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Gastrointestinal and Systemic Monitoring of Posaconazole in Humans After Fasted and Fed State Administration of a Solid Dispersion

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ABSTRACT

The purpose of this study was to explore the intraluminal behavior and systemic exposure of posaconazole in humans after oral intake of a novel delayed-release tablet (Noxafil®), containing posaconazole dispersed in a matrix of hydroxypropyl methylcellulose acetate succinate. Five healthy volunteers were asked to ingest the tablet in the fasted and fed state condition, after positioning one aspiration catheter in the stomach and one in the jejunum. Subsequently, gastric and jejunal fluids were aspirated and analyzed for posaconazole. In parallel, blood samples were collected. In gastric aspirates, dissolved concentrations were negligible regardless of the test condition, confirming the delayed-release properties of the tablet. In fasted state jejunal aspirates, sustained supersaturation was observed during an average period of time of 93 ± 78.2 min, with a mean maximum degree of supersaturation of 7.28 ± 8.81. In the fed state condition, supersaturation was negligible in the jejunum with a pronounced presence of solid posaconazole, suggesting the importance of more distal intestinal regions for posaconazole absorption.

Introduction

Understanding how interacting gastrointestinal processes affect drug behavior after oral intake is extremely challenging. Nonetheless, gathering knowledge about the interplay among disintegration, dissolution, precipitation, and permeation is critical to optimize the biorelevance of *in vitro* and *in silico* models for an improved prediction of the *in vivo* performance of oral drug products across all stages of drug development. Poor performance prediction especially applies for Biopharmaceutics Classification System class 2/4 compounds with a poor intrinsic potential for intestinal absorption due to low aqueous solubility, because the gastrointestinal behavior of absorption-enabling formulations is often insufficiently characterized.[1,2]

Over the past decade, the interest in amorphous solid dispersions has grown substantially.[3-5] This type of formulation can be defined as an amorphous dispersion of the drug in an inert and compatible carrier. Due to the amorphous state, the drug will benefit from an increased dissolution rate and possibly intraluminal concentrations that exceed the drug's thermodynamic solubility in gastrointestinal fluids (supersaturation), resulting in a higher driving force for intestinal absorption and increased oral bioavailability. Although supersaturation is favorable for absorption, precipitation may limit its benefits.[6-9] In previous studies, we already explored intraluminal processes affecting absorption of the weakly basic drug posaconazole (Biopharmaceutics Classification System class 2), administered as a solution or as suspensions.[10,11] Fasted state posaconazole absorption appeared limited and variable, strongly depending on (i) gastric pH and extent of gastric dissolution, and (ii) duodenal precipitation following transfer from the stomach. To circumvent these sources of variability for posaconazole absorption, formulation scientists focused on the development of a delayed-release solid dispersion: amorphous posaconazole is dispersed by hot-melt extrusion in a pH-sensitive polymer matrix consisting of hydroxypropyl methylcellulose acetate succinate (HPMC-AS).[12] This strategy should circumvent the problems of (i) altered gastric pH in patients by working with HPMC-AS (pKa 5.5) as a gastro-resistant polymer and (ii) intensive intestinal precipitation by using this polymer as a precipitation/recrystallization inhibitor in the intestinal tract.[13-15] Clinical studies revealed that

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this tablet outperforms the oral suspension in terms of posaconazole absorption, without the need for food intake to maximize bioavailability.[16-19] Although it is believed that the molecularly dispersed posaconazole will create a state of supersaturation along the gastrointestinal tract to improve intestinal absorption, it is still questionable how physiological variables will determine or influence gastrointestinal concentrations of posaconazole along the GI tract after oral intake. Therefore, the aim of this study was to assess the impact of this formulation type on different gastrointestinal processes (e.g., drug release, dissolution, supersaturation, precipitation, and intestinal absorption) by monitoring the gastrointestinal behavior and systemic exposure of posaconazole, after administration of the delayed-release solid dispersion to healthy volunteers (HVs), in both the fasted and fed state condition.

Materials and Methods

Chemicals

Posaconazole was kindly donated by the Chemical Research Division of MSD (MSD Research Laboratories, Merck Sharp & Dohme Corporation, Kenilworth, NJ), whereas itraconazole was kindly donated by Janssen Research Foundation (Beerse, Belgium). The marketed delayed-release tablet of posaconazole, Noxafil® (100 mg), was purchased from the University Hospitals Leuven (Leuven, Belgium). Dimethyl sulfoxide (DMSO) and methanol (MeOH) were received from Acros Organics (Geel, Belgium), while BHD Laboratory Supplies (Poole, UK) supplied HCl and NaOH. Acetonitrile, NaCl, and diethylether were received from Fisher Scientific (Leicestershire, UK). Sodium acetate and acetic acid were purchased from VWR (Leuven, Belgium). Biorelevant (Croydon, UK) provided SIF powder in order to prepare fasted state simulated gastric fluid (FaSSGF). Water was purified using a Maxima system (Elga Ltd., High Wycombe Bucks, UK).

To prepare FaSSGF, 60 mg SIF powder was dissolved per liter FaSSGF buffer, which contains NaCl (34 mM) and HCl (pH 1.6). Ensure Plus-based fed state simulated gastric fluid ($FeSSGF_{Ensure\ Plus}$) was prepared by mixing FaSSGF and Ensure Plus in a 1:1 ratio and adjusting to pH 5.

Clinical Study

In a cross-over study, 2 experimental conditions were tested in 5 HVs (1 woman and 4 men, aged between 21 and 26 years). After oral intake of the delayed-release tablet of posaconazole, gastric, jejunal, and systemic concentrations were monitored in the fasted as well as in the fed state condition. In the case of the fed state condition, one volunteer (HV 4) dropped out. Gastric concentrations were monitored in all volunteers, except for HV 4. In a preliminary set of experiments, one extra volunteer (HV A) was recruited to monitor duodenal concentrations of posaconazole in the fasted and fed state condition.

All volunteers provided written informed consent to participate in the clinical study. Following the tenets of the Declaration of Helsinki, the clinical study was approved by the Committee of Medical Ethics of the University Hospitals Leuven (Leuven, Belgium; ID S58133) and the Federal Agency of Health and Medicines (EudraCT ID 2015-002703-28). Exclusion criteria for this clinical study were gastrointestinal disorders, infection with hepatitis B, hepatitis C, or HIV, use of medication, pregnancy, and frequent X-ray exposure. These criteria were checked for every volunteer during a medical examination.

After an overnight fasting period of at least 12 h, volunteers were asked to come to the hospital. A customized aspiration 3-channel catheter (outer diameter 6.3 mm, lumina 0.8 and 2.9 mm, body length 150 cm; MUI Scientific, Mississauga, ON) was introduced via the mouth/nose and positioned in the jejunum (first segment, approximately 50 cm from the pylorus). Subsequently, a second double-lumen polyvinyl catheter (Argyle Salem Sump Tube, 14 Ch (external diameter 4.7 mm); Sherwood Medical, Tullamore, Ireland) was positioned in the antrum of the stomach. Positioning was checked by fluoroscopy (Fig. 1). In the case of the extra volunteer HV A, one double-lumen polyvinyl catheter was positioned in the duodenum (D2/D3) instead of the jejunum. During the entire experiment, volunteers were sitting in an upright position. They were asked to ingest the tablet in 2 different test conditions, that is, fasted and fed state condition, on 2 different test days (minimum 7 days between each test condition). In the first test condition, one tablet of 100 mg posaconazole was taken orally with 240 mL of water. In the second test condition, volunteers were asked to drink 400 mL of Ensure Plus® nutrient shake (Abbott Laboratories B.V., Zwolle, The Netherlands), 20 min prior to oral intake of the tablet with 240 mL of water (Fig. 2).

After oral administration, gastrointestinal fluids were aspirated for 4 h; samples were taken at 15, 35, and 60 min during the first hour and every 15 min for the next 3 h. The sampling volume was kept as small as possible (<4 mL per time point). Immediately after aspiration of fluids, pH was measured (Hamilton Knick Portamess®, Bonaduz, Switzerland) and the determination of dissolved and total posaconazole was initiated (see below). Blood samples were collected in heparinized tubes (BD Vacutainer systems, Plymouth, UK) at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, and 24 h after oral administration. Blood samples were centrifuged (2880 × *g*, 10 min, 4°C) and the obtained plasma was stored at −26°C until analysis (see below: Analysis of Posaconazole in Plasma).

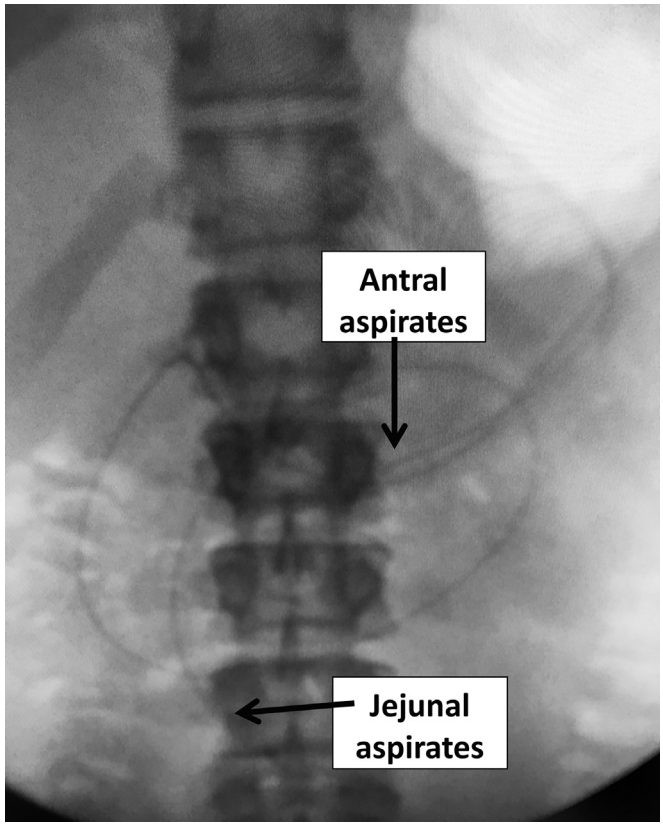

Figure 1. Fluoroscopic image of the position of a 3-channel catheter in the jejunum and a double-lumen catheter in the antrum of a healthy volunteer.

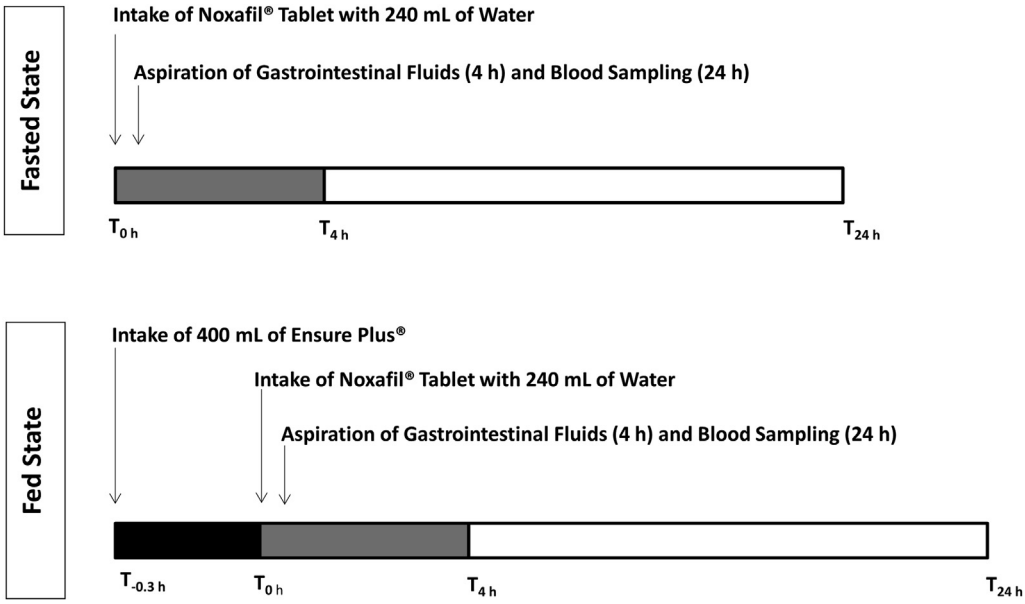

Figure 2. Clinical study protocol in the fasted and fed state test condition as a function of time. Aspiration of gastrointestinal fluids was performed at 15, 35, and 60 min for the first hour and every 15 min for the next 3 h. In parallel, blood samples were collected for 24 h.

Posaconazole in Gastrointestinal Fluids: Dissolved Concentration, Total Content, and Solubility

In order to determine dissolved concentrations of posaconazole in gastrointestinal fluids, aspirates were immediately centrifuged (20,817 × *g*, 5 min) and the supernatant was 20-fold diluted in mobile phase (methanol: 25 mM acetic acid buffer pH 3.5 [85:15 vol/vol]). To determine the total posaconazole content (i.e., solute + solid), aspirates were directly diluted 20-fold in mobile phase. In both cases, precipitated proteins were separated with an additional centrifugation step (20,817 × *g*, 5 min, 37°C). Samples were analyzed by HPLC-FLUO (see below).

The thermodynamic solubility of posaconazole was determined in all aspirated gastric, duodenal, and jejunal samples as previously described by Hens et al.[10] Briefly, an excess of posaconazole (20 μL of the 40 mg/mL marketed suspension Noxafil) was added to 800 μL of the fluid. After 24 h of shaking in a 37°C pre-warmed incubator (175 rpm) (KS4000i incubator, Ika, Staufen, Germany), fluids were centrifuged (20,817 × *g*, 15 min, 37°C). After removing the surface layer of the fluid, a sample was taken from the supernatant and diluted 20 times with mobile phase (methanol: 25 mM acetic acid buffer pH 3.5 [85:15 vol/vol]). Precipitated proteins were separated with an additional centrifugation step (20,817 × *g*, 5 min, 37°C). Subsequently, 50 μL of the supernatant was injected into the HPLC system and analyzed for posaconazole (see below).

Based on the dissolved concentration, the total content, and the solubility of posaconazole in the intestinal fluids, the degree of supersaturation (DS) and the fraction of solid amount (π) were calculated according to Equations 1 and 2:

$$DS = \frac{C}{C_{eq}} \quad (1)$$

$$\pi = 1 - \frac{C}{C_t} \quad (2)$$

where C stands for the dissolved concentration of posaconazole in the intestinal fluid sample at the time of aspiration, C_{eq} stands for the thermodynamic solubility of the drug in the corresponding intestinal fluid sample, and C_t stands for the total content of posaconazole (i.e., dissolved and undissolved, expressed in μM). Based on the value of DS, a solution can be defined as supersaturated, subsaturated, or saturated whenever DS > 1, DS < 1, or DS = 1, respectively.

Analysis of Posaconazole in Diluted Gastrointestinal Samples

The diluted gastrointestinal samples (compare supra) were analyzed for posaconazole using HPLC with fluorescence detection. The HPLC system consisted of an Alliance 2695 separations module and a Novapak C-18 column under radial compression (Waters, Milford, MA); detection was performed by fluorescence (Waters 2475 Multiwavelength Fluorescence Detector) at an excitation wavelength of 240 nm and an emission wavelength of 385 nm. An isocratic run with methanol (25 mM acetic acid buffer pH 3.5 [85:15 vol/vol]) was performed with a flow rate of 1 mL/min to generate a retention time of 4.3 min. After 6 min, the column was rinsed for 1 min with methanol (25 mM acetic acid buffer pH 3.5 [75:25 vol/vol]), followed by 2 min with water (25 mM acetic acid buffer pH 3.5 [75:25 vol/vol]), and subsequently re-equilibrated with the initial mobile phase for 2 min. Calibration curves were made in mobile phase based on a stock solution of posaconazole in DMSO (7 mM). Linearity was observed between 20 μM and 39 nM. The accuracy and precision errors were less than 9% and 6%, respectively, for a concentration of 10 μM in human intestinal fluids collected in the fasted state. Quality control samples of 5, 2.5, and 1.25 μM posaconazole in human intestinal fluids collected in the fasted state or fed state (depending on the test condition), which were analyzed together with the samples of the *in vivo* study, resulted in a relative standard deviation and accuracy error of less than 9% and 7%, respectively.

Analysis of Posaconazole in Plasma

Analysis of plasma concentrations was performed by extracting posaconazole from the collected samples as described by Walravens et al.[11] Briefly, 100 μL of internal standard solution (2.5 μM itraconazole in 0.2 N HCl) was added to 1000 μL of plasma. Subsequently, the sample was alkalized with 500 μL of 2 N NaOH. After addition of 5

mL diethylether, samples were vortexed for 30 s and directly centrifuged (2880 × *g*, 10 min, 4°C). Finally, the water layer was discarded and the organic layer was evaporated to dryness under a gentle stream of air. A volume of 300 µL of mobile phase (methanol: 20 mM acetic acid buffer pH 3.3 [76:24 vol/vol]) was added to the remaining residue. After centrifugation (2880 × *g*, 1 min, 4°C), 50 µL of the supernatant was injected into the Hitachi Elite LaChrom HPLC system (VWR International) and analyzed by an L-2480 fluorescence detector (excitation wavelength 240 nm, emission wavelength 385 nm). A gradient run of 19 min was performed in order to obtain retention times of 7.9 and 12 min on the Novapak C-18 column for posaconazole and itraconazole, respectively. A calibration curve in plasma was made based on stock solutions of posaconazole and itraconazole in DMSO. Linearity was observed between 2000 nM and 7.8 nM. Quality control samples of 500 and 50 nM, which were analyzed together with the plasma samples, resulted in accuracy and precision errors of less than 6% and 4%, respectively.

In Vitro *Formulation Behavior in FaSSGF and FeSSGF$_{Ensure\ Plus}$*

In order to explore the formulation behavior in the simulated fluids FaSSGF and FeSSGF$_{Ensure\ Plus}$, a Noxafil tablet was added to 50 mL of gastric media in a beaker with a magnetic stirrer rotating at a speed of 400 rpm. After 15 min, the intactness of the tablet was visually evaluated ($n = 3$). In addition, samples were taken and analyzed for posaconazole by HPLC-FLUO (compare supra).

Data Presentation and Statistical Analysis

For the clinical study, *in vivo* data are presented as mean + standard error of the mean; $n = 5$ for the fasted state condition and $n = 4$ for the fed state condition. Pharmacokinetic parameters (plasma C_{max}, t_{max}, and area under the curve [$AUC_{0\text{-}8h}$]) were compared using a paired t-test (after logarithmic transformation of C_{max} and $AUC_{0\text{-}8h}$); differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Release of Posaconazole in the Stomach

As briefly mentioned in the introduction, one of the major drawbacks of the marketed oral suspension of posaconazole is the uncertainty in systemic exposure due to variability in gastric pH levels among patients.[16,20] In this respect, formulation scientists focused on the development of a gastro-resistant tablet. Because HPMC-AS was processed together with the active compound in the core of the tablet, drug release in the stomach cannot be excluded.[12] Figure 3 shows the average gastric profiles of posaconazole for 4 volunteers in the fasted

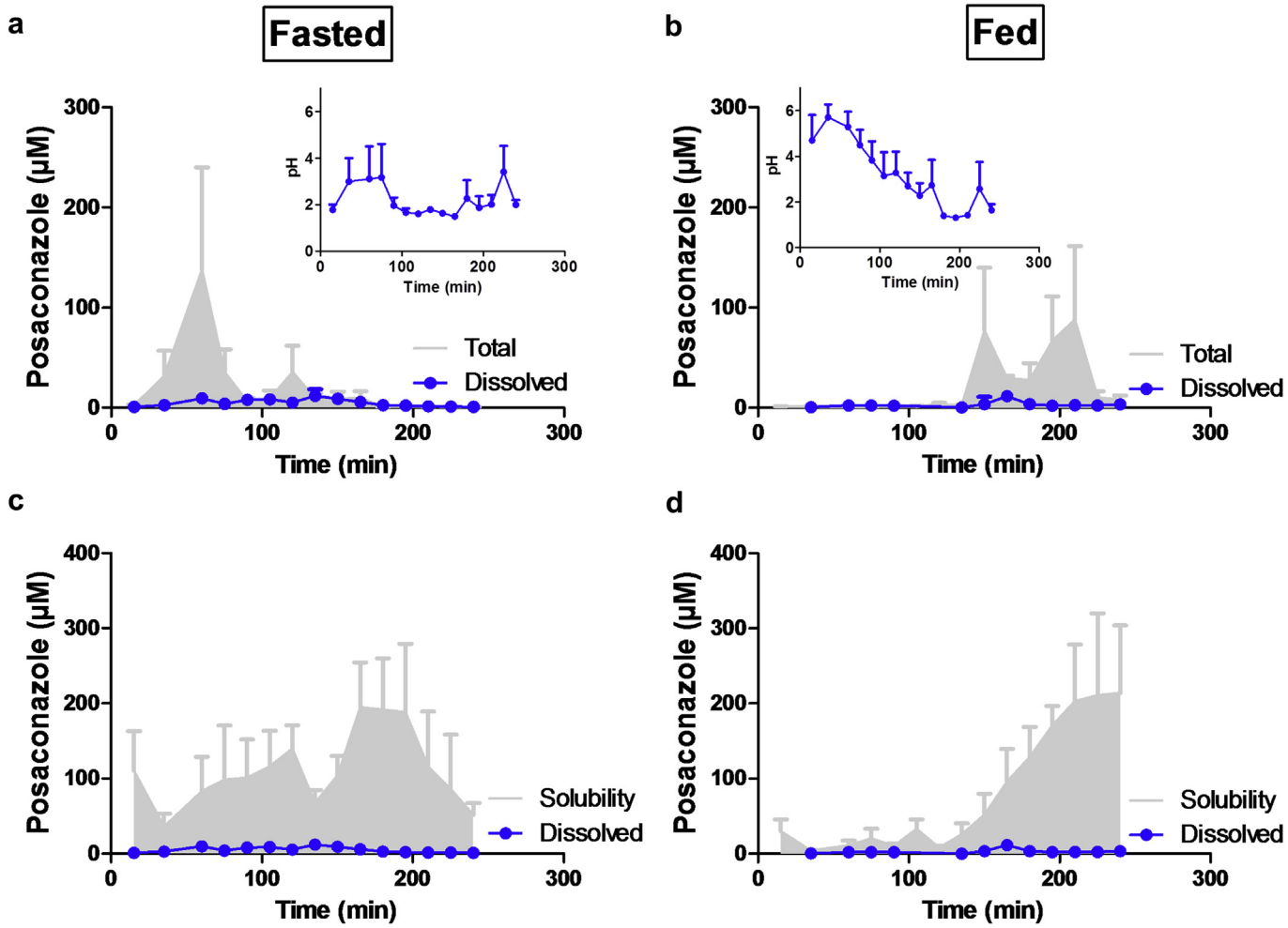

Figure 3. Posaconazole assessment in the stomach after oral administration of the delayed-release tablet Noxafil 100 mg in the fasted (a, c) and fed (b, d) state condition. Upper graphs: gastric concentration-time profiles for dissolved (●) and total (gray curve) posaconazole. The inserts depict gastric pH profiles. Lower graphs: gastric concentration-time profiles for dissolved posaconazole (●) and posaconazole solubility (gray curve) (mean + standard error of the mean, $n = 4$).

(left column) and the fed state (right column). The upper graphs show dissolved concentrations versus total concentrations, while the lower graphs show dissolved concentrations versus the solubility of posaconazole in the corresponding gastric fluid. Although dissolved gastric concentrations were negligible, relatively high total concentrations (i.e., dissolved and undissolved posaconazole) were observed. This may indicate the presence of small particles that eroded off the tablet as a result of partial disintegration due to contraction waves in the stomach (depending on the phase of the inter-digestive migrating motor complex).[21-23] However, the fact that dissolved concentrations were negligible compared to the solubilizing capacity of these gastric fluids for posaconazole confirmed the shielding effect of the polymer to prevent posaconazole dissolution and thus the gastro-resistant properties of the tablet.[17]

In the case of postprandial condition, the gastric pH level exceeded the pKa value of 5.5 for HPMC-AS (5.5) during the first 35 min. Although disintegration of the tablet could be expected, no release was observed. Only when the gastric pH dropped below 2 after more than 2.5 h, tablet disintegration appeared to initiate (as indicated by increased total posaconazole content, analogous to the fasted state). The effect of food on tablet disintegration has widely been discussed in literature.[24] It has been shown, both *in vitro* and *in vivo*, that the presence of food can induce the formation of a film around the tablet, hampering disintegration and subsequent dissolution of the drug substance.[25,26] This film formation can be visualized using MRI, but the resulting impaired degradation can also be identified in a simple *in vitro* dissolution experiment in the presence of a liquid meal.[27,28] After a gastric residence time of 15 min, the posaconazole tablet appeared still intact in $FeSSGF_{Ensure\ Plus}$ (pH 5) but not in FaSSGF (pH 1.6) (Fig. 4). Dissolved posaconazole concentrations were limited in FaSSGF (39.7 ± 8.17 μM) and not detectable in $FeSSGF_{Ensure\ Plus}$. The observations in the stomach already suggest differences in formulation behavior between the fasted and fed state condition, due to differences in gastric media.

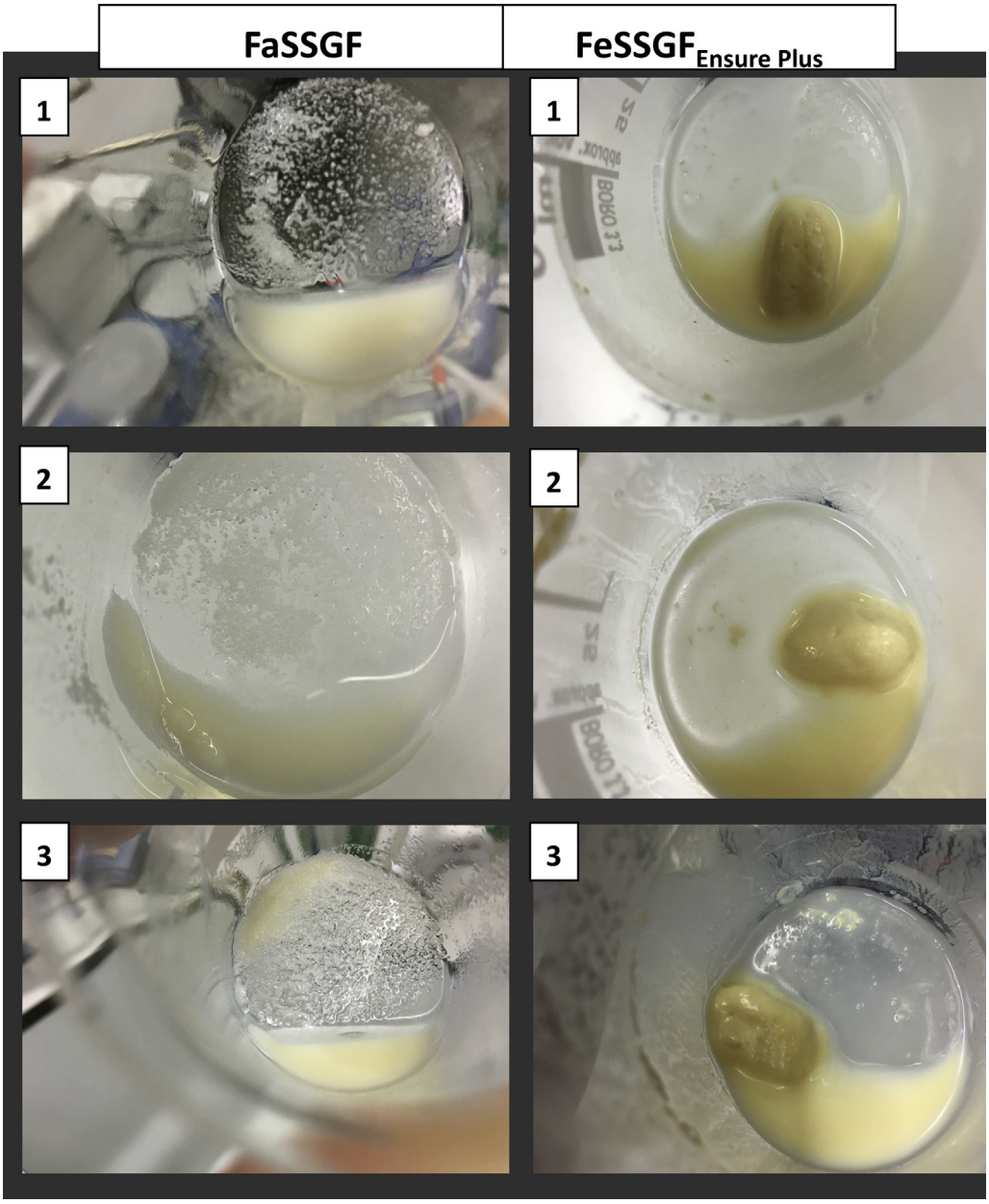

Figure 4. Pictures of the *in vitro* disintegration of 3 delayed-release tablets Noxafil 100 mg after 15 min of residence time in FaSSGF and $FeSSGF_{Ensure\ Plus}$.

Release of Posaconazole in the Duodenum

In one volunteer (HV A), the intraluminal behavior of posaconazole was explored by sampling fluids from the duodenum. Figure 5 illustrates the obtained duodenal profiles of posaconazole for HV A in the fasted state (left column) and fed state condition (right column). The upper graphs show dissolved concentrations versus total concentrations, while the lower graphs show dissolved concentrations versus the solubility of posaconazole in the corresponding duodenal fluid. A maximum total content of 48 μM posaconazole was observed in the postprandial condition, of which only a small amount was in the solution. Moreover, comparing dissolved concentrations and solubility in both the fasted and fed state condition reveals unsaturated concentrations, and not the supersaturated state which would be expected based on formulation design. Taking into account the delayed-release characteristics of the formulation, these results suggest that the duodenum (with its limited length of approximately 25 cm) is not the most critical site in the intestine to judge the behavior of the posaconazole tablet. We therefore decided to assess posaconazole release and dissolution further down the small intestine, in the proximal jejunum.

Release of Posaconazole in the Jejunum

Figure 6 illustrates the concentration-time profiles of posaconazole in samples obtained from the proximal jejunum in the fasted (left column) and fed (right column) state condition. The upper graphs depict dissolved concentrations versus total concentrations, while the lower graphs show dissolved concentrations versus the solubility of posaconazole in the corresponding jejunal fluid aspirates. Comparing dissolved and total concentrations in the fasted state condition, a high fraction of solid material appeared available, as a result of undissolved and precipitated posaconazole. Notwithstanding the high fraction of solid material, supersaturated concentrations of posaconazole were present in jejunal fluids of all volunteers. Supersaturation was observed for, on average, 93 ± 78 min (ranging from 30 to 205 min; Table 1), with a mean maximum DS of 7.3 ± 8.8 (ranging from 1.8 to 20.8). The time window of supersaturation observed in the jejunum after intake of the tablet was more sustained compared to supersaturation in the duodenum after intake of an acidified suspension (approximately 45 min) or a solution (approximately 8 min) of posaconazole, as described in a recent study.[10] The gradual release from an amorphous solid dispersion and the presence of a precipitation inhibitor can explain this mechanism of sustained supersaturation in the jejunum. It is worth mentioning that fluctuations of intestinal volumes as a function of time will influence the dissolved amount of posaconazole, which may affect the fraction absorbed.[29]

The relatively low yet stable DS, maintaining the driving force for intestinal absorption, resulted in a mean plasma C_{max} of 318 ± 114 nM after intake of the 100 mg tablet (Fig. 7). This was

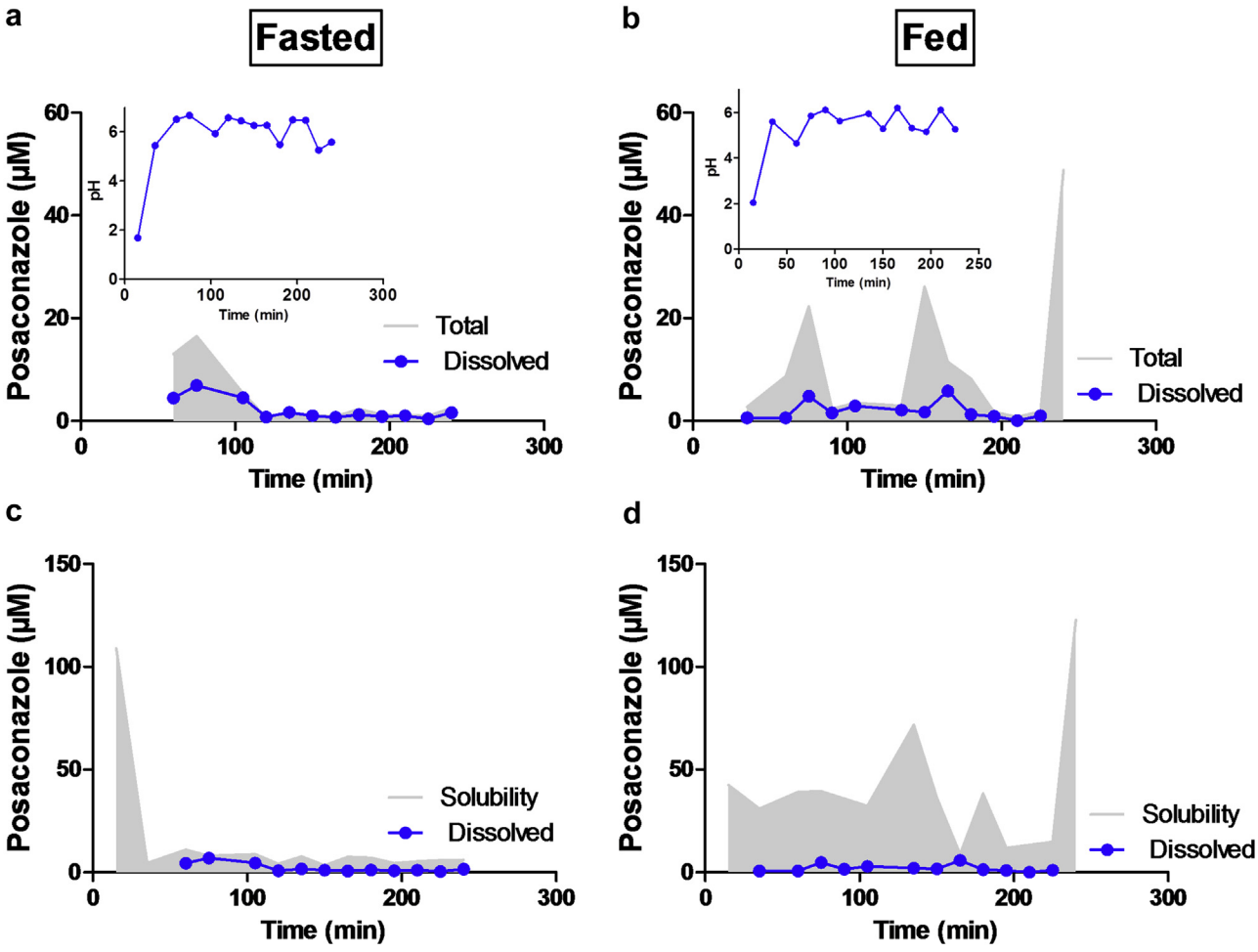

Figure 5. Posaconazole assessment in the duodenum after oral administration of the delayed-release tablet Noxafil 100 mg to HV A in the fasted (a, c) and fed (b, d) state condition. Upper graphs: duodenal concentration-time profiles for dissolved (●) and total (gray curve) posaconazole. The inserts depict duodenal pH profiles. Lower graphs: duodenal concentration-time profiles for dissolved posaconazole (●) and posaconazole solubility (gray curve).

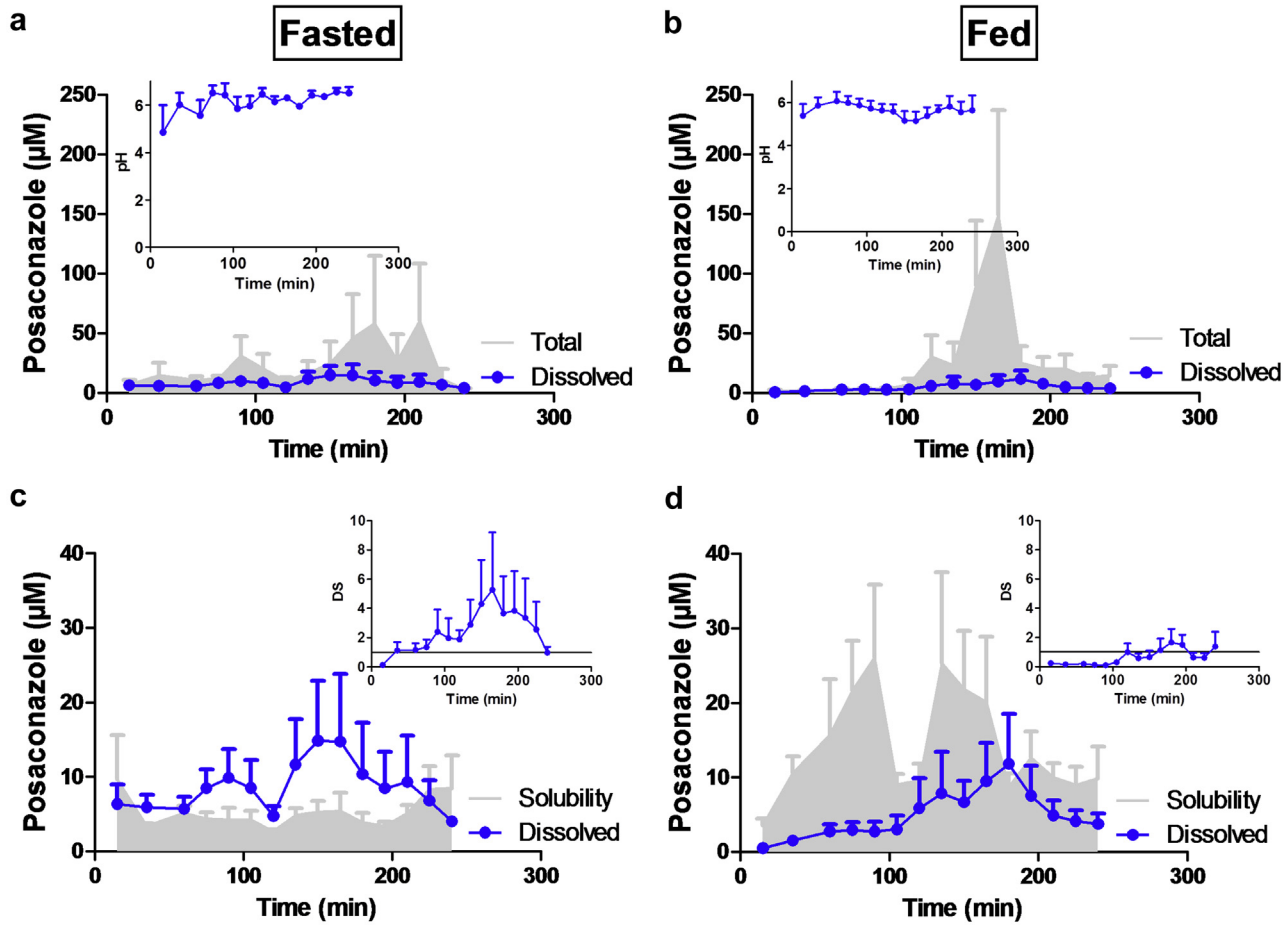

Figure 6. Posaconazole assessment in the jejunum after oral administration of the delayed-release tablet Noxafil 100 mg in the fasted (a, c) and fed (b, d) state condition. Upper graphs: jejunal concentration-time profiles for dissolved (●) and total (gray curve) posaconazole, including jejunal pH profiles. Lower graphs: jejunal concentration-time profiles for dissolved posaconazole (●) and posaconazole solubility (gray curve). The inserts depict the DS as a function of time, determined as the ratio of posaconazole concentration to solubility in individual fluid samples (mean + standard error of the mean, $n = 5$).

substantially higher than the plasma C_{max} observed after intake of the 400 mg suspension (155 ± 46 nM, as observed in a previous study),[11] confirming improved absorption of posaconazole from the solid dispersion compared to the suspension.[9,30] In line with this result, Krishna et al. studied systemic exposure of posaconazole in a single dose (100 mg) cross-over study in the fasted and fed state. Based on these results, administration of the posaconazole solid dispersion resulted in an increase in C_{max} of approximately 75% compared to the suspension, with a minimal food effect on systemic exposure.[16]

Table 1
Individual and Mean Descriptive Parameters of the Jejunal and Systemic Concentration-Time Profiles Following Oral Administration of Posaconazole as a Delayed-Release Tablet to Healthy Volunteers in the Fasted ($n = 5$) and Fed State ($n = 4$)

Variable	HV 1	HV 2	HV 3	HV 4	HV 5	Mean ± SD
Fasted state						
Jejunum						
Maximum DS	20.8	8.33	2.50	1.76	3.01	7.28 ± 8.81
Duration of supersaturation (min)	120	205	55	30	55	93 ± 78.2
$AUC_{0\text{-}4h}$ (μM·h)	62.6	37.5	10	11.2	23.8	29 ± 21.8
Plasma						
$AUC_{0\text{-}8h}$ (nM·h)	1066	1404	1032	1360	745	1122 ± 269
C_{max} (nM)	284	396	263	469	179	318 ± 114
T_{max} (h)	6	3.5	2.5	2.5	6	4.1 ± 1.8
Fed state						
Jejunum						
Maximum DS	2.93	3.67	0.39	NA	0.17	1.47 ± 1.70
Duration of supersaturation (min)	90	60	0	NA	0	37.5 ± 45
$AUC_{0\text{-}4h}$ (μM·h)	37.8	22.5	3.1	NA	2.8	16.6 ± 16.9
Plasma						
$AUC_{0\text{-}8h}$ (nM·h)	1783	1677	1835	NA	442	1434 ± 664.8
C_{max} (nM)	430	468	471	NA	182	388 ± 138
T_{max} (h)	5	3.5	6	NA	7	5.4 ± 1.5

NA, not available; SD, standard deviation.

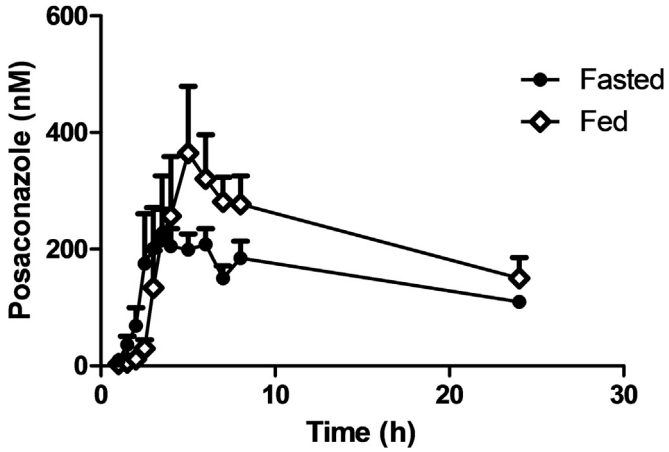

Figure 7. Systemic concentration-time profiles of posaconazole following oral administration of the delayed-release tablet Noxafil 100 mg in the fasted (●, $n = 5$) and fed (□, $n = 4$) condition (mean + standard error of the mean).

It is interesting to note that the substantial inter-individual variability in both degree (ranging from 1.76 to 20.8) and duration (ranging from 30 to 205 min) of jejunal supersaturation was not related to variations in the systemic exposure (Table 1). This suggests that a full characterization of the intraluminal behavior of the solid dispersion in relation to the systemic exposure requires drug concentration monitoring over a longer segment of the intestine. Small inter-individual variations in drug release kinetics and gastrointestinal transit may cause critical intraluminal events (including supersaturation) to occur at varying positions in the intestine.

In the postprandial condition, the presence of solid material was more pronounced than in the fasted condition (Fig. 6b), while dissolved concentrations were slightly lower (jejunal $AUC_{0\text{-}4h}$: 16.6 ± 16.9 μM·h in the fed state vs. jejunal $AUC_{0\text{-}4h}$: 29 ± 21.8 μM·h in the fasted state). Combined with the increased solubilizing capacity (Fig. 6d) in fed state fluids, this resulted in (i) a lower maximum DS (1.47 ± 1.70) and (ii) a smaller time window of supersaturation (37.5 ± 45 min), as depicted in the insert of Figure 6d. However, the systemic exposure was slightly higher in the fed state condition (Fig. 7); the difference was not statistically significant ($p > 0.05$), as also observed by Krishna et al.[16] Combined with the impaired disintegration of the tablet in the postprandial stomach (Figs. 3 and 4), these observations indicate delayed drug release and suggest the importance of more distal regions in the intestine for posaconazole absorption in the fed state condition. This is supported by a delayed plasma T_{max} (5.4 ± 1.5 h in the fed state vs. 4.1 ± 1.8 h in the fasted state).

Conclusion

In contrast to the oral suspension, administration of the HPMC-AS-based delayed-release solid dispersion of posaconazole results in sustained supersaturation in the human intestine, which may contribute to improved fasted state absorption. The different behavior of the solid dispersion in the upper gastrointestinal tract after intake of a meal does not result in a food effect on the systemic exposure, suggesting the importance of more distal intestinal regions for posaconazole absorption.

Acknowledgments

This work is dedicated to the memory of my father, Patrick Hens (1957-2015), and to the memory of Dr. Marcus Brewster (1957-2014).

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