Drug Dissolution: Investigation of Different Fluor Containing Substances using ^{19}F-MRI

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Introduction:

Several techniques have been developed to investigate the transit and dissolution of oral application forms like tablets or capsules in the gastrointestinal tract (e.g. ultrasonic and magnetic marker monitoring). Yet another promising method is MRI of fluor containing substances. It was already shown that the visualization of perfluorocarbone and the determination of gastrointestinal transit times are feasible[1,2]. The aim of the present study is the development of an MRI technique that allows for in vivo investigation of oral applied pharmaceutical substances. Therefore, different fluor containing substances were analyzed with regard to relaxation times and signal quality. First measurements with tablets that contained perfluoro-15-crown-5-ether and a semifluorinated alkane were performed.

Methods:

All measurements were performed on a 1.5T MRI system (Siemens, Magnetom Avanto, Germany) using a purpose-built, home-made ^{19}F transmit/receive coil. It was optimized for a 1.5-mL-microcentrifugetube. The investigated substances were perfluoro-15-crown-5-ether (PFCE, ChemPur, Germany), PFCE-emulsion (40% wt/wt PFCE), commercially available toothpaste jelly (contains: NaF, $C_{27}H_{60}F_2N_2O_3$ and $C_{18}H_{38}FN$, GABA GmbH, Germany) and two novel semifluorinated alkanes (SFA) in the following referred to as SFA1 and SFA2. Further, specimens containing SFA (1.5 mL) mixed with 30 µL Gd-DOTA, a specimen containing SFA2-emulsion (40% wt/wt) and a specimen containing SFA2-gadolinium-emulsion (4.5 mM Gd-DOTA) were prepared. Spectroscopic saturation recovery sequence and spin echo sequence were utilized to determine T_1 and T_2 of all substances, respectively. Spectra and images were acquired using a FID-sequence and a gradient echo (GRE-) sequence. In addition, a porous SFA2 and a PFCE loaded tablet were imaged using a GRE-sequence and a TrueFISP-sequence, respectively.

Substance	T_1 [ms]	T_2 [ms]	^{19}F-atoms per 1.5 mL [$\cdot 10^{21}$]	Peaks in spectrum
PFCE ($C_{10}F_{20}O_5$)	933 ± 3	719 ± 3	55	1
PFCE-emulsion	1155 ± 30	538 ± 5	13	1
Jelly	422 ± 19	135 ± 2	<1	1 (4)
SFA1	1629 ± 49	156 ± 35	36	4
SFA1 + Gd	1635 ± 35	153 ± 26		
SFA2	940 ± 6	150 ± 10	36	5
SFA2+ Gd	922 ± 10	126 ± 11		
SFA2-emuls.	896 ± 39	90 ± 7	11	
SFA2-Gd-emuls.	883 ± 18	22 ± 2	11	

TAB.1: T_1 and T_2 relaxation times, amount of fluor atoms and the amount of detected peaks in the spectra of the investigated substances.

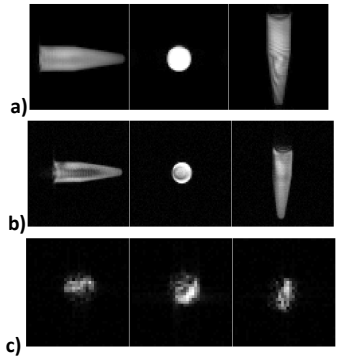

FIG.1: Images of PFCE and SFA2 in a 1.5-mL-centrifuge-tube with a resolution of 0.6x0.6 mm. a) PFCE (SNR = 430), b) SFA (SNR = 50) and c) SFA2 loaded tablet (SNR = 25).

Results:

All substances provide an MR measurable signal (c.f. FIG.1). The pure PFCE yielded high signal intensity in short measurement times (seconds) without signal averaging. The jelly offered poor signal in comparison to PFCE substances and SFA. The relaxation times are listed in TAB.1. A significant influence of Gd-DOTA on the relaxation times of the pure SFA was not observed. The emulsion of SFA2 has a slightly shorter T_1 in comparison to the pure SFA2, but the difference is not significant. T_2 in comparison is considerably shortened. While the spectra of PFCE and the PFCE-emulsion showed only one resonance peak the jelly spectrum consists of at least four peaks that agglomerate to one broadened peak. In contrast, the resonance peaks of SFA1 and SFA2 separate in four and five peaks, respectively while one peak is clearly separated from the others (see exemplarily FIG.2). Tablets containing SFA2 and PFCE were successfully prepared and imaged (see FIG.1 c).

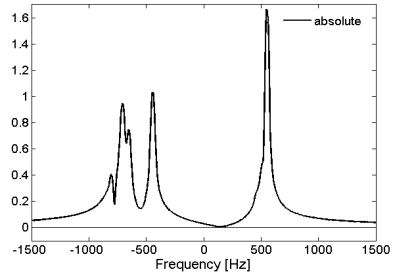

FIG.2: Spectrum of the SFA2 loaded tablet.

Discussion:

In this study we investigated different ^{19}F containing substances. Due to the small amount of ^{19}F-atoms inside the measured volume the jelly yielded the lowest signal intensity. A higher concentration of ^{19}F containing substances within the jelly may overcome this problem but would increase the toxicity of the jelly. The SFA were identified as the most advantageous substances for further studies of the dissolution process of oral application forms. Indeed PFCE provides high signal intensity but is hydro- and lipophobic and therefore its molecules would rather agglomerate than distribute within an examined volume. Therefore, PFCE needs to be emulsified. The SFA are biological inert and possess both a hydrophilic and a lipophilic character which makes them attractive for the use with other pharmaceutical substances. Here, first successful trials of imaging tablets loaded with pure SFA2 and PFCE are presented.

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References: [1] Hahn T., et al., Magn Reson Med 2011;66(3):812-820, [2] Schwarz R., et al., Magn Reson Med 1999;41(1):80-86