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Research paper

Food-dependent disintegration of immediate release fosamprenavir tablets: In vitro evaluation using magnetic resonance imaging and a dynamic gastrointestinal system

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ABSTRACT

In the present study, we demonstrated the value of two advanced tools, the TNO gastric and small Intestinal Model (TIM-1) and magnetic resonance imaging (MRI), for the in vitro evaluation of food-dependent disintegration of immediate release fosamprenavir tablets. Upon introduction of a tablet with the nutritional drink Scandishake Mix® in the stomach compartment of TIM-1, simulating the fed state, disintegration and fosamprenavir dissolution were significantly postponed compared to the fasted state (lag time 80 ± 23 min). This resulted in a lag in the appearance of bioaccessible fosamprenavir (<5% during the first 2 h), even though the nutritional state did not significantly alter the cumulative bioaccessibility after 5 h. These results were in agreement with the previously observed postprandial delay in gastric fosamprenavir tablet disintegration and subsequent amprenavir absorption in healthy volunteers. Therefore, TIM-1 can be used in tablet development to identify food-induced disintegration issues causing unexpected clinical behavior. From a mechanistic perspective, we applied MRI to illustrate impaired water ingress in fosamprenavir tablets immersed in the nutritional drink compared to simulated gastric fluid. This effect may be attributed to both competition between nutritional components and the tablet for the available water (indicated by reduced rotational and translational diffusion) as well as the possible formation of a food-dependent precipitation layer on the HPMC-coated tablet.

1. Introduction

Gastrointestinal disintegration of a solid dosage form, enabling drug dissolution, is a first but crucial step in the cascade of processes leading to intestinal drug absorption. For an immediate release tablet, disintegration in the stomach should occur fast and not limit the rate of drug absorption. However, Abrahamsson et al. have showed a food-induced delay in disintegration of immediate release tablets in vitro and in the stomach of dogs [1]. The observed delay (between 5 min and more than 1 h) depended on the composition of both tablet and food. To further investigate the mechanisms underlying impaired tablet disintegration in the postprandial state, advanced techniques such as magnetic resonance imaging (MRI) may be of great assistance. The capacity of MRI to visualize and distinguish ^{1}H nuclei based on their mobility (e.g. ^{1}H nuclei in highly mobile water molecules versus bound water molecules versus solid material) may provide mechanistic insight into tablet hydration and water ingress, being the first essential steps in tablet disintegration [2,3].

Recently, we demonstrated the potential impact of delayed postprandial disintegration of immediate release tablets on a drug's pharmacokinetic profile in a clinical study with the phosphate ester prodrug (fosamprenavir) of the HIV protease inhibitor amprenavir [4]. Upon administration of the immediate release tablet of fosamprenavir (Telzir®) to healthy volunteers, drug concentrations in stomach, duodenum and blood were simultaneously monitored. Compared to the fasted state, prior intake of a high-fat nutritional drink resulted in postponed intraluminal tablet disintegration, fosamprenavir dissolution and conversion to the parent drug amprenavir. Eventually, this postprandial behavior caused a significant lag in absorption of amprenavir (between 60 and 90 min) and an average shift in plasma t_{max} of about 2 h.

Obviously, such delayed absorption may have pharmacodynamic implications, especially when a rapid onset of action is required, or when the dosing interval is critical to maintain

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effective concentration levels. Therefore, it is essential to detect a possible food-induced delay in disintegration and its impact on drug absorption during the in vitro evaluation of novel or generic immediate release tablet formulations. Static in vitro disintegration or dissolution tests in a single medium simulating the postprandial stomach suffice to identify potential food-induced disintegration issues [1,5,6]. However, these static tests do not simulate the continuously evolving composition of the postprandial gastric content and do not combine gastric disintegration and dissolution with other processes affecting absorption (including transit). Therefore, these simple tests do not allow forecasting the extent of disintegration delay in the dynamic postprandial gastrointestinal environment in vivo, and, even more important, the impact on absorption. For instance, Kalantzi et al. demonstrated delayed disintegration of paracetamol tablets in milk, both in vitro and in canine stomach [5]. However, no correlation between disintegration times and the onset of plasma levels was observed; probably, gastric emptying, and not tablet disintegration, limited the rate of paracetamol absorption. The above-mentioned fosamprenavir tablets remained largely intact in the nutritional drink for at least 4 h using a static in vitro dissolution test; this overestimates the in vivo behavior, where postprandial gastric disintegration significantly increased after ca. 2 h, presumably due to the changing composition of gastric content [4]. These examples illustrate the need for a more dynamic in vitro model of intraluminal drug and formulation behavior to predict the impact of food-dependent tablet disintegration on drug absorption kinetics.

In this regard, the TNO gastrointestinal model (TIM), developed by TNO Quality of Life (Zeist, The Netherlands), may be an interesting option. TIM is a multicompartmental and dynamic in vitro system of the human stomach, small and large intestine [7,8]. The TIM-1 system consists of gastric and small intestinal compartments and mimics intraluminal pH, enzymatic activity, bile salt concentrations, peristaltic movements, and gastrointestinal transit in a computer-controlled way. As such, intraluminal processing of drug dosage forms, including transit, release and dissolution, can be simulated in a dynamic system. Removal of dissolved drug molecules from the intestinal compartments allows the assessment of the so-called bioaccessible fraction, i.e. the fraction of drug potentially available for small intestinal absorption. Previous studies demonstrated the use of TIM-1 to simulate the behavior of orally administered drug dosage forms under various physiological conditions [7,9,10].

The present study pursued to demonstrate the value of two advanced tools, MRI and TIM-1, for the in vitro evaluation of food-dependent disintegration of immediate release tablets. First, MRI was applied for the mechanistic investigation into preprandial and postprandial gastric disintegration of fosamprenavir tablets. Secondly, we evaluated the capacity of the gastric and small intestinal system TIM-1 to simulate the food-dependent delay in disintegration of fosamprenavir tablets and to forecast its clinically observed impact on drug absorption.

2. Materials and methods

2.1. Materials

2.1.1. Drug and dosage form

For analytical purposes, amprenavir and its phosphate ester prodrug fosamprenavir calcium were kindly provided by GlaxoSmithKline (Middlesex, UK). In the MRI and TIM-1 experiments, commercially available immediate release tablets (Telzir®), containing 700 mg of fosamprenavir calcium and coated with a film of hydroxypropyl methylcellulose (HPMC), were used as dosage form. The tablets used in this study belonged to the same batch (B145842) as in the previously mentioned clinical study [4].

2.1.2. Nutritional drink

Scandishake Mix® (Nutricia) was used to simulate a high-fat meal. Preparation as instructed (85 g powder mixed with 240 ml fresh whole milk) resulted in a nutritional drink (300 ml) with a total energy content of 2505 kJ, of which fat, carbohydrates and proteins constituted 46%, 46% and 9%, respectively. The osmolarity amounted to 890 mOsm/l and the pH was 6.7.

2.2. MRI monitoring of tablet disintegration

The disintegration of fosamprenavir tablets was monitored in media simulating gastric conditions in both fasted and fed state. In addition, the mobility of water was measured in terms of diffusion and T_2 relaxation NMR. A single tablet was added to 15 ml of either USP simulated gastric fluid (SGF) without pepsin (HCl 84 mM and NaCl 34.2 mM at pH 1.2) or the nutritional drink Scandishake Mix® in a Perspex sample holder with an internal diameter of 2.69 mm and outside diameter of 2.84 mm. The sample holder was loaded from the top into the MRI system to achieve a minimal influence of gradient vibrations during the MRI experiments. A Bruker wideline vertical bore NMR magnet system operating at a resonance frequency for protons of 300.13 MHz was used. The system was equipped with a micro imaging probehead (micro 2.5) with a 30 mm diameter resonator insert. All experiments were performed at 22 °C.

2.2.1. Magnetic resonance imaging

A turbo spin echo or rare sequence was used with a field of view of 30 mm × 30 mm × 30 mm and a spatial resolution of 469 μm × 469 μm × 234 μm in the x y z direction with a repetition time TR = 500 ms. For the USP SGF, a rare factor = 64 was used with an echo time TE = 3 ms and for the Scandishake Mix® a rare factor = 32 with an echo time TE = 2 ms resulting in a total scan time of 64 and 128 s, respectively. Measurements were started in repetitive mode with a repetition delay time between experiments of 2 s. The scan delay time after the addition of the fosamprenavir tablet and sample holder loading was 20 s. Data acquisition was performed with Paravision 3.02 and processed with ImageJ.

2.2.2. Diffusion NMR

A stimulated echo sequence was used to measure the translational diffusion of water in the media with a diffusion time = 100 ms, gradient pulse duration time = 2 ms and a gradient strength between 10 and 500 Gauss/cm.

2.2.3. Relaxation NMR

A relaxation T_2 CPMG sequence was used to measure the rotational diffusion of water in the media with an echo time, 2τ = 1.2 ms and a 180° echo train of 4 k pulses. Data acquisition and processing were performed with XWinNMR Bruker software.

2.3. Drug release and dissolution from fosamprenavir tablets in TIM-1

2.3.1. TIM-1

Gastrointestinal release and dissolution of fosamprenavir from its commercially available immediate release tablet formulation in both fasted and fed state were evaluated in the gastric and small intestinal system TIM-1. TIM-1 consists of four serial compartments representing the stomach, duodenum, jejunum and ileum (Fig. 1). This dynamic, computer-controlled system has been described elsewhere [11]. Each compartment is composed of two glass units with a flexible silicone inner wall, enclosing the lumen. The space between the inner and outer walls is filled with warm water, maintaining the luminal content at body temperature (37 °C). By periodically applying water pressure (ca. 0.5 bar), the flexible inner walls are squeezed, simulating peristaltic movements of

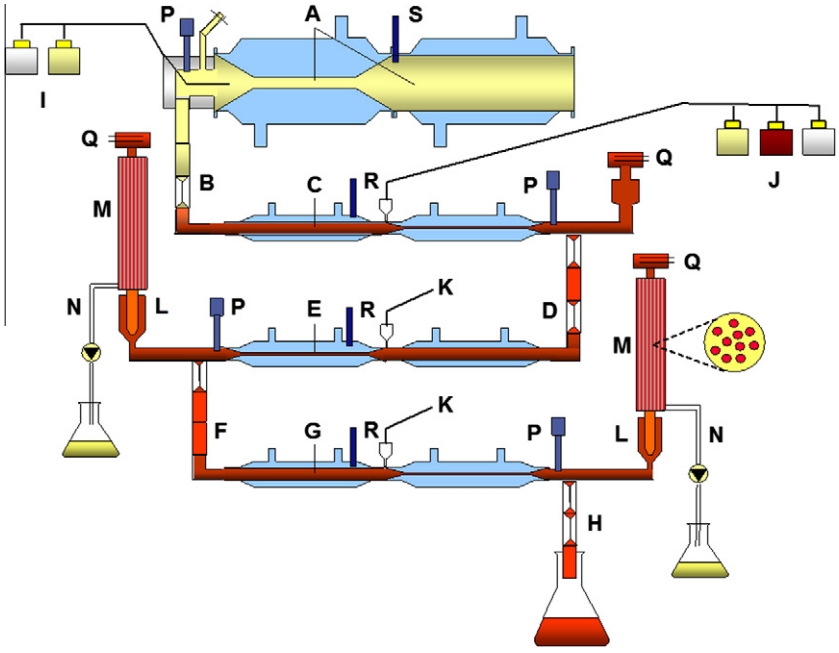

Fig. 1. Schematic representation of TIM-1. (A) Stomach compartment; (B) pyloric sphincter; (C) duodenum compartment; (D) peristaltic valve; (E) jejunum compartment; (F) peristaltic valve; (G) ileum compartment; (H) ileocecal sphincter; (I) stomach secretion; (J) duodenum secretion; (K) jejunum/ileum secretion; (L) prefilter; (M) hollow fiber filtration module; (N) water absorption; (P) pH electrodes; (Q) level sensors; (R) temperature sensors; (S) pressure sensor.

the gastrointestinal tract and mixing of chyme. Specifically, the units of the stomach compartment are alternatingly squeezed and relaxed three times per minute. This resulted in three peristaltic mixing contractions per minute. The units of the small intestinal compartments are alternatingly squeezed and relaxed six times per minute. Additionally, six times per minute both units are completely squeezed together. This resulted in 12 peristaltic mixing contractions per minute. The frequency of contractions is based on the work of Davenport (1977) [12]. In each compartment, the pH is monitored continuously and regulated by 'secretion' of hydrochloric acid in the stomach compartment and sodium bicarbonate in the intestinal compartments. Chyme transit is regulated by opening and closing the peristaltic valves that connect the compartments. The stomach and ileum compartments are emptied according to a power exponential function [13]. The volume in each compartment is monitored by a level sensor connected to the computer. Simulated gastric (0.5 ml/min; pepsin and lipase), biliary (0.5 ml/min; fresh pig bile) and pancreatic (0.25 ml/min; pancreatic juice) secretions are introduced into the corresponding compartments by computer-controlled pumps. Hollow fiber filtration modules are connected in-line with the jejunum and ileum compartment, allowing filtration of dissolved drug molecules from the corresponding intraluminal fluids. Additional secretion of bile into the jejunum compensates for the removed bile salts (as mixed micelles) through filtration.

2.3.2. Initiation of release studies

A single fosamprenavir tablet in a wide mashed net was introduced in the stomach compartment together with either water (simulating the fasted state) or the nutritional drink Scandishake Mix® (simulating the fed state). The net was located in between the two glass units of the compartment, so that the formulation was exposed to physiologically relevant waves of chyme mixing, but not to direct pressure forces. All parameters of TIM-1 were adjusted to simulate average gastrointestinal conditions in healthy adults, as summarized in Table 1.

2.3.3. Sampling

Release and dissolution of fosamprenavir were followed in the stomach and duodenum compartment by taking luminal samples (0.5 ml) every 15 min. Gastric samples were taken during 90 min (fasted state) or 180 min (fed state); duodenal samples were taken during 120 min (fasted state) or 210 min (fed state). The luminal samples were immediately centrifuged (14,000g, 10 min) to remove any non-dissolved fosamprenavir. Subsequently, the supernatant was diluted at least 10-fold in a mixture of KH_2PO_4 (25 mM, pH 6.5) and methanol (40:60, v/v) prior to HPLC analysis.

To determine the bioaccessible fraction of fosamprenavir, i.e. the fraction potentially available for small intestinal absorption, samples of the jejunum and ileum filtrate were collected every 60 min (ca. 35 ml) during 5 h (fasted state) or 6 h (fed state). Filtrate samples were 50-fold diluted in a water:methanol mixture (40:60,v/v) prior to HPLC analysis.

Ileum efflux samples were collected every 2 h and acidified with HCl 1 M to pH 2 to ensure complete dissolution of fosamprenavir. Subsequently, a 10-fold dilution in a mixture of KH_2PO_4 (25 mM, pH 6.5) and methanol (40:60, v/v) was analyzed by means of HPLC.

At the end of each experiment, the residues from all compartments were collected. Subsequently, the compartments were rinsed with (1) HCl pH 3 and (2) a mixture of ethanol:water (50:50, v/v). Residues and rinsing fluids were pooled and analyzed for fosamprenavir. Fosamprenavir in ileum efflux samples, residues and rinsing fluids constituted the non-bioaccessible fraction.

2.3.4. Quantitative HPLC analysis of fosamprenavir

Fosamprenavir was determined in the above-mentioned samples by means of a previously described HPLC analysis with fluorescence detection [4]. In addition to fosamprenavir, the analysis allowed detection of the parent drug amprenavir. However, in the samples generated in the present study, the amprenavir/fosamprenavir ratio was always below 0.1%; therefore, amprenavir levels were not considered in the calculations.

Table 1
TIM-1 parameters used to simulate gastrointestinal behavior of fosamprenavir tablets in the fasted and fed state in healthy adults.

	Fasted state	Fed state
Stomach compartment		
Dosing	1 Tablet + 200 ml water + 95 g artificial saliva + 5 g gastric residue	1 Tablet + 250 ml Scandishake Mix® + 45 g artificial saliva + 5 g gastric residue
pH t = 0 min	2.2	6.5
pH t = 30 min	1.7	5.5
pH t = 60 min	1.6	4.0
pH t = 90 min	1.5	3.0
pH t > 180 min	1.5	1.7
Secretions	20% level	100% level
Gastric emptying[a]		
Time of half emptying $t_{1/2}$	20 min	80 min
β coefficient	1	2
Residence time tablet[b]	60 min	180 min
Duodenum compartment		
Volume	55 ml	55 ml
pH	6.4	6.5
Secretions	Bile/pancreas 20%	Bile/pancreas 100%
Residence time tablet[b]	10 min	10 min
Jejunum compartment		
Volume	130 ml	130 ml
pH	6.8	6.8
Residence time tablet[b]	80 min	80 min
Ileum compartment		
Volume	130 ml	130 ml
pH	7.2	7.2
Ileal emptying[a]		
Time of half emptying $t_{1/2}$	150 min	220 min
β coefficient	1.8	2.5

[a] The stomach and ileum compartments were emptied according to the following equation: $f = 1 - 2^{-\left(\frac{t}{t_{\frac{1}{2}}}\right)^{\beta}}$, where f = fraction of chyme emptied, t = time of emptying, $t_{1/2}$ = half-life of emptying, and β = coefficient that describes the shape of the curve [12].
[b] In case of incomplete disintegration, the tablet was replaced manually to the next compartment (i.e. stomach to duodenum, duodenum to jejunum) after completion of compartmental residence time.

2.3.5. Recovery

At the end of each experiment, the overall recovery of fosamprenavir was determined based on a mass balance between the administered dose (700 mg of fosamprenavir calcium, based on the manufacturer's information) and total amount of fosamprenavir detected in the above-mentioned samples. The recovery varied between 95.1% and 123.8%, with no statistically significant differences between experiments performed in the fasted versus the fed state (t-test, $p > 0.05$). For comparison purposes, all data were corrected for the total recovery of the experiment.

2.3.6. Data presentation and statistical analysis

TIM-1-data are expressed as the mean ± sd of three experiments. Results from experiments simulating the fasted and the fed state were compared using unpaired t-tests. Differences were considered statistically significant at $p < 0.05$.

3. Results and discussion

3.1. MRI monitoring of tablet disintegration in fasted versus fed conditions

MRI can assist in understanding the mechanisms underlying tablet disintegration [2,3]. The disintegration process can be divided into three physical effects, which occur in a repetitive order until full disruption of the tablet: (1) initial ingress of the water, (2) swelling due to the uptake of water and (3) disintegration of the wetted layer due to dissolution of ingredients and/or expansion in the presence of filler phases (e.g. cellulose). Setup of an MRI experiment is a balance between spatial resolution, time, proton mobility and sensitivity. In practice, this means that compromises have to be made for at least one of the parameters to allow for proper measurement of the other parameters. Here, the proton mobility scale was compromised as this typically involves low resolution and long measurement times. The acquired images therefore show swelling and disintegration behavior.

In Fig. 2A, a series of images is visible as a function of time for the fosamprenavir tablet immersed in SGF. The original shape of the tablet is recognizable. The tablet itself does not have a response on the intensity scale (indicated with black) due to the low mobile protons inside the tablet. The SGF surrounding the tablet obviously consists of highly mobile protons and is indicated with yellow. The tablet was completely swollen and disintegrated within 52 min. Note that in vivo, stomach wall grinding and fluid mixing may accelerate disintegration and dissolution. MRI experiments, however, are performed under static conditions and therefore lack these processes, resulting in slower disintegration. The purpose of MRI is more geared towards understanding water ingress effects, compared to compendial dissolution tests which provide no information on this.

Fig. 2B shows a series of images for the fosamprenavir tablet immersed in the nutritional drink Scandishake Mix®. Compared to SGF (Fig. 2A), disintegration in the nutritional drink is clearly delayed; even after 3 days in the MRI setup, the tablet was not disintegrated. In the nutritional drink, only swelling was observed, whereas in SGF swelling and disintegration were stepwise.

Both the rotational (T_2) and translational diffusion (D) of water clearly differed between SGF and the nutritional drink, as reported in Table 2. The low T_2 value of the water protons in the nutritional drink indicates a higher degree of interaction with matrix components in the drink versus SGF. Obviously, SGF is a much simpler compositional system, void of such interaction possibilities. In

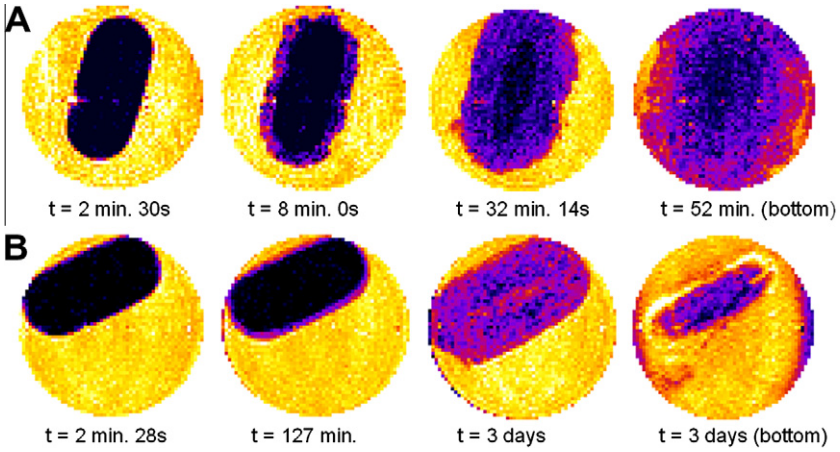

Fig. 2. MRI 2D slice selection of tablet center (axial view) as a function of time for fosamprenavir tablets in USP SGF (A) and the nutritional drink Scandishake Mix® (B). Yellow indicates highly mobile proton intensity, while black indicates no-mobile proton intensity. The images at the right hand side (bottom 2D slices) show complete tablet disintegration in SGF (A) versus swelling but no disintegration in the nutritional drink (B).

addition, the diffusion coefficient D of the water molecules was lower in the nutritional drink compared to SGF. These observations suggest that, in the nutritional drink, hydration of the tablet surface, water ingress and swelling is slowed down by a competitive effect for the available water between the matrix and the tablet.

It should be noted that, in case of fosamprenavir tablets, the reduced availability of water is presumably not the only reason for the impaired water ingress in the nutritional drink. As observed by Abrahamsson et al., the presence of nutritional components may cause the formation of a precipitation layer on the tablet surface, which hinders water ingress and delays tablet disintegration [1]. This effect was most pronounced using a mixture of proteins, carbohydrates and lipids, as in Scandishake Mix®, the nutritional drink used in the present study. A precipitation layer was observed in the presence of several individual excipients, including HPMC [1]. As fosamprenavir tablets are coated with an HPMC film, the formation of a precipitation layer on the tablet surface in the nutritional drink seems likely and may contribute to impaired water ingress and tablet disintegration.

In addition to impaired water ingress, the actual disintegration of the tablet (after swelling) may be delayed in the nutritional drink. The reduced translational diffusion D (Table 2) indicates an increased viscosity of the water phase in the nutritional drink, which may hinder disintegration by fixation of the water phase around the tablet. Presumably, this effect is less pronounced in vivo due to increased fluid movement compared to the MRI setup.

3.2. Fosamprenavir tablet behavior in TIM-1

In vitro disintegration and dissolution tests in static systems using fed state simulating media are useful tools to identify potential postprandial issues and to gain insight into the underlying mechanisms. However, forecasting the impact of impeded tablet disintegration on drug absorption requires a more dynamic test system of the gastrointestinal tract, which simulates both gastrointestinal transit and time-dependent changes in intraluminal conditions. Therefore, we evaluated the behavior of fosamprenavir tablets in the dynamic, multicompartmental system TIM-1, simulating both fasted and fed state in healthy adults (see Table 1).

Table 2
NMR physical parameters of the water phase upon immersion of a fosamprenavir tablet in either USP SGF or the nutritional drink Scandishake Mix®.

	T_2 (ms)	D (m^2/s)
USP SGF	1126	2.05×10^{-9}
Scandishake Mix®	17	1.04×10^{-9}

3.2.1. Release and dissolution of fosamprenavir

Upon introduction of a single fosamprenavir tablet in the stomach compartment of TIM-1, luminal fosamprenavir concentrations were determined in both the stomach (Fig. 3A) and duodenum (Fig. 3B) compartment. In the fasted state (administration with water), the tablet started to disintegrate immediately, resulting in detectable gastric and duodenal fosamprenavir levels ($\geqslant 8$ μM) at the first sampling point (15 min). However, in the fed state (administration with Scandishake Mix®), disintegration and, consequently, gastric dissolution and duodenal appearance of fosamprenavir were significantly postponed with lag times between 60 and 105 min. This resulted in a significant increase ($p < 0.05$) in median gastric t_{max} from 60 min (range: 45–75 min) in the fasted state to 165 min (range: 135–180 min) in the fed state. Maximum gastric concentrations were not significantly affected by the nutritional state: 7 ± 1 mM and 9 ± 4 mM in the fasted and fed state, respectively. Compared to gastric concentrations, maximum duodenal concentrations were on average 2.3- and 2.8-fold lower in the fasted and fed state, respectively.

As tablet disintegration in the fed state was not complete within 180 min of gastric emptying, the net containing the remains of the tablet was manually replaced from the stomach compartment into the duodenum compartment. After 10 min, the tablet was further replaced into the jejunum compartment, where disintegration was completed. This reflects expelling solids from the stomach into the intestine due to intense contractions ('housekeeper wave') and further small intestinal transit. In vivo, tablet behavior may be affected by forces related to these intense contractions [14]; in the current TIM-1 setup, however, tablets will not experience these forces due to their fixed location and manual replacement.

The standard deviations in Fig. 3A demonstrate that fosamprenavir release in the postprandial stomach compartment of TIM-1 was a highly variable process. Taking into account the strictly controlled conditions in TIM-1, this is quite remarkable and may indicate a considerable intrinsic variability of water ingress and subsequent tablet disintegration in fed state conditions.

3.2.2. Bioaccessible fosamprenavir fraction

Fosamprenavir present in the filtrate of the jejunum and ileum compartments of TIM-1 constituted the fraction of fosamprenavir

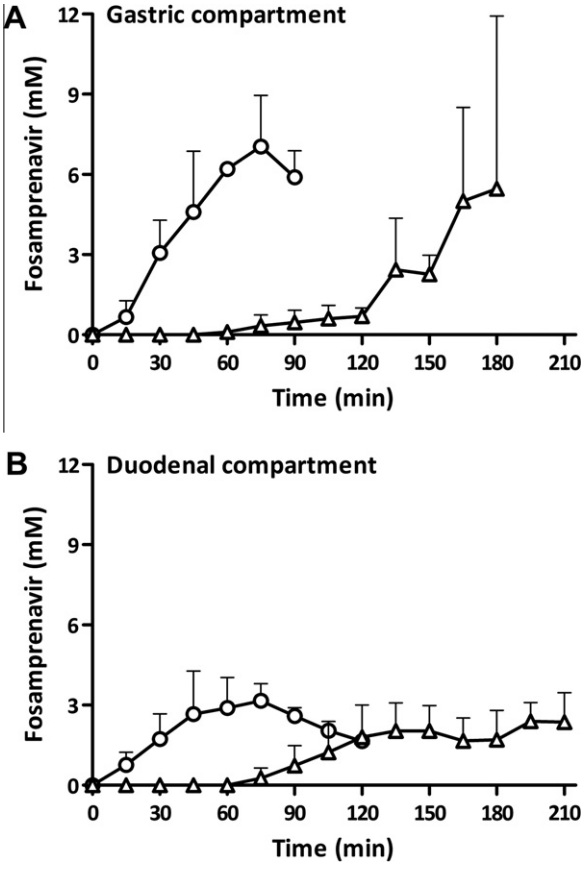

Fig. 3. Fosamprenavir concentration–time profiles in the stomach (A) and duodenum (B) compartment of TIM-1, simulating the fasted (open circles) and fed (open triangles) state. Results are expressed as mean ± sd ($n = 3$).

potentially available for small intestinal absorption. Fig. 4 reports the cumulative bioaccessible fosamprenavir fraction as a function of time. For up to 3 h, the bioaccessibility of fosamprenavir was significantly lower in the fed versus fasted state ($p < 0.05$). In the fasted state, fosamprenavir became already available for absorption in the first hour, with a maximum bioaccessibility in the second hour. In the fed state, however, fosamprenavir was not available for absorption during the first hour and had a maximum accessibility between 2 and 4 h after administration. Interestingly,

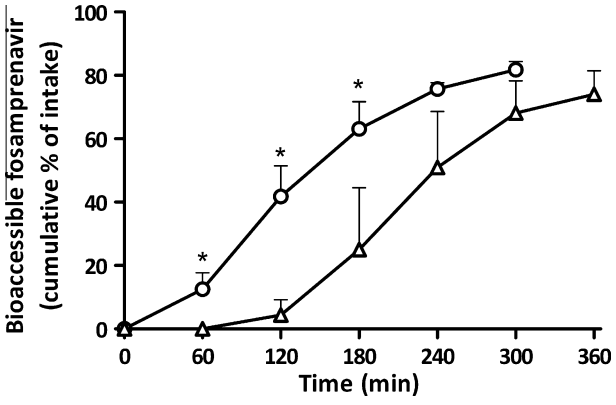

Fig. 4. Cumulative bioaccessible fraction of fosamprenavir as a function of time in TIM-1, simulating the fasted (open circles) and fed (open triangles) state. The bioaccessible fraction consisted of fosamprenavir present in hourly jejunum and ileum filtrate samples. Results are expressed as mean ± sd ($n = 3$). *: significant difference between fasted and fed state (*t*-test, $p < 0.05$).

the nutritional state did not significantly affect the cumulative bioaccessible fraction after 4 and 5 h ($p > 0.05$). Hence, these results suggest a pronounced postprandial effect on the absorption rate, but not on the extent of absorption. It should be noted that, in vivo, the phosphate ester prodrug fosamprenavir cannot cross the intestinal mucosa; dephosphorylation to amprenavir by alkaline phosphatase present in the apical membrane of enterocytes is a prerequisite for absorption [15,16]. As TIM-1 lacks an intestinal mucosa with enterocytes, dephosphorylation cannot be simulated. However, our clinical study with fosamprenavir clearly demonstrated that duodenal appearance of fosamprenavir, rather than intestinal dephosphorylation, limits the rate of amprenavir absorption [4]. As such, assessing the bioaccessible fosamprenavir fraction in TIM-1 should be relevant for amprenavir absorption in vivo.

3.3. Fosamprenavir tablet behavior in TIM-1 versus humans

In order to evaluate the capacity of TIM-1 to predict postprandial disintegration issues with immediate release tablets and their impact on drug absorption, we compared the data on fosamprenavir tablet behavior in TIM-1 to previously obtained clinical data in five healthy volunteers [4]. As already mentioned in the Introduction, this clinical study simultaneously monitored gastric, duodenal and plasma concentrations of (fos)amprenavir upon oral intake of a single fosamprenavir tablet in the fasted or fed (Scandishake Mix®) state.

In Table 3, the effect of the nutritional drink on fosamprenavir tablet behavior as predicted by TIM-1 is compared to the in vivo observations. This comparison clearly demonstrates that the mean postprandial delay in fosamprenavir gastric disintegration/dissolution and duodenal appearance, as observed in healthy volunteers, is quite accurately predicted by TIM-1. In contrast, static dissolution tests in a nutritional drink-based medium overestimated the extent of delay, as fosamprenavir tablets did not disintegrate for at least 4 h in Scandishake Mix® (data not shown).

In addition, the bioaccessibility profiles obtained in TIM-1 suggest that intake of the nutritional drink postpones drug absorption from fosamprenavir tablets by at least 1 h and that maximal absorption is only reached between 2 and 4 h upon tablet administration. This corresponds to the postprandial effect on amprenavir plasma concentrations observed in humans: a lag in absorption between 90 and 150 min (132 ± 27 min) and a t_{max} of 240 ± 60 min compared to 82 ± 43 min in the fasted state. Finally, the TIM-1 data forecast no effect of food on the extent of absorption, in agreement with the comparable AUC- and C_{max}-values of the amprenavir plasma concentration–time profiles in the fasted versus fed state in vivo.

Table 3
Fosamprenavir tablet behavior in TIM-1 versus healthy volunteers. Data are expressed in minutes (mean ± sd).

	Predicted behavior (TIM-1, $n = 3$)	Observed behavior in vivo[a] (healthy volunteers, $n = 5$)
Gastric t_{lag}		
Fasted	No lag	No lag
Fed	80 ± 23	112 ± 13
Gastric t_{max}		
Fasted	60 ± 15	43 ± 15
Fed	160 ± 23	178 ± 40
Duodenal appearance		
Fasted	15 ± 0[b]	10 ± 0[b]
Fed	85 ± 17	101 ± 19
Absorption t_{lag}		
Fasted	No lag	No lag
Fed	Between 60 and 120 min	132 ± 27

[a] Data from [4].
[b] First sampling point.

4. Conclusion

Food effects on tablet disintegration may have significant impact on drug absorption as they can cause immediate release tablets to behave like enteric-coated dosage forms in the postprandial stomach. The present study demonstrated the value of two advanced tools in evaluating food-dependent tablet disintegration. Using MRI, we clearly illustrated the impaired water ingress into HPMC-coated fosamprenavir tablets immersed in a nutritional drink. As such, MRI can be of great assistance in further mechanistic investigations into the role of both tablet and meal composition in postprandial disintegration.

Accurate prediction of impaired postprandial disintegration and its effect on drug absorption in vivo can be achieved using the dynamic TIM-1 system of the upper gastrointestinal tract, as we illustrated by comparing the behavior of fosamprenavir tablets in TIM-1 versus healthy volunteers. Hence, the evaluation of novel or generic immediate release tablets in TIM-1 during formulation development allows the identification of postprandial disintegration issues causing unexpected and undesired clinical behavior.

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