Accelerated 4D MRI for investigating release and dispersion of an ingested drug model inside the human stomach

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Introduction: The delivery of therapeutic agents to the different organs is most commonly facilitated by oral means through the gastro intestinal (GI) tract. The assessment of the in-vivo and especially the intragastric perfromance of the therapeutic agent is of main importance for effective drug delivery design. The real-time monitoring of the dispersion of a drug inside a gastric-retentive delivery system can provide important dynamic information on its release characteristics, intragastric distribution and also gastric emptying. Such data may improve the development of drug delivery systems and provide crucial information for pharmacokinetic and -dynamic models [1]. We therefore wish to take a first step in this direction by proposing a MRI method for 4D monitoring of the release and distribution of a drug model from a standard hard gelatine capsule within the human stomach. **Methods:** For proof-of-principle, in vivo experiments in one volunteer were conducted on a 1.5T scanner (Achieva, Philips Healthcare, Best, The Netherlands) with a 5-element cardiac coil array. After the volunteer received a 400 mL 10% glucose solution labeled with 200µL DOTAREM® to increase GI contrast with respect to the surrounding tissue, a double-shell hard gelatin capsule filled with 800 ul pure DOTAREM (drug model) was administered. A capsule of size 0 (2,16cm x 0,75cm) was inserted into a capsule of size 00 (2,3cm x 0,84cm). 3D image data was acquired with a spoiled gradient echo sequence, TR/TE=3.66/1.5ms, flip angle=10°, FOV=300x300x72mm^3,voxel size=1.8x1.8mm^2, slice thickness=6mm. A volume of 12 slices was acquired with a stack of stars golden angle acquisition scheme. 21 profiles were sampled per slice leading to an acceleration factor of 13 and a temporal resolution of 907ms. The acquisitions were performed during 30s breath-holds. 3D dynamic image data was reconstructed by a k-t SPIRiT [2] based method. The total scan time was around 90 minutes. Gastric content was thresholded and semi-automatically segmented and volumes computed. The **dispersion dynamics** of the drug model were determined by plotting the fraction of gastric content mixed with contrast agent (CA) and total gastric content volume over time.The mixing rate as a first deterimant of subsequent intestinal bioavailability was approximated by a linear fit. Flow patterns of the drug model within gastric content were computed using optical flow methods from the 30 seconds dynamic volumes acquisitions. The **release dynamics** of the drug model were determined by extracting and plotting the change in absolute MR signal intensity over time in a region adjacent to the capsule.

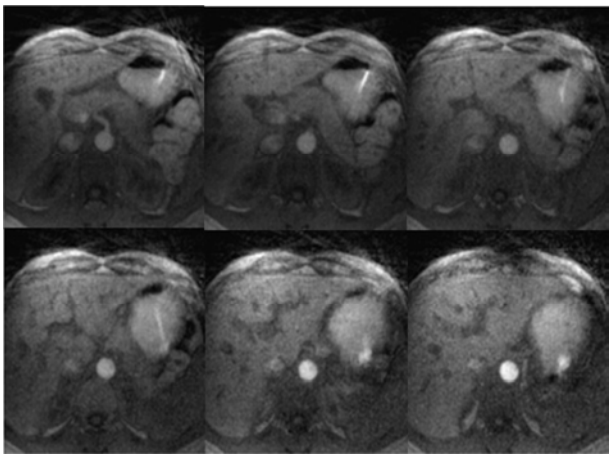


Figure 2. 6 slices from a temporal volumetric acquisition, 10 minutes after capsule intake. The capsule descended along the gravitational direction from the meal surface to the proximal stomach wall. CA dispersion is visible i.e the bright patches and stripes

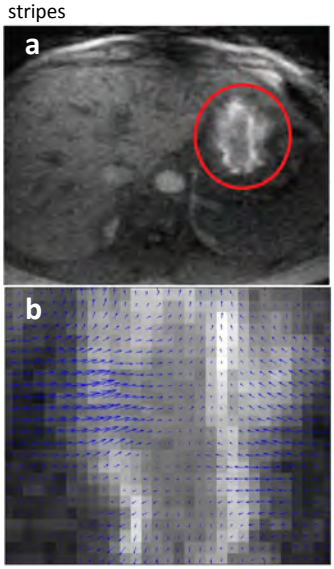


Figure 3. a-the red circle shows two CA columns;
b-displacement vectors computed inside the ROI

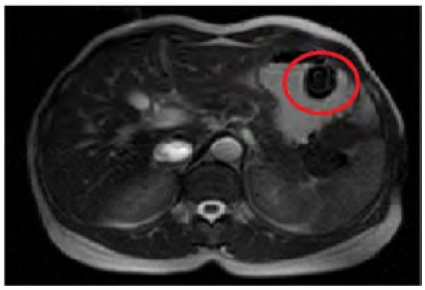
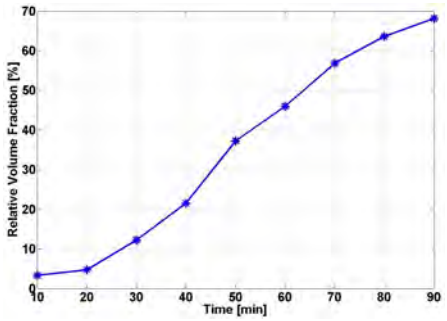
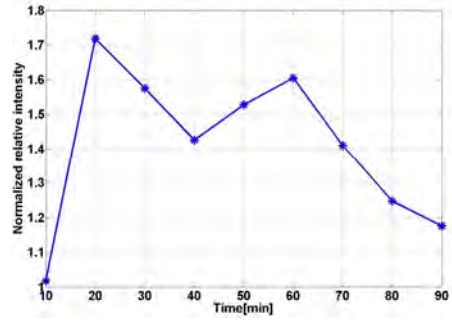


Figure 1. Capsule's position 2 minutes after intake



a



b

Figure 4.a-Dispersion dynamic represents the fraction of the dispersed CA to the total volume over time; **b- Release dynamic** represents the approximate release of the CA from the capsule over time

Results: After intake, the capsule appeared as a black signal void in the acquired cine images due to the high concentration of CA inside (Figure 1). During dissolution of the gelatine capsule, the paramagnetic CA , i.e. DOTAREM®, was released and mixed with the surrounding gastric content causing local increases in MR signal intensity of gastric content. Figure 2 shows 6 slices of a dynamic volume data set at 10 minutes after capsule intake with the positioned in the proximal stomach. Gastric peristaltic activity transported the released CA against gravitation along the gastric wall towards the distal stomach. In figure 3a the ROI shows the regions of increased CA for which displacement vectors were computed. Theseare depicted in Figure 3b. The displacement vectors corresponded to the movements visible in the cines. Figure 4a presents the dispersion dynamics plotted over 90 minutes. The total gastric content steadly decreased, while the volume fraction containing the CA steadly increased. A dispersion rate of 0.9 $\frac{\%}{minute}$ was detected. Figure 4b depicts the release dynamics detected for the same time period. Release rate was maximal at the beginning with a 1.7 fold increase in MR signal intensity. Different dynamics of dispersion and release resulted in unsteady MR signal changes during the first 60 min. After complete capsule disintegration after 1 hour, signal intensity continuously decreased due to ongoing mixing and emptying.**Discussion:** This preliminary work represents the proof-of-principle that accelerated 3D dynamic MRI is feasible in visualizing release and dispersion of an orally ingested drug model during gastric empyting at temporal resolutions of up to 1 second. The feasibility of this approach to extract flow patterns of a labeled drug model in gastric content has been indicated by applying optical flow methods.

References: [1] Steingoetter A et al. Pharm Res.2003;20(12):2001-2007 [2] Santelli C et al. MRM 2014;72:1233-1245