

Quantification of gastrointestinal liquid volumes following a 240 mL dose of water

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Target Audience: Pharmaceutical industry, image analysis scientists with an interest in abdominal MRI.

Introduction: While solid oral delivery is the most frequently used route for administration of pharmaceutical drug products, development of solid oral dosages that perform effectively can be challenging, due to the behavior of drugs in the gastrointestinal tract. In addition to other physiological parameters, the rate and extent of drug dissolution, dispersion and subsequent absorption from solid oral dosage forms depends on the volume and distribution of liquid in the gastric and small intestinal spaces [1]. Previous imaging studies have shown that in fasted humans, liquid in the small intestine is distributed in small pockets [2], but there have been few attempts to quantify these pockets or monitor changes over time or after consuming water. This information will be of considerable interest to the pharmaceutical industry. This study aimed to use MRI to quantify changes in the volume and number of liquid pockets in the gut of fasted healthy humans following ingestion of 240 mL of water; the conditions recommended for Bioavailability/Bioequivalence (BA/BE) studies [3].

Methods: The study was carried out using a 1.5T Philips Achieva Scanner with a 16 Element SENSE torso coil. Twelve healthy volunteers (4 male, 8 female) aged 18 – 25 years, with BMI in the range 18.6 – 24.8 kg m⁻² underwent abdominal MRI scans before drinking 240 mL of water. They were then scanned at intervals of 2 minutes initially, followed by 15 minute intervals for a total time of 2 hours, to generate MRI data on intragastric and small bowel liquid distribution. Intragastric volume was measured using a bTFE: TE/TR 1.5/3.0 ms, SENSE 2.0, in-plane resolution 2.0 x 1.77 mm², FOV 400 x 320 mm², FA 80°, 50 transverse slices 5 mm thick, acquired in a single 13 second breath-hold. Small bowel liquid was measured using single shot, fast spin echo TSE sequence, TR/TE_{eff} 8000/320 ms, with in-plane resolution 0.78 x 0.78 mm², ACQ res 1.56 x 2.90 mm², 24 coronal slices of thickness of 7 mm acquired in a breath hold [4].

Data analysis: Gastric volumes of liquid (Figure 1A) were measured by a single operator using an intensity based, semi-automatic method which

defined the bright liquid stomach contents on each image slice [5]. Plots of volume against time (up to 24 minutes) were created and used to determine the time to half empty the initial volume T_{50%} by fitting the individual gastric emptying curves to a standard model [5, 6]. Small bowel liquid volumes were assessed as previously described and validated [4]. Briefly, regions of interest were drawn manually around the small bowel on each slice, using in-house software on an IDL® platform (IDL 6.4; Research Systems Inc., Boulder, CO, USA). The software then identified (in the 3-dimensional multi-slice data set) all small bowel regions with an intensity above a threshold calibrated using the corresponding subject's cerebrospinal fluid. The number and volume of separate intestinal liquid

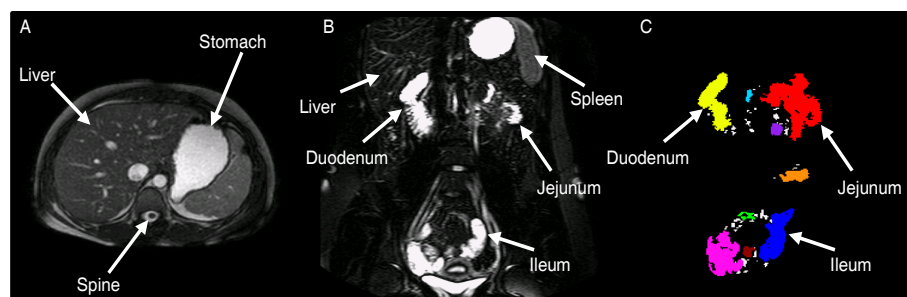


Figure 1: Examples of MR images of a healthy volunteer, acquired after drinking 240 mL of water (A) an axial image of the water in stomach, (B) a heavily T2 weighted coronal image used to assess small bowel liquid volume, (C) multiple intensity projection of all individual small bowel water pockets, extracted from images such as (B) and colour coded for individual pockets

pockets larger than 0.5 mL were assessed as follows. A mask was generated from the small bowel liquid volumes regions of interest using a previously validated threshold [4], and a region-growing algorithm was used to determine the size of each connected region (Figure 1B and C).

Results: The study procedures were well tolerated and good quality images were obtained. Upon drinking, the gastric fluid rose to 242 ± 9 mL and then declined rapidly with T_{50%} of 13 ± 1 minutes. The fasting small bowel contained a total liquid volume of 43 ± 14 mL distributed in 8 ± 1 pockets of 4 ± 1mL each on average. The mean pocket volume increased with time to about 7 mL after water ingestion (Figure 2).

Conclusion: T2 weighted MRI of the small bowel, combined with novel analysis techniques provided unprecedented insights on the time course, number and volume of liquid pockets in the small intestine after the ingestion of 240 mL of water. These 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 solid dosage forms.

References: [1] Mudie et al. Mol. Pharmaceutics: 2010: 7: 1388-1405. [2] Schiller et al. Aliment. Pharmacol. Ther., 2005: 22:971-979. [3] FDA, Guidance for industry. Bioavailability and bioequivalence studies for orally administered drug products: general considerations, in: C. U.S. Department of Health and Human Services F (Ed.): 2003. [4] Hoad et al. Phys. Med. Biol., 2007: 52:6909-6922. [5] Parker et al. Gastroenterology 2012: 142: S610. [6] Fruehauf et al. Neurogastroenterol. Motil., 2011: 23: 854-861.

Acknowledgements: NIHR Biomedical Research Unit.

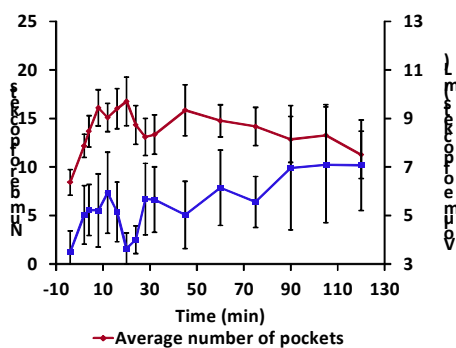


Figure 2: Average (±SEM) amount and volume of small bowel liquid pockets for 12 healthy volunteers before and after drinking 240 mL of water