Fasted State Magnetic Resonance Imaging Quantification of Colonic Liquid in Healthy Humans under Bioavailability/Bioequivalence Testing Conditions
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Purpose
The rate and extent of drug dissolution and absorption from solid oral dosage forms is highly dependent on the volume of gastrointestinal tract (GIT) liquid. However, little is known about the time courses of liquid volumes in vivo in an undisturbed gut. Previous Magnetic Resonance Imaging (MRI) studies offered novel insights on GIT liquid distribution in fasted humans and showed that freely mobile liquid in the intestine is distributed in small pockets [1, 2]. Based on our previous study [2] and pilot data we hypothesized that: 1) it is possible to quantify the volume and number of liquid pockets in the undisturbed colon of fasted healthy humans following ingestion of 240mL of water (conditions recommended for Bioavailability/Bioequivalence (BA/BE) studies), using non invasive MRI methods; 2) the amount of freely mobile water in the fasted human colon is of the order of a few mL only.

Methods
Twelve healthy volunteers fasted overnight and underwent abdominal MRI scans before drinking 240mL (8 fluid ounces) of water [2], Figure 1. After ingesting the water they were scanned at rapid intervals for 2 hours. The drink volume, inclusion criteria and fasting conditions matched the international standards for BA/BE testing in healthy volunteers. The images were processed using previously described methods [2] that quantify freely mobile fluids with long MRI relaxation times. The data analysis focused here on regional (ascending, transverse and descending) and total colon liquid volumes and on the number and volume of separate colonic liquid pockets.

Results
(mean±SEM) The fasted colon contained 11±5 pockets of resting liquid with a total volume of 2±1mL. The colonic fluid peaked 30 minutes after the water drink to 7±4mL (Figure 2). This peak fluid was distributed in 11±4 separate liquid pockets in the colon. The regional analysis showed that the colonic fluid was found primarily in the ascending colon. The individual variability was very high with subjects having a range of number of colonic fluid pockets from none to 89 and total colonic freely mobile fluid volume from zero to 49mL.

Conclusion
The data from this initial study confirmed our hypotheses. MRI provided unprecedented insights on the fasting time course, number and volume of liquid pockets in the human, undisturbed colon under conditions that represent standard BA/BE studies. The fasting colon contained only a few mL of freely mobile water, distributed in small pockets and these were located primarily in the ascending colon region. These new data add to our current understanding of gastrointestinal physiology and will help improve physiological relevance of in vitro testing methods and in silico transport analyses for prediction of bioperformance of oral dosage forms. Novel insights on the colonic fluid environment will be particularly relevant to improve understanding and modeling of controlled release formulations.

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References