.5-mL-microcentrifuge-tube filled with pure water containing 1.25 g $NiSO_4$ x $6H_2O$, 5 g NaCl per 1000 g H_2O. The temporal dissolution process is depicted in FIG. 2a. The measurement of dry fluor tablets at t = 0 min showed no signal. Instantaneously after adding water the ^{19}F signal intensity increased and showed an exponential behavior. A time constant $\tau = 2.8 \pm 0.3$ min of the release process of the ingredient was determined. Furthermore, PFCE-emulsion alginate was successfully produced and imaged with high signal intensity (c.f. FIG. 2c). Relaxation times could be determined ($T_1 = 1618 \pm 3$ ms; $T_2 = 851 \pm 2$ ms).

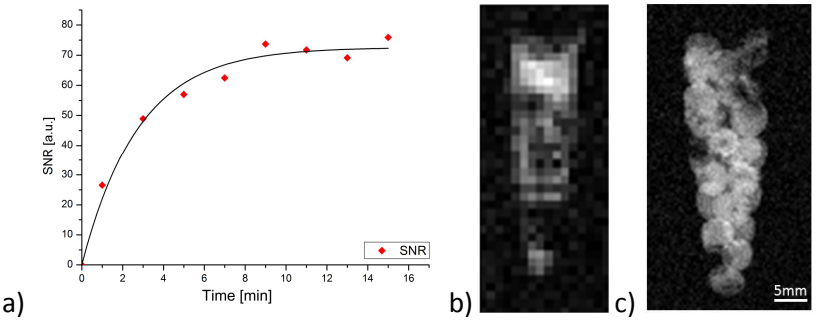

FIG. 2: a) Signal development of fluor tablets during the dissolution determined by MRS. b) Gradient echo image of fluor tablets dissolved in water. c) Gradient echo image of PFCE-emulsion alginate pellets.

Discussion

The present results show that it is possible to investigate the dissolution and release processes of fluorinated ingredients in tablets and capsules by using an optimized MR coil. The solenoid coil yielded a homogenous RF transmission and signal detection throughout the whole measurement volume. Thus, the dissolution process of commercially available fluor tablets could be visualized and characterized. Furthermore, PFCE-emulsion-alginate was exemplarily imaged and the relaxation times were determined.

In conclusion, this work shows that it is possible to visualize the dissolution process of fluorinated ingredients in vitro. To cover the whole gastrointestinal tract of humans with high sensitivity a phased array coil [1] would be the next approach for in vivo measurements [2]. Since the ^{19}F concentration in the human body is low images can be acquired with no background noise. By using a double resonant full body ^{1}H/^{19}F RF coil the complementary anatomical information could be acquired additionally.

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References

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