Gastrointestinal Transit of Pharmaceutical Capsules Observed with ^{19}F-MR Projection Imaging in Man

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INTRODUCTION

Gastrointestinal dwell- and transit times have been recognised as crucial factors for the oral drug administration of solid dosage forms since precise knowledge of the anatomical location of drug release *in situ* allows the pharmaceutical potential of oral drugs to be maximised. A variety methods have been applied for assessing gastrointestinal transit times, motility, and drug release. Orally ingested capsules containing radio-opaque material or gamma emitters have been followed by X-ray (1) and scintigraphic techniques (2). Non-invasive techniques such as ultrasound (3), metal detectors (4), and magnetic field detectors (5) have been used to avoid the adverse effects of ionising radiation. However, the use of all these methods has been severely restricted due to intrinsic constraints such as low temporal or spatial resolution, the lack of complementary anatomical information, or spatial information limited to two dimensions only. In contrast, MRI-techniques would offer a convenient non-invasive modality for monitoring gastrointestinal transit. However, ^{1}H-MRI has generally failed in tracing small objects in the bowel due to large and intricate local signal changes. Specific tagging of pharmaceutical capsules with conventional contrast agents has not mitigated this latter problem. Conversely, ^{19}F-MRI of fluorinated agents has provided excellent selective contrast in images of the murine gastrointestinal tract (6,7). In the present work, the concept of ^{19}F-markers has been expanded to the assessment of oral drug delivery of solid dosage forms by ^{19}F-MR. Here, we demonstrate the potentiality of ^{19}F-MR projection imaging of pharmaceutical capsules filled with a bio-compatible perfluorocarbon for monitoring gastrointestinal transit in man.

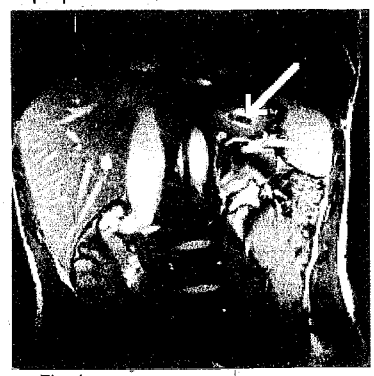

Fig. 1

MATERIALS AND METHODS

For the gastrointestinal examinations, a pharmaceutical capsule (Lilly size 0, 7*22 mm, made of polychlortrifluorethylene (PCTFE)) was filled with 350 µl of perfluorononane (C_9F_{20}). A male volunteer who had fasted overnight ingested the capsule while lying inside the magnet. The abdominal region was assessed continuously with ^{1}H- and ^{19}F-MR over seven periods of 30 min duration starting immediately before and at 1¾, 3¼, 5, 10½, 55, and 75 h after the ingestion of the capsule. During the breaks, the volunteer was allowed to stand up, walk around and eat according to his usual habits.

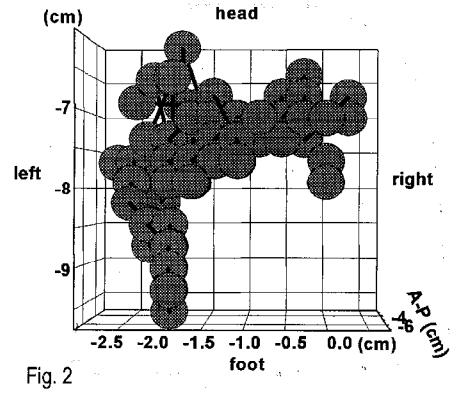

Fig. 2

MR-measurements were performed on a clinical 1.5 T Siemens Magnetom Vision scanner (Siemens, Erlangen) using a home-built ^{19}F surface coil, which was integrated into the patient bed, and a commercial ^{1}H flexi-coil placed diametrically to the ^{19}F coil. While the capsule was in the stomach, the volunteer was in supine position, whereas afterwards the assessment was continued with the volunteer being in prone position. The three-dimensional spatial location of the capsule was determined by using projections obtained with a modified TrueFISP-sequence which had the slice- and phase gradients removed. 128 scans for each of the three spatial directions were averages interleaved with a repetition time of 5.9 ms, resulting in a total acquisition time of 2.3 sec. A spatial resolution of 2.7 mm was obtained for the ^{19}F images by acquiring 128 data points over a field of view (FOV) of 35 cm. Conventional anatomical ^{1}H-MR images were obtained with a TrueFISP sequence. Coronal slices with a thickness of 6 mm, a FOV of 35x35 cm^2, and TR/TE set to 4.8 ms/ 2.3 ms were acquired into a data matrix of 256^2 points.

RESULTS AND DISCUSSION

Figure 1 shows a typical coronal view of the abdominal region obtained shortly after ingestion of a pharmaceutical capsule filled with perfluorononane. Due to complete proton-depletion, the capsule could be identified as a black bar (arrow) in the stomach, the latter being partially filled with gastric juice. However, as soon as the capsule had left the stomach and had entered the intestine, ^{1}H-MRI failed to depict the small capsule due to the large changes in contrast and intensity resulting from the intricate arrangement of the intestine. In contrast, ^{19}F-MR projection imaging always provided unequivocal spatial information on the location of the gastrointestinal probe and allowed the capsule to be followed throughout the entire gastrointestinal tract with high temporal and spatial resolution. Figure 2 shows a 3D-plot of the capsule's passage through a part of the small intestine 208-213 min after ingestion of the capsule. Over this period, the capsule was pushed along one of the many loops of the intestine, resulting in an L-shaped movement from right to left and head to foot. The path of the capsule was superimposed with jitters, which was ascribed to the rhythmic movement of the intestines due to respiration. The most extensive movements of the capsule, however, were observed after each period of light physical exercise the volunteer was asked to carry out outside the magnet. Complementary ^{1}H-MR images ensured a nearly perfect repositioning of the volunteer for subsequent scans and provided a means for correlating the position of the capsule with the anatomical structures of the gastrointestinal tract. After its ingestion, the capsule remained in the stomach for 2 h before the gastric emptying occurred. Thereafter, the capsule could be followed along its path through the small intestine and colon. The capsule was ultimately excreted after 57 h as was confirmed by the absence of signal in the last ^{19}F-MR assessment at 75 h after ingestion.

In conclusion, ^{19}F-MR projection imaging in combination with ^{1}H-MRI provides a novel non-invasive modality for assessing gastrointestinal transit which features high temporal and spatial resolution in three dimensions, and provides functional and anatomical information. The concept of ^{19}F magnetic labelling can easily be extended to the simultaneous observation of several chemically different probes. Moreover, non-toxic contrast agents, such as perfluorononane, allow the location of disintegration of pharmaceutical capsules to be evaluated *in situ*.

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