Journal of Pharmaceutical Sciences 106 (2017) 2472-2482

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

The Effect of Sparkling Water on Intraluminal Formulation Behavior and Systemic Drug Performance

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ARTICLE INFO

Article history:
Received 28 February 2017
Revised 28 March 2017
Accepted 30 March 2017
Available online 7 April 2017

Keywords:
oral drug delivery
biopharmaceutics
clinical pharmacokinetics
gastrointestinal
oral absorption
bioequivalence
disposition

ABSTRACT

In the context of mediating intra- and interindividual variability in systemic drug exposure after oral drug administration, this small-scale, crossover study aimed to investigate the effect of drug intake with sparkling water on fasted state gastric motor function and subsequent (variability in) intraluminal and systemic drug disposition. For this purpose, healthy human volunteers were asked to ingest a conventional paracetamol tablet with either tap or sparkling water, after which antroduodenal motility and intraluminal and systemic drug disposition were monitored as a function of time. Ingestion of sparkling water led to the occurrence of transient pressure events in the upper gastrointestinal tract for all volunteers, although the duration and frequency of the observed effect were subject to variability. Based on systemic drug disposition parameters, drug intake with sparkling water resulted in a trend toward faster and less variable absorption of paracetamol from the gastrointestinal tract. Faster and less variable intragastric tablet disintegration, due to (i) a direct effect (i.e., *in vivo* dissolution rate) and (ii) an indirect effect (i.e., gastrointestinal motility) of sparkling water, is likely to contribute to this observation.

Introduction

Intra- and interindividual variability in systemic drug exposure after oral drug administration has been widely reported in literature, especially for compounds suffering from low oral bioavailability.[1-3] As unpredictable pharmacokinetic drug behavior may lead to both toxic and subtherapeutic drug concentrations at the site of action, variability in systemic drug pharmacokinetics has been widely accepted to require important consideration during the drug development process and in bioequivalence studies.[3-8]

Several processes contribute to overall systemic drug pharmacokinetics: intestinal drug absorption, distribution, drug metabolism, and excretion. These processes in turn are influenced by underlying factors subject to (intra- and inter-) variability, introducing variability in overall systemic drug exposure.[4,5] With regard to oral drug absorption, the dynamic nature of the gastrointestinal environment is an important factor introducing variability in both the rate and extent of drug uptake from the intestine (i.e., main absorptive site). For instance, processes such as dosage form disintegration and drug transfer from stomach to duodenum, important prerequisites for intestinal drug absorption to occur, are affected by gastric motility. Under fasted state conditions, gastric motility is determined by the so-called "migrating motor complex" (MMC), which is a pattern of cyclically recurring phases of contractile activity differing in contractile frequency and intensity.[9-11] Although MMC phase I is characterized by a general absence of contractions, MMC phases II and III are periods of moderate and intense contractile activity, respectively. As motility displays time-dependent fluctuations, it seems plausible that the timing of oral drug intake relative to MMC phase will have a marked impact on dosage form disintegration and gastric emptying. For instance, several authors have previously reported an increase in gastric emptying rate of fluids in the presence of gastric contractile activity.[12,13] Motility-dependent drug delivery at the site of absorption may, therefore, contribute to the often reported variability in systemic drug exposure. In this context, Talattof et al.[6] computationally hypothesized the influence of fasted state gastrointestinal motility on the outcome of bioequivalence studies for BCS class I and III compounds, suggesting that for certain compounds, mainly BCS class I drugs with short half-life, these studies may fail solely as a result of motility-induced variability.

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http://dx.doi.org/10.1016/j.xphs.2017.03.039
0022-3549/

In the present study, it was hypothesized that normalizing the variability in gastric contractile activity at the moment of oral drug intake may reduce intra- and interindividual variability in intestinal drug absorption and subsequent systemic drug disposition, resulting in more predictable systemic drug behavior. For this purpose, this study investigated the possibility of using sparkling water to evoke a reproducible effect on fasted state gastric motor function. The effects of carbon dioxide and bicarbonate, both present in sparkling water, on gastric emptying have received extensive attention in the past.[14-22] However, many of these studies were conducted with caloric beverages and underfed state conditions and may, therefore, not be representative of the fasted state situation. Furthermore, as gastric emptying is only an indirect measure of gastric contractile activity, a direct effect of sparkling water on gastric motility has not been demonstrated so far. Therefore, this exploratory study aimed to directly measure the effect of sparkling water on fasted state gastric motility in healthy volunteers using high-resolution manometry. Second, the implications of administering a drug with sparkling water for (variability in) intraluminal drug disposition and systemic drug exposure were investigated, using paracetamol as model drug compound.

Materials and Methods

Chemicals

Acetonitrile was purchased from Fisher Scientific (Leicestershire, UK; HPLC grade), whereas methanol was supplied by Acros Organics (Geel, Belgium; HPLC grade). Acetic acid and sodium chloride were ordered from VWR Belgium (Haasrode, Belgium; 99-100% p.a.). Water was purified via a Maxima System (Elga Ltd., High Wycombe Bucks, UK). Paracetamol and theophylline powder for analytical purposes were purchased from Sigma-Aldrich (St. Louis, MO). Sodium acetate trihydrate was supplied by Chem-Lab (Zedelgem, Belgium). Simulated gastric fluids for *in vitro* purposes were made using simulated intestinal fluid powder as indicated by the manufacturer (Biorelevant.com, London, UK).

Clinical Trial

Clinical Trial Medication

Dafalgan® tablets (500 mg paracetamol; Bristol-Myers Squibb, New York City, NY) to be administered to healthy volunteers were ordered from the hospital pharmacy of the University Hospitals Leuven (UZ Leuven, Leuven, Belgium).

Clinical Trial Design

Six healthy volunteers (age range 22-31 years old; 5 males, 1 female) participated in a crossover study in which the following conditions were tested:

- Administration of 1 tablet of Dafalgan® (500 mg paracetamol) with 330 mL of tap water during MMC phase I (control condition).
- Administration of 1 tablet of Dafalgan® (500 mg paracetamol) with 330 mL of sparkling water (Chaudfontaine®; The Coca-Cola Company, Atlanta, GA) during MMC phase I (test condition).

All volunteers underwent a medical examination by a physician affiliated to the Department of Gastroenterology (UZ Leuven) before enrolment in the study. Volunteers suffering from hepatitis B/C and/or HIV infection were excluded from participation to guarantee the safety of the study personnel. Furthermore, illness at the time of the study, medication use, a history of acute/chronic gastrointestinal disease(s), (possible) pregnancy, and frequent exposure to radiation during the previous year were criteria for exclusion.

Table 1
Ionic Composition of Tap Water and Sparkling Water ($mg \cdot L^{-1}$)

Variable	Tap Water	Sparkling Water
Calcium (Ca^{2+})	120	65
Magnesium (Mg^{2+})	12	18
Sodium (Na^{+})	21.8	44
Potassium (K^{+})	3	2.5
Bicarbonate (HCO_3^-)	/	305
Chloride (Cl^-)	51	35
Sulphate (SO_4^{2-})	80	40
Nitrate (NO_3^-)	31	<1
Fluoride (F^-)	<0.4	0.4

Clinical Trial Approval

The study was approved by the Federal Agency for Medicines and Health Products (EudraCT reference number 2016-001439-11) and the Medical Ethics Committee of the University Hospitals Leuven (S59214) and was performed following the tenets of the Declaration of Helsinki. All volunteers provided written informed consent before the start of the study.

Study Protocol

Volunteers were asked to refrain from eating and to only drink water 12 hours before the start of the study to ensure fasted state conditions. On arrival at the hospital, 1 double-lumen catheter (Salem Sump™ PVC Gastroduodenal tube, 14 Ch [4.7 mm] × 108 cm; Medtronic, Dublin, Ireland) was positioned in the antral region of the participant's stomach via oral or nasal intubation to enable the aspiration of gastric fluids. The correct position of the aspiration catheter was guided and verified by fluoroscopic imaging. Similarly, a high-resolution manometry catheter (Sierra Scientific Instruments, Los Angeles, CA) was positioned in the duodenum or, in case the catheter could not be guided across the pylorus, as closely to the pylorus as possible. This catheter consists of 36 solid-state pressure channels (spaced 1 cm apart), recording local pressure events in the gastrointestinal tract. By connecting the catheter to a computer console, a pressure topographic tracing is generated in real time, facilitating the accurate tracking of antroduodenal motility as a function of time.[23] After positioning both catheters, participants were asked to remain seated in a hospital bed (i.e., semi-supine position) and to put no external pressure on their stomach (e.g., laptop) not to influence pressure measurements. Within 5-10 min after the end of MMC phase III, volunteers were asked to take 1 tablet of Dafalgan® (500 mg paracetamol) with 330 mL of either tap or sparkling water (compare Clinical Trial Design section). The composition of both beverages is summarized in Table 1. After oral drug intake, gastrointestinal pressure events were continuously recorded for 4 h. In addition, gastric aspirates (<3 mL) and venous blood samples were collected at predetermined time points. Gastric fluids were aspirated for 4 h, that is, 2, 7, 12, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225, and 240 min after drug intake. pH of the collected gastric fluids was measured immediately after sampling (Portamess®; Hamilton Knick, Bonaduz, Switzerland). Venous blood samples were collected in heparinized tubes (BD Vacutainer Systems, Plymouth, UK) for 8 h, that is, 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 360, 420, and 480 min after drug intake. Participants were prohibited from drinking or consuming food for the first 4 h after drug intake. After 4 h, participants were allowed to drink and/or eat ad libitum.

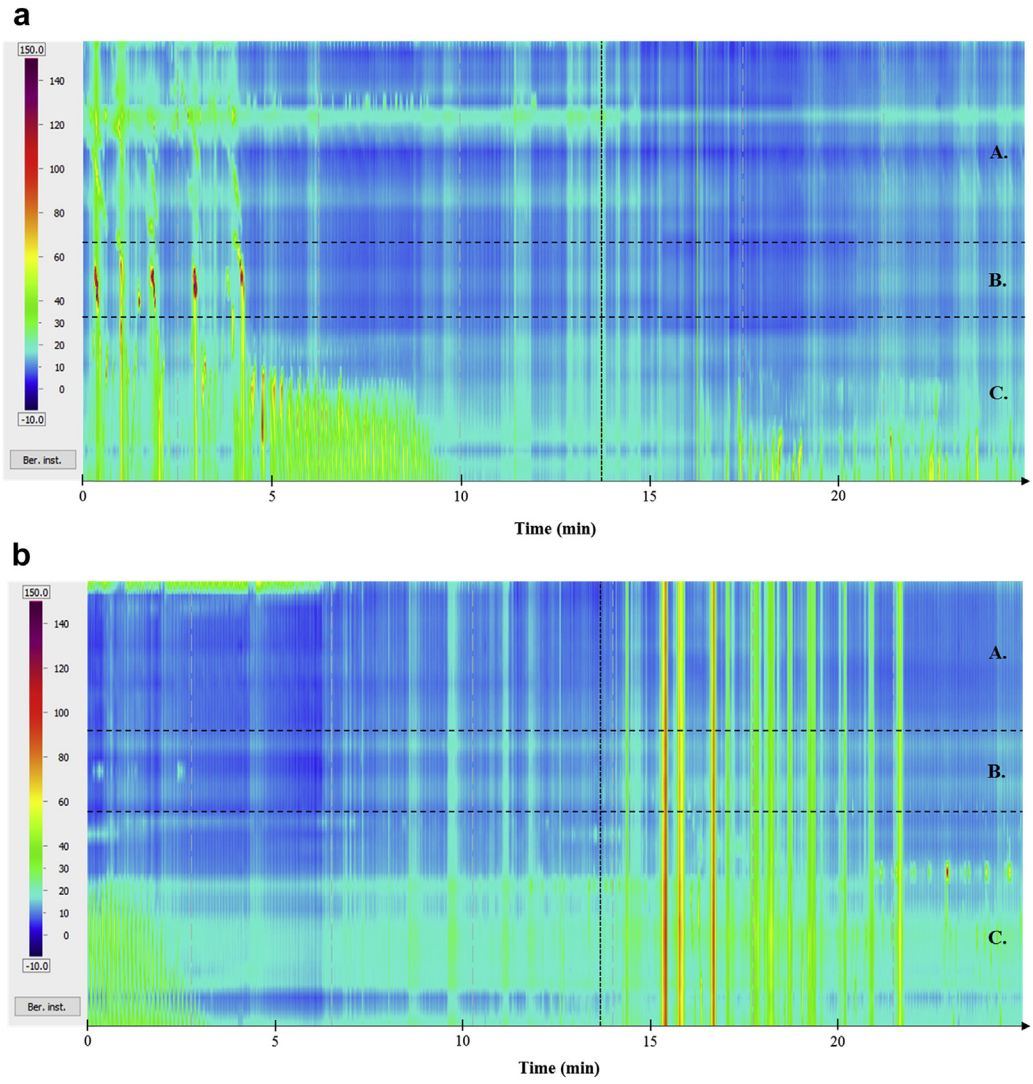

Figure 1. Typical examples of high-resolution manometry recordings obtained after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with either 330 mL of tap water (a) or 330 mL of sparkling water (b). The vertical dotted line marks the moment at which the drug was administered to the healthy volunteer. Several regions of the gastrointestinal tract can be identified on the recording: (A) proximal part of the stomach (corpus), (B) distal part of the stomach (antrum), and (C) proximal duodenum. Colors indicate pressure amplitude (mm Hg). After drug intake with sparkling water, transient pressure changes could be identified in the stomach and proximal part of the duodenum, which were absent when drug was administered with tap water.

Sample Preparation and Analysis

Gastric Aspirates

Immediately after aspiration, part of the gastric samples was centrifuged (20,817 × *g*, 5 min; Microcentrifuge 5424; VWR International) to separate solid from dissolved content. After centrifugation, supernatant was diluted using a mixture of acetonitrile and water (10:90 vol/vol). Diluted samples were kept on ice during the course of the experiment, pending determination of drug content on the same day. Samples were analyzed using RP-HPLC with UV detection (254 nm; Chromaster 5410 UV detector; VWR International). Separations were performed on a Novapak C18 column under radial compression (4 μm, 8 × 100 mm; Waters, Milford, MA). After injection of 100 μL sample, paracetamol was isocratically eluted using a mixture of acetonitrile and water (10:90 vol/vol) at a flow rate of 1.0 mL·min^{-1} for 10 min, resulting in a retention time of 6.5 min. After 10 min, a washing step was performed with acetonitrile:water (90:10 vol/vol) and water:25 mM sodium acetate buffer, pH 3.5 (75:25 vol/vol) for 2 and 1 min, respectively. Finally, the column was reconditioned with acetonitrile:water (10:90 vol/vol) for 2 min. The analytical method was validated for accuracy, repeatability, and intermediate precision in relevant media. Linearity was observed in a range from 100 μM to 6 nM. All criteria met the Food and Drug Administration requirements for bioanalytical method validation.

Venous Blood Samples

Blood samples were stored on ice during the course of the experiment. Afterward, samples were centrifuged (1699 × *g*, 15 min, 37°C; Centrifuge 5804R; Eppendorf, Hamburg, Germany) and the supernatant (plasma) was stored at −26°C pending analysis. To quantify drug concentrations in plasma, 200 μL plasma was added to 200 μL acetonitrile containing an internal standard (100 μM theophylline). After thoroughly vortexing the mixture, samples were centrifuged at 20,817 × *g* for 10 min. Supernatant was then transferred to an Eppendorf tube (Eppendorf) and centrifuged at 20,817 × *g* for 3 min. Subsequently, supernatant was diluted with acetonitrile:water (7:93 vol/vol) before analysis. Samples were analyzed

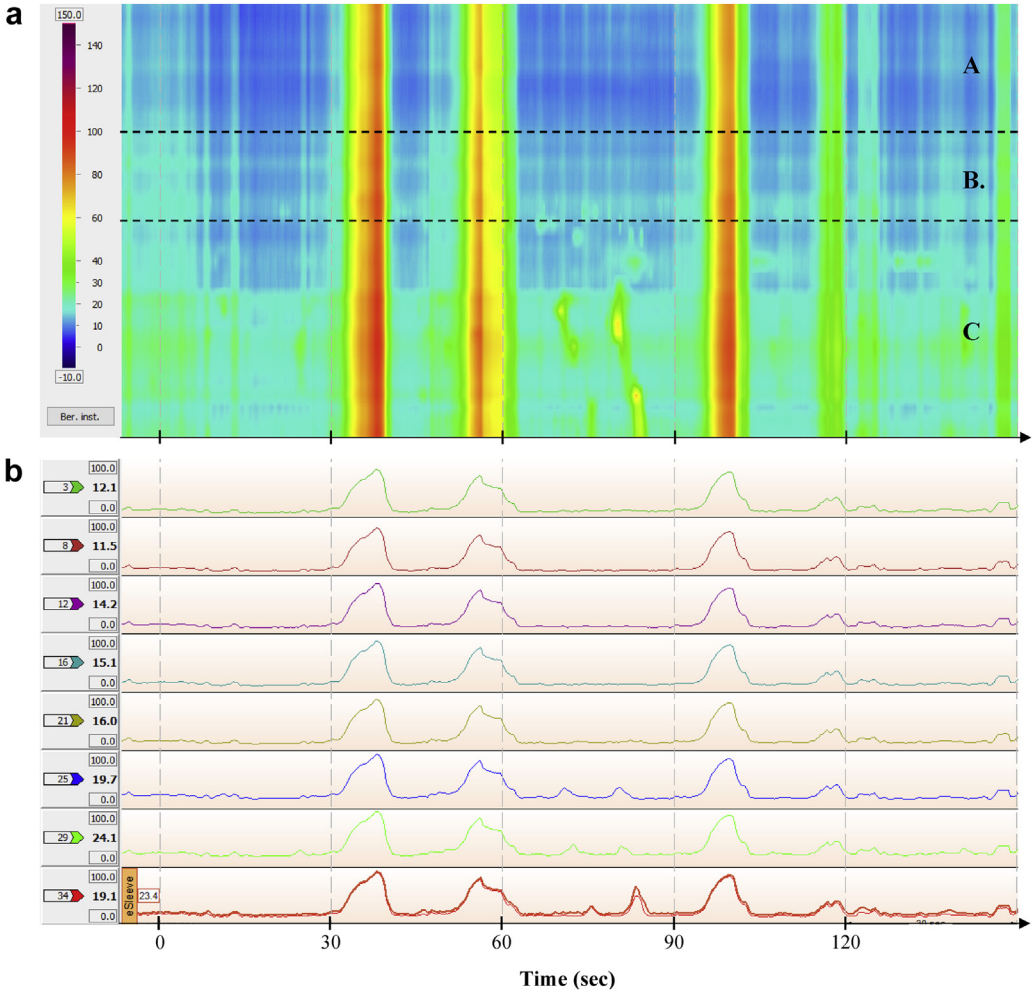

Figure 2. Close-up of increases in intraluminal pressure after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with 330 mL of sparkling water. (a) Topographic representation. (A) Proximal part of the stomach (corpus), (B) distal part of the stomach (antrum), and (C) proximal duodenum. (b) Line plot presentation. Each line represents changes in pressure recorded by a single pressure channel (i.e., 3, 8, 12, 16, 21, 25, 29, and 34) as a function of time. Pressure events were transient in nature and occurred simultaneously along the upper gastrointestinal tract.

using RP-HPLC with UV detection (254 nm; Chromaster 5410 UV detector; VWR International) with separations being performed on a Novapak C18 column under radial compression (4 μm, 8 × 100 mm; Waters). After injection of 100 μL sample, paracetamol was isocratically eluted using a mixture of acetonitrile and water (7:93 vol/vol) at a flow rate of 1.2 mL·min^{-1} for 10 min, resulting in a retention time of 6.2 min. After 10 min, a washing step was performed with acetonitrile:water (90:10 vol/vol) and water:25 mM sodium acetate buffer, pH 3.5 (75:25 vol/vol), for 2 and 1 min, respectively. Finally, the column was reconditioned with acetonitrile:water (7:93 vol/vol) for 2 min. The analytical method was validated for accuracy, repeatability, and intermediate precision. Linearity was observed in a range from 10 μM to 19.5 nM. All criteria met the FDA requirements for bioanalytical method validation.

In Vitro *Dissolution Experiments*

In vitro experiments were performed using a conventional USP II dissolution apparatus (SR8-PLUS dissolution test station; Hanson Research, Chatsworth, CA), comparing the dissolution behavior of paracetamol in tap water with that in sparkling water at different stirring rates. Dissolution vessels were filled with 50 mL of fasted state

Table 2
Quantification of Pressure Events Observed After Administering 1 Tablet of Dafalgan® (500 mg paracetamol) With 330 mL of Sparkling Water to Healthy Volunteers ($n = 6$)

Volunteer ID	# Pressure Events	Amplitude Pressure Events (mmHg)		Duration Single Pressure Event (s)	Overall Duration (min)
		Mean (±SD)	Range	Mean (±SD)	
HV1	3	29.1 ± 9.1	18.6-34.6	3.8 ± 2.1	14.5
HV2	16	26.5 ± 11.1	15.3-52.3	5.1 ± 2.8	11.7
HV3	3	32.4 ± 18.8	17.6-53.5	3.5 ± 0.9	8.6
HV4	26	22.2 ± 3.9	17.1-30.4	4.4 ± 2.1	15.6
HV5	19	40.0 ± 10.5	16.8-54.2	6.3 ± 3.3	25.9
HV6	1	34.6		1.6	7.5
Overall (mean ± SD)	**11.3 ± 10.4**	**29.3 ± 26.1**		**4.1 ± 5.3**	**14.0 ± 6.7**

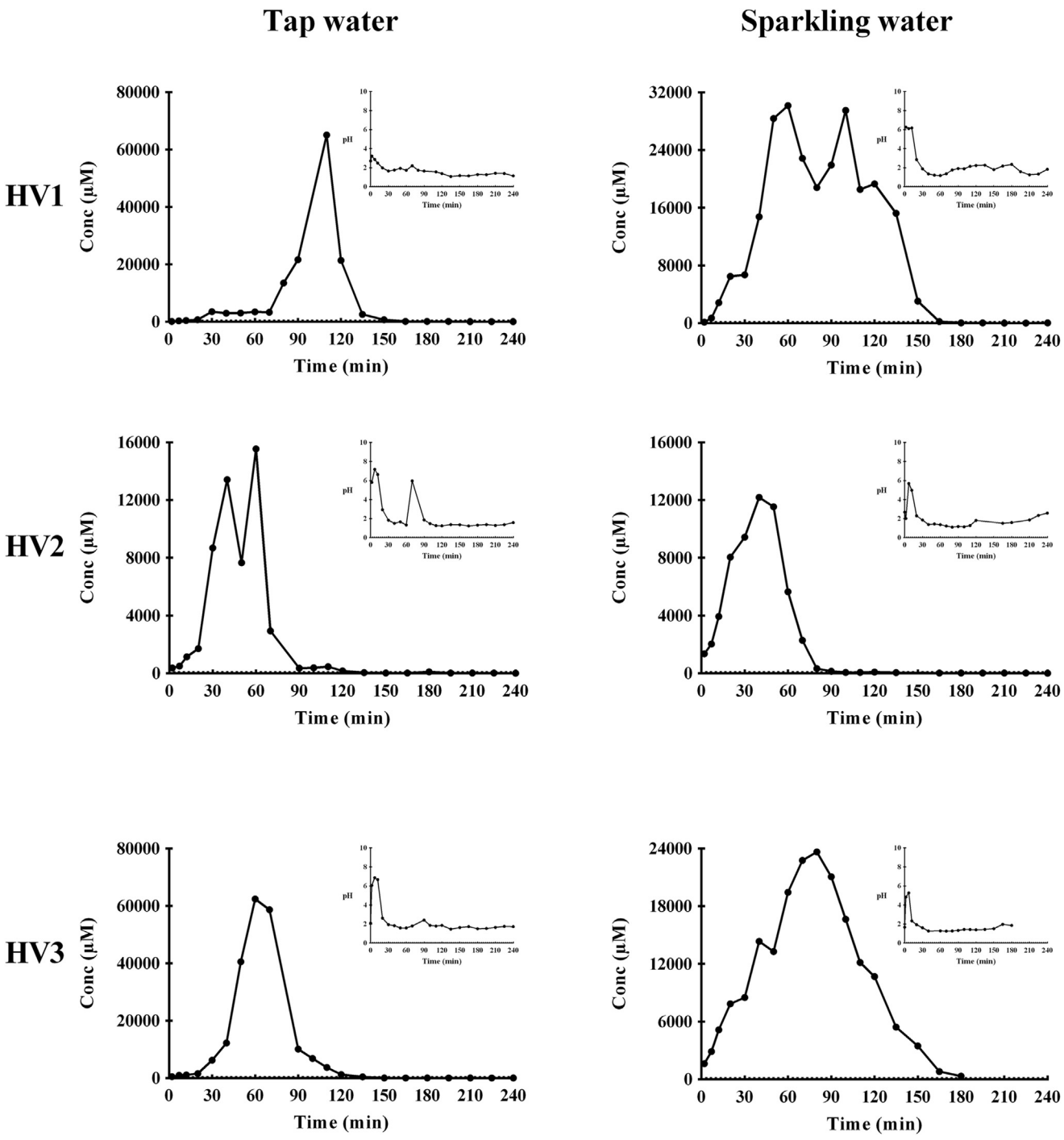

Figure 3. Drug concentration determined in gastric fluids aspirated from healthy volunteers (HV1 - 6) as a function of time after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with either 330 mL of tap water (left) or 330 mL of sparkling water (right). Inserts depict the pH of gastric aspirates as a function of time.

simulated gastric fluids (FaSSGF), pH 1.6. Medium was kept at a constant temperature of 37°C and was stirred at a rate of either 30 or 75 rpm using a paddle stirrer positioned approximately 3-4 cm from the bottom of the dissolution vessel. Subsequently, 1 tablet of Dafalgan® (500 mg paracetamol) was added to the dissolution vessel together with either 330 mL of tap water or 330 mL of Chaudfontaine® sparkling water at room temperature; 1-mL samples were collected at predetermined time points, that is, 5, 10, 20, 30, 40, 50, 60, 75, 90, and 120 min after drug addition. Immediately after aspiration, samples were centrifuged (20,817 × *g*, 5 min; Microcentrifuge 5424; VWR International), after which supernatant was appropriately diluted with acetonitrile:water (10:90 vol/vol). Finally, samples were analyzed using RP-HPLC as previously described (cfr. "Gastric Aspirates" section). Each set of experiments was performed in triplicate.

Data Presentation

Quantification of Pressure Events

High-resolution manometry recordings were analyzed using specialized computer software (Manoview Analysis™, version 3.0.1; Given Imaging, Los Angeles, CA). To correct for thermal drift during the course of the experiment, an interpolated

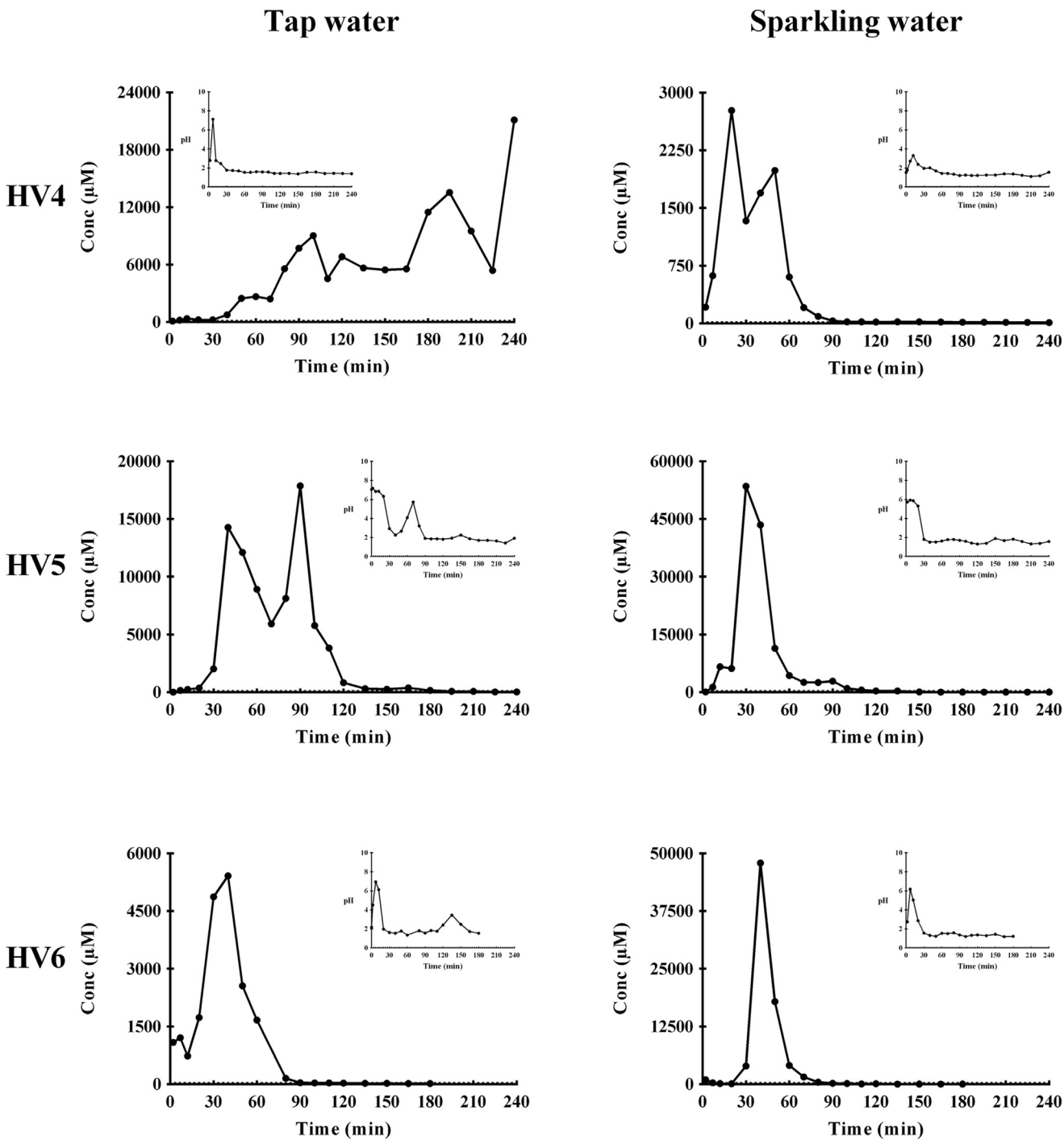

Figure 3. (*continued*).

thermal compensation was performed. Subsequently, pressure events were visually identified on the recording. Duration of pressure events was calculated by manually determining the beginning and end of each event. Furthermore, by exporting pressure amplitude data, recorded by each pressure sensor in 0.01-second intervals, to Microsoft Excel (Microsoft Office Professional Plus 2016, Redmond, WA), the mean amplitude of each pressure event could be determined by calculating the difference between the thermally corrected data and baseline pressure. Baseline was defined as the mean amplitude measured by all 36 pressure channels over a 5-min period before drug intake in MMC phase I.

Changes in gastrointestinal pressure were identified as transient pressure events based on the following criteria:

(i) Transient increase in pressure along the entire upper gastrointestinal tract,
(ii) Mean increase in amplitude compared with baseline $\geq$15 mm Hg,[10,24,25]
(iii) Duration of the pressure event $\geq$1 s.[10]

Subsequently, following parameters were determined for each healthy volunteer: number of transient pressure events, mean (±SD) and range of pressure event amplitude, mean (±SD) duration

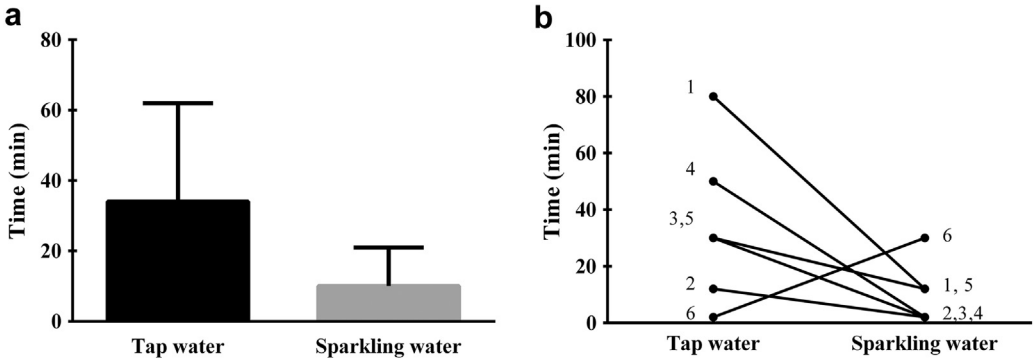

Figure 4. (a) Mean (+SD) time to initiation of intragastric tablet disintegration after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with either 330 mL of tap water or 330 mL of sparkling water (n = 6). (b) Individual data points for all 6 healthy volunteers. Numbers correspond to the respective volunteer ID.

of a single transient pressure event, and overall period during which these events could be identified.

Intraluminal and Systemic Drug Disposition Parameters

Data in text are presented as mean ± SD, unless stated otherwise. Initiation of tablet disintegration was defined as the first time point at which the dissolved drug concentration in the aspirated gastric fluids exceeded 5% of the maximal dissolved drug concentration recovered from the stomach. Systemic pharmacokinetic parameters (i.e., t_{max}, $AUC_{0\text{-}30min}$, C_{max}, and $AUC_{0\text{-}8h}$) were calculated using GraphPad Prism® (version 6.01; GraphPad Software Inc, La Jolla, CA). A nonparametric Wilcoxon test was performed to evaluate the statistical significance of the obtained *in vivo* results; differences between test conditions were considered statistically significant at $p < 0.05$.

Results

Influence of Sparkling Water on Upper Gastrointestinal Motility

In this study, participants ingested a conventional tablet containing 500 mg paracetamol with either tap or sparkling water during a period of contractile quiescence in the stomach (i.e., MMC phase I). Typical examples of high-resolution manometry recordings obtained from these participants in both test conditions are presented in Figure 1. Administration with tap water did not result in any changes in gastric motility, that is, in none of the volunteers, pressure events could be identified in the stomach immediately after drug intake (Fig. 1a).

On drug administration with sparkling water, increases in intraluminal pressure were recorded for all 6 healthy volunteers (Fig. 1b). Pressure events were transient in nature and occurred simultaneously along the entire gastric wall and the proximal part of the duodenum (Fig. 2). Characteristics of these events are summarized in Table 2. Transient increases in upper gastrointestinal pressure were observed over a mean period of 14.0 ± 6.7 min after drug intake (range 7.5-25.9 min). During this period, an average of 11.3 ± 10.4 events could be identified (range 1-26 pressure events). Mean duration of a single pressure event amounted to 4.1 ± 5.3 seconds (range 1.6-6.3 s). Increases in upper gastrointestinal pressure up to 54.2 mm Hg were recorded (range 15.3-54.2 mm Hg). For all healthy volunteers, mean amplitude of the identified pressure events fell within a range of 22.1-40.0 mm Hg (mean overall amplitude: 29.3 ± 26.1 mm Hg).

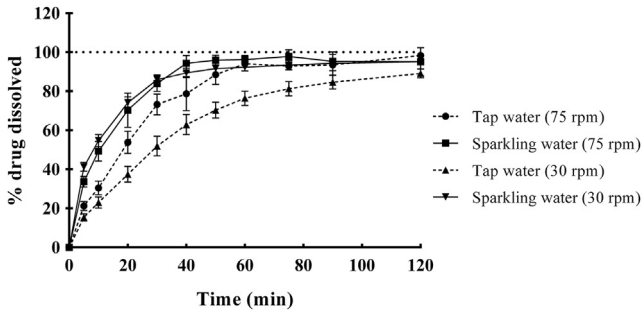

Figure 5. *In vitro* dissolution profiles for paracetamol in the presence of tap or sparkling water at different stirring rates (mean ± SD, n = 3).

Influence of Sparkling Water on Intragastric Drug Disposition

Figure 3 depicts the drug concentration in the aspirated gastric fluids of each volunteer as a function of time for both test conditions. Based on these profiles, initiation of intragastric tablet disintegration was calculated (Fig. 4). Drug administration with tap water resulted in a mean time to initiation of tablet disintegration of 34 ± 28 min (range 2-80 min), whereas paracetamol tablets started to disintegrate within 30 min for all participants when administered with sparkling water (mean: 10.0 ± 11 min, range 2-30 min, $p > 0.1$). With the exception of HV6, tablet disintegration initiated faster when the drug was administered with sparkling water compared with administration with tap water.

To investigate a possible direct effect of the co-administered beverage on *in vivo* disintegration/dissolution behavior, *in vitro* dissolution experiments were performed in both tap and sparkling water at different stirring rates (Fig. 5). At low stirring rate (i.e., 30 rpm), the dissolution rate was markedly increased in the presence of sparkling water compared with tap water (% drug $dissolved_{30min}$: 86.0 ± 2.4 vs. 52.0 ± 5.0%, respectively). Increasing hydrodynamics (i.e., stirring rate: 75 rpm) partly negated this difference in dissolution rate (% drug $dissolved_{30min}$: 83.9 ± 3.9 vs. 73.2 ± 5.3%, respectively).

Influence of Sparkling Water on Systemic Drug Disposition

Individual systemic drug concentration–time profiles for both test conditions are shown in Figure 6, whereas both mean and individual systemic PK parameters (t_{max}, $AUC_{0\text{-}30min}$, C_{max}, and $AUC_{0\text{-}8h}$) are graphically presented in Figure 7. A 2.8-fold change in mean t_{max} was observed when comparing administration with sparkling water to administration with tap water (mean: 32.2 ± 9.7 vs. 95.0 ± 77.3 min, respectively; $p > 0.1$). Although t_{max} was reached within a range of 20-45 min after drug intake with sparkling water for all

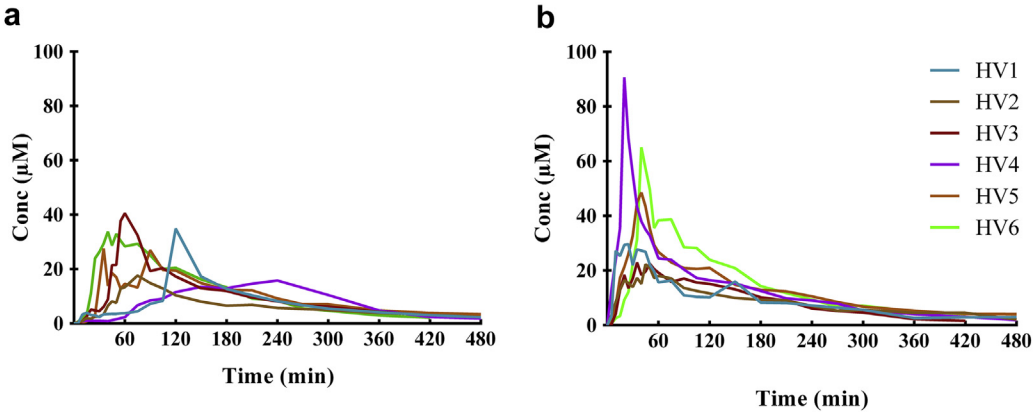

Figure 6. Individual systemic drug concentration–time profiles after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with either 330 mL of tap water (a) or 330 mL of sparkling water (b) (n = 6).

volunteers, variability in t_{max} was markedly higher in the control condition (range 35-240 min). For 5 of 6 volunteers, initial systemic drug exposure was higher after drug intake with sparkling water (mean $AUC_{0\text{-}30min}$: 529 ± 404 vs. 91 ± 92 µmol·L^{-1}·h, respectively; $p > 0.05$). Furthermore, an increase in C_{max} was observed in 4 of 6 volunteers after intake with sparkling water compared with the control condition (mean C_{max}: 46.5 ± 27.3 vs. 28.4 ± 9.9 µM, respectively; $p > 0.1$). Similarly, $AUC_{0\text{-}8h}$ was found to be increased in 5 of 6 volunteers after drug was administered with sparkling water (5,123 ± 1,215 vs. 4,104 ± 751 µmol·L^{-1}·h, respectively; $p > 0.05$).

Discussion

In this small-scale clinical study, administration of sparkling water induced increases in upper gastrointestinal pressure, recorded and quantified using high-resolution manometry, that were not observed after intake of tap water (Fig. 1). These pressure events appeared to be transient in nature and to occur simultaneously along the entire upper gastrointestinal tract (i.e., stomach and proximal duodenum) (Fig. 2). This observation is contrary to the propagation of a peristaltic contraction wave from the proximal to the distal stomach, characterizing typical fasted state gastrointestinal motility.[26,27] Therefore, sparkling water seems to evoke an effect on upper gastrointestinal motility other than "jumpstarting" normal fasted state motility. To investigate whether oral drug disposition was affected by these changes in gastrointestinal motility, participants were asked to ingest a commercially available tablet of paracetamol with either tap or sparkling water. As motility effects on (variability in) intraluminal and systemic drug disposition will be most pronounced for compounds for which motility-related processes are the major determinants of intestinal drug absorption, paracetamol was selected as a model drug compound. Due to its borderline BCS class I properties (good solubility, borderline good permeability), intragastric dosage form disintegration and gastric emptying are considered the rate-limiting steps in absorption of paracetamol from the small intestine, both processes that are affected by gastrointestinal motility.[28,29]

By aspirating gastric fluids as a function of time after drug intake, initiation of dosage form disintegration could be assessed in both test conditions (Figs. 3 and 4). After co-administration with sparkling water, tablets started to disintegrate earlier compared with the control condition. In addition, initiation of tablet disintegration turned out to be less variable after intake with sparkling water. Therefore, these results do not only suggest a faster but also a more reproducible initiation of dosage form disintegration after drug intake with sparkling water. It should be noted that the observed change in intraluminal tablet disintegration behavior may not be (solely) due to changes in gastrointestinal motility but may also result from a direct effect of the co-administered liquid on *in vivo* dissolution rate. Similar to observations by Kelly et al.,[21] a marked difference between *in vitro* dissolution rate in the presence of tap water or sparkling water was observed when using low hydrodynamic conditions (30 rpm, Fig. 5). By increasing agitation (75 rpm) inside the dissolution vessel, however, the difference in dissolution rate between both conditions was less pronounced. Although a paddle-stirred, static model may not be an adequate representation of the dynamic gastric environment, it can be hypothesized from these experiments that *in vivo* dissolution rate may, indeed, contribute to the observed difference in tablet disintegration behavior between test conditions in this study, the extent of which is determined by *in vivo* hydrodynamics. Apart from its influence on tablet disintegration, gastrointestinal motility drives emptying of gastric contents into the duodenum. Considering the close link between motility and gastric emptying,[12,13] it could be hypothesized that gastric emptying of drug in the duodenum may be affected after drug intake with sparkling water. Unfortunately, the present study design did not allow us to directly measure the effect of changes in upper gastrointestinal pressure induced by sparkling water on emptying of drug from the stomach. Therefore, an effect of sparkling water on gastric emptying behavior could not be confirmed. In this context, advanced visualization techniques (e.g., gamma-scintigraphy) may aid in further elucidating a potential effect of the co-administered liquid on intraluminal drug disposition.

Although a moderate trend toward an increase in systemic C_{max} (4 of 6 volunteers) and overall systemic drug exposure (5 of 6 volunteers) was observed after drug intake with sparkling water (Fig. 7), the contribution of intraluminal drug disposition to these observed trends may be confounded by several other processes (i.e., distribution, metabolism, and excretion). Therefore, a difference in intraluminal drug disposition between both test conditions was expected to be best reflected in systemic pharmacokinetic parameters that are predominantly influenced by intestinal absorption. After drug intake with sparkling water, an overall trend toward a shorter t_{max} and an increase in initial systemic drug exposure ($AUC_{0\text{-}30min}$) was observed, suggesting faster intestinal drug absorption compared with the control condition (Fig. 7).[16,30] As a result, a faster initiation of the drug's analgesic and antipyretic effect may be inferred, which is desirable for rapid mediation

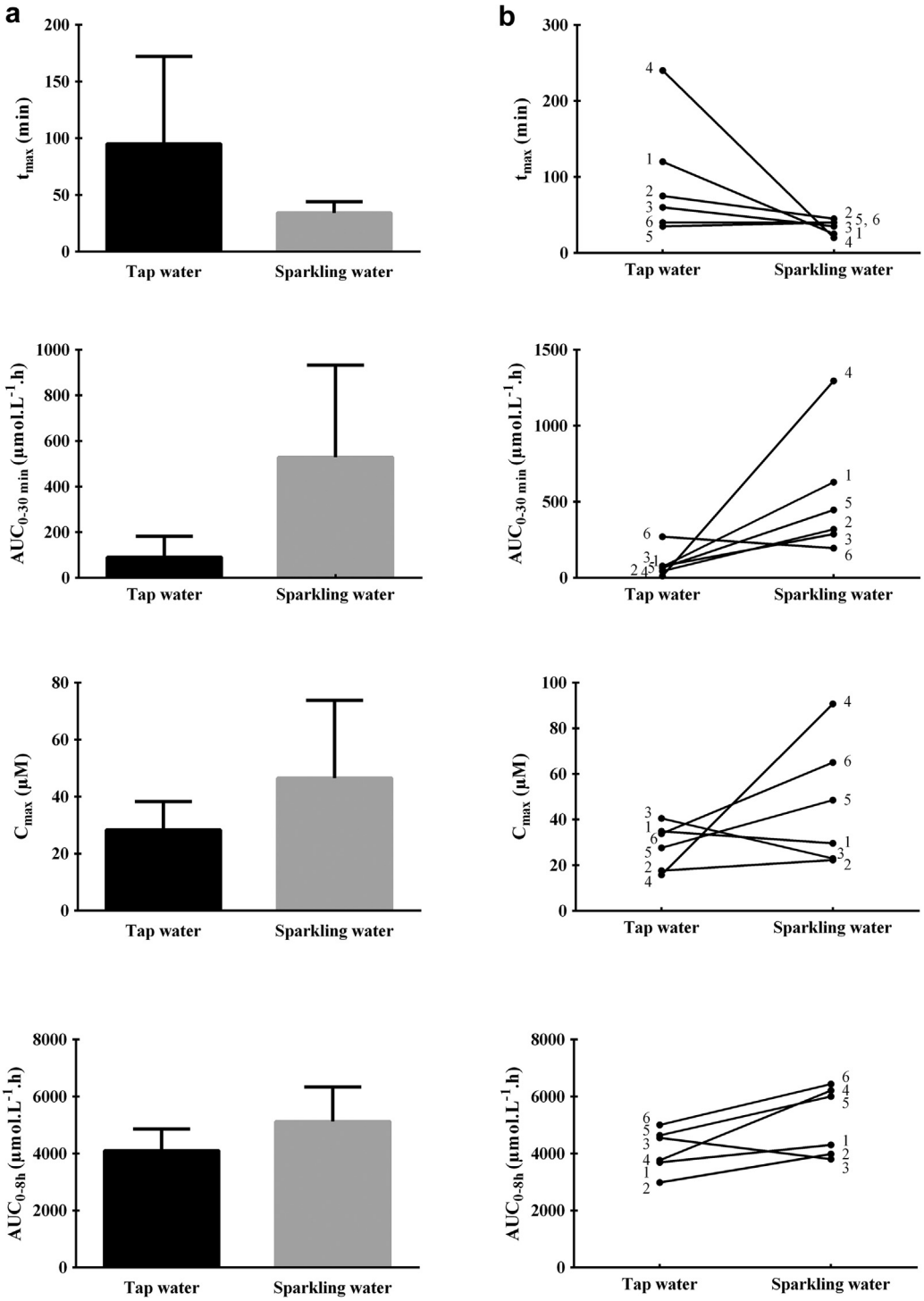

Figure 7. (a) Comparison of systemic pharmacokinetic parameters (i.e., t_{max}, $AUC_{0\text{-}30min}$, C_{max}, and $AUC_{0\text{-}8h}$) after intake of 1 tablet of Dafalgan® (500 mg paracetamol) with either 330 mL of tap water or 330 mL of sparkling water (mean ± SD, $n = 6$). (b) Individual data points for each healthy volunteer for each pharmacokinetic parameter. Numbers correspond to the respective volunteer ID.

of acute pain symptoms in patients. Importantly, variability in systemic t_{max} was markedly less pronounced after drug administration with sparkling water compared with the control condition. Although in the control condition t_{max} was found to be delayed for several hours in 2 of 6 volunteers, maximal systemic drug concentrations were reached within 45 min for all volunteers after drug intake with sparkling water. Thus, drug administration with sparkling water may offer a simple way to promote a faster and more reproducible onset of its therapeutic effect. It should be noted that in this study, drug intake was controlled to coincide with the occurrence of MMC phase I, as a potential effect of sparkling water on fasted state motility would be best noticeable during a period of contractile quiescence. In daily practice, however, drug intake may occur at any moment during the MMC cycle, potentially

introducing additional interindividual variability. Therefore, it may be worth investigating the influence of sparkling water on variability in intraluminal and systemic drug disposition when a drug is administered regardless of gastric contractile activity at that given moment.

Although transient increases in upper gastrointestinal pressure were recorded in all participants after drug intake with sparkling water, some differences with regard to the frequency and duration of these events were observed (Table 2). This variability may be related to the rate at which the administered sparkling water is emptied from the participant's stomach. Rapid emptying of sparkling water from the stomach may either facilitate or hamper its effect on upper gastrointestinal motility, depending on the site of action of the mechanism underlying the observed phenomenon. Although the study design did not allow identifying this exact mechanism, several possible scenarios can be hypothesized based on earlier published literature reports, including (i) bicarbonate-stimulated secretion of gastrin, (ii) an osmotic effect on gastrointestinal motility, and (iii) abdominal straining in an effort to vent gas from the stomach.

Bertoni et al.[14] reported a beneficial effect of bicarbonate-alkaline mineral water on alleviating dyspeptic symptoms in man. Preclinical rat studies suggested changes in gastric emptying to contribute to these observations as a (modest) increase in gastric emptying rate was reported after dosing bicarbonate-alkaline mineral water to rats over a period of 30 days; these findings were later corroborated by Fornai et al.[31] using experimental rat models of gastrointestinal disorders. As a possible explanation for the observed effect, Bertoni et al. suggested a rise in gastric pH due to the presence of bicarbonate to result in an increased stimulation of gastrin secretion in the stomach, hereby promoting antral gastric motility. Although a sustained rise in gastric pH may be possible after chronic administration of bicarbonate-alkaline mineral water, it seems unlikely that this will be the case after a single administration. In this study, ingestion of sparkling water did not result in a prolonged rise in gastric pH compared with ingestion of tap water (Fig. 3 inserts). Furthermore, a transient rise in pressure along the entire upper gastrointestinal tract was observed in this study, in contrast to the induction of isolated antral contractions suggested by Bertoni et al.

Early publications by Hunt and Pathak have suggested a concentration-dependent osmotic effect of several ions (e.g., Na^+, Cl^-, HCO_3^-) on gastric emptying of liquids, and thus gastrointestinal motility, most likely via interactions with osmoreceptors present in the duodenum.[32-34] In this context, several reports have been published comparing gastrointestinal drug disposition and systemic pharmacokinetics of a sodium bicarbonate (630 mg)–containing tablet of paracetamol with a conventional paracetamol tablet in fasted humans. In these studies, a trend toward faster intestinal drug absorption was observed when paracetamol was administered in the sodium bicarbonate–containing dosage form compared with the conventional tablet.[15,16,21,22] Several authors partly attributed this finding to an increase in gastric emptying rate with the bicarbonate-containing dosage form due to the presumably high concentration of sodium bicarbonate in the gastrointestinal tract, as suggested by Hunt and Pathak.[32,33] Using gamma-scintigraphy, Kelly et al.[21] confirmed a trend toward faster emptying of the drug from the stomach when administered in the sodium bicarbonate–containing dosage form compared with the conventional tablet. Although osmotically active components are, indeed, present in the sparkling water used in this study, intraluminal concentrations are presumed to be considerably lower compared with the earlier mentioned studies (e.g. $[HCO_3^-]_{sparkling\ water}$: 305 $mg \cdot L^{-1}$, Table 1). Therefore, whether osmotic components in sparkling water are, indeed, responsible for changes in gastric motility observed in this study needs further investigation. Regardless of the underlying mechanism, both our own findings and those by Kelly et al. suggest that bicarbonate directly affects fasted state gastric motility. Based on these observations, the use of bicarbonate, either as a formulation excipient or as a component of the co-administered liquid, may hold promise not only as a disintegration aid but also as a means to influence gastric motility.

Alternatively, the observed transient changes in intragastric pressure may be related to gaseous carbon dioxide that is both initially present in sparkling water and can be formed by the reaction of bicarbonate with gastric acid. To alleviate gas build-up in the stomach, air can be vented from the stomach in the orad direction, so-called gas gastro-esophageal reflux. Several studies have identified transient relaxation of the lower esophageal sphincter in response to gastric air distension as the main mechanism allowing trapped air to escape from the stomach.[35-41] However, in some cases (4-26%), these gas reflux events were observed to occur due to abdominal straining in an effort to vent gas from the stomach.[37,40] Wyman et al.[37] reported a brief increase in upper intragastric pressure due to this straining effect, potentially explaining the transient pressure events observed in this study. Furthermore, it seems plausible that abdominal straining will result in changes in pressure along the entire gastric wall, similar to the simultaneous changes in pressure recorded after ingestion of sparkling water in the present study. Given the focus of this study on gastric and duodenal motility, however, manometry recordings did not include measurements of intra-esophageal pressure. Therefore, whether the observed transient change in intragastric pressure after drug intake with sparkling water resulted in gas gastroesophageal reflux, indicative of abdominal straining in an effort to vent gas from the stomach, could not be confirmed.

Conclusions

In this small-scale, exploratory study, ingestion of sparkling water led to the occurrence of transient pressure events in the upper gastrointestinal tract. Based on systemic drug disposition parameters, drug intake with sparkling water resulted in a trend toward faster and less variable absorption of paracetamol from the gastrointestinal tract, indicating a more uniform intraluminal drug disposition after intake with sparkling water. Faster and more reproducible intragastric tablet disintegration, due to (i) a direct effect (i.e., *in vivo* dissolution rate) and (ii) an indirect effect (i.e., gastrointestinal motility) of sparkling water, is likely to contribute to this observed effect. As a result, co-administration of a conventional tablet with sparkling water may be a simple way to promote a faster and more reproducible onset of therapeutic effect. Further investigation should focus on the underlying mechanism of the effect of sparkling water on gastrointestinal motility and on a better understanding of the implications of co-administration with sparkling water on intraluminal processes (e.g., gastric emptying) and systemic drug disposition.

Acknowledgments

This work has received support from the Innovative Medicines Initiative Joint Undertaking (http://www.imi.europa.eu) under Grant Agreement No. 115369 (OrBiTo), resources of which are composed of financial contribution from the European Union's Seventh Framework Program and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies in kind contribution. Eveline Deloose is a postdoctoral fellow of the FWO (Fonds Wetenschappelijk Onderzoek–Vlaanderen).

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