Towards novel contrast agents for bowel imaging based on ^{19}F compounds

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Introduction

Contrast agents based on fluorine (^{19}F) compounds have several advantages over T1 or T2 based contrast agents. Since ^{19}F does not occur naturally in the human body, the ^{19}F agents have a high intrinsic specificity and there is no need for pre-contrast imaging. The use of perfluorocarbon (PFC) emulsions as ^{19}F contrast agents has been studied before[1]. Here we show the use of non-targeted polymeric micro-capsules for bowel imaging. These particles have the advantage that they are expected to be more stable, and hence, more suitable for applications in the bowel. For the detection of the fluorine compounds we already demonstrated the advantages of the Fluorine ultrafast Turbo Spectroscopic Imaging (F-uTSI) sequence[2,3]. The sequence can be applied to any PFC compound and can also be used to distinguish between different compounds, thereby allowing for multi-color imaging[4]. We have already demonstrated that these micro-capsules can be targeted towards human EGFR and that they bind to human cancer cell lines[5,6].

Methods

Polymeric microcapsules were prepared by a modified solvent emulsification-evaporation process in order to obtain core-shell microcapsules encapsulating perfluorooctyl bromide (PFOB)[7]. The microcapsules were physico-chemically characterized and the encapsulated amount of PFOB was quantified by ^{19}F NMR. All animal experiments were conducted on black mice (C57BL/6) in accordance with guidelines. For anesthesia, an intra-peritoneal (IP) injection of KMA mix (Ketamine 75 mg/kg; Medetomidine 1.0 mg/kg; Atropine 0.04 mg/kg) was used. During *in-vivo* scanning the anesthesia was maintained by continuous IP infusion of the KMA mix. In all experiments a solution (0.3% v/v) of non-targeted microcapsules was given orally. ^{19}F spectroscopic imaging was performed on a 3T whole-body MRI scanner (Achieva, Philips Healthcare) and equipped with dual ^{19}F/^{1}H capabilities. ^{19}F ultra-fast Turbo Spectroscopic Imaging (F-uTSI)[2,3] was used to acquire a 3D data set with a resolution of 48x48x12 and an isotropic voxel size of 2 mm. The TR/TE/ES were 284/5/5 ms, NSA: 2, and a scan-time of 11 min. Spatial reconstruction was done using the standard software available on the scanner. These data were exported and ^{19}F images were created by integrating the signal intensity of the $-CF_2$ resonances, using the 3DiCSI software package. The anatomical ^{1}H images were recorded with a gradient echo sequence; the in-plane resolution is 0.2x0.2 mm and a 2 mm slice thickness; TR/TE = 180/4.6 ms; scan-time 6 minutes. We detected the ^{19}F signals *in-vivo* (n=2), oral administration was done at several time points with a maximum 400 µl. In order to assess the transit time after oral ingestion (400 µl), animals (n=9) were sacrificed at different time points: 2, 4, 6, 8 14, 24 and 48hrs after administration. Post-mortem ^{19}F images were obtained using a 3D F-uTSI sequence, with a 32x23x31 resolution. In all animals, the GI tract was removed after euthanasia and imaged separately using a 2D F-uTSI scan with a 32x32 resolution. Organs were collected for further chemical analysis.

Results and Discussion

The *in-vivo* data obtained 4 hrs after oral administration is shown in fig 1. The ^{19}F signals could be detected in the bowel of this animal. The post mortem images of the GI tract showed that most of the agents have reached the cecum(fig. 2). The transit time study showed that the agent reached the cecum within 4 hrs of administration. Furthermore, time to evacuation was more than 8 hrs but less than 14 hrs.

Conclusion

Polymeric microcapsules can be developed into promising ^{19}F-MRI contrast agents for bowel imaging using ^{19}F spectroscopic imaging methods. The bowel transit time of these agents is around 10 hrs in black mice.

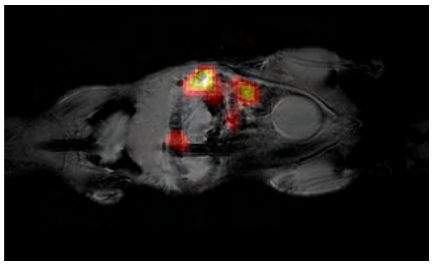

Figure 1. *In vivo ^{19}F image taken 4 hrs after oral administration. The ^{19}F image is overlaid on a proton anatomical image*

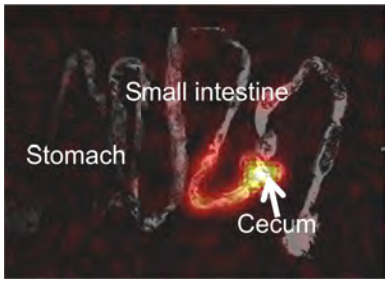

Figure 2*. Ex-vivo ^{19}F image of the GI tract of the same animal shown in figure 1. The image shows that most of contrast agent has reached the cecum*

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