dx.doi.org/10.14227/DT330126P06

Can Biorelevant Dissolution Testing Help Elucidate Salt Formulation Effects on Plasma Levels and Onset of Action? A Study of Ibuprofen and Its Salts

Niklas Rudolph[1#], Laurin Zöller[1#], Sandra Klein[2], Christoph Saal[3], and Jennifer Dressman[1*]
[1]*Fraunhofer Institute for Translational Medicine and Pharmacology, Frankfurt am Main, Germany.*
[2]*Department of Pharmacy, Institute of Biopharmaceutics and Pharmaceutical Technology, University of Greifswald, Greifswald, Germany.*
[3]*Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany.*

email: dressman@em.uni-frankfurt.de

ABSTRACT

Introduction: Salt formulations are widely used in the pharmaceutical industry to increase drug solubility and accelerate dissolution. In this work, the enhancing effect of salt formulations on the absorption rate of ibuprofen was investigated in both the fasted and fed states, using biorelevant dissolution testing. **Methods:** The dissolution behavior of two different ibuprofen salts was studied using two commercially available formulations: Dolormin, containing the lysinate salt of ibuprofen, and Spedifen, containing the arginate salt. Their dissolution was compared to that of the orodispersible tablet formulation containing the free acid (Nurofen) at different dose levels in both single and two-stage dissolution tests. **Results:** When administered in the fasted state, the rapid onset of action of the pharmaceutical salt formulations is directly related to their dissolution behavior, highlighting the importance of choosing suitable dissolution media and methodology to link in vitro with in vivo data. In the fed state, gastric emptying becomes rate-limiting to absorption, such that even fast-dissolving products are not able to provide a short onset of action. **Conclusion:** Biorelevant dissolution delivers key data for determining pharmaceutical salt formulation effects on dissolution in the fed and fasted states.

KEYWORDS: pharmaceutical salts, ibuprofen, biorelevant media, dissolution, fasted and fed state dissolution, two-stage testing

INTRODUCTION

Ibuprofen (IBU) is the non-steroidal anti-inflammatory drug (NSAID) most commonly prescribed to manage inflammatory diseases and pain modulation (*1*). The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin levels, which are pro-inflammatory signaling molecules (*2*). Consequently, NSAIDs represent a pivotal component in the treatment of inflammatory diseases (*3*). However, the influence of NSAIDs extends beyond inflammation, as they also function as analgesic and antipyretic agents, capable of reducing fever and providing relief from mild to moderate acute pain of diverse origins (*2*, *4*, *5*). Acute pain, which is defined as a physiological response to noxious stimuli that is intended to avert actual or potential tissue injuries, typically has a sudden onset (*6*). Consequently, achieving therapeutic drug levels as quickly as possible is imperative to pain relief.

Since the introduction of IBU in 1969, pharmaceutical companies have diligently sought to modify its release and absorption kinetics (*1*). Alongside the introduction of orodispersible formulations (e.g., Nurofen orodispersible tablets) as fast-dissolving alternatives, there has been a focus on formulations containing pharmaceutical salts to accelerate dissolution and consequently reduce the time to onset of action (*7*). This has resulted in the emergence of commercially available IBU products containing different pharmaceutical salts. A comprehensive understanding

*Corresponding author, #Equal first authors

of the extent to which these pharmaceutical salts can influence IBU release from the formulation, under both fasted and fed state conditions, is key to determining when a salt formulation will be advantageous over formulations of the free acid for the treatment of acute pain.

In the present study, the dissolution performance of three different formulations of IBU was investigated: Nurofen orodispersible tablets containing IBU free acid, Dolormin film-coated tablets containing the lysinate salt, and Spedifen granules containing the arginine salt. Single stage-dissolution was investigated in biorelevant media simulating the fasted state simulated gastric fluid (FaSSGF) and fed (FEDGAS) states to investigate the influence of formulation on the in vivo dissolution of IBU when given either on an empty stomach or after a meal.

The first objective of the studies was to determine whether the gastric pH at the time of ingestion has an effect of IBU release from the various formulations. When the dose is taken on an empty stomach, the volume of water swallowed with the dose dilutes any residual gastric acid, which in turn impacts the pH in the stomach. To standardize the volume ingested, the FDA Guidance on bioequivalence studies requires participating subjects to take tablets and capsules with a glass of water, a volume of approximately 8 oz (~240 mL) (*8*). Although patient information leaflets for most solid oral dosage forms also advise ingesting the dose with a glass of water, in practice, many patients take the dose with only a swallow or two of fluid. For orally disintegrating tablets, patients are advised that they can ingest the dose without water.

The biorelevant medium FaSSGF was designed to reflect the average pH in the stomach (pH 1.6) after ingestion of a glass of water in the fasted state (*9*). However, it has since been demonstrated that this results in a temporary increase in the pH of gastric fluids to a value of pH 3–4 (*10*). To more accurately replicate the conditions of release immediately after ingestion of a glass of water, Tsume et al. introduced a new medium, $FaSSGF_{DIL}$ ("diluted FaSSGF"), which has a higher pH of 2.34 (*11*). In these studies, dissolution of the products was tested in both media to reflect both the average (FaSSGF) and peak ($FaSSGF_{DIL}$) pH values in the fasted stomach. In addition to single-stage testing, two-stage testing was carried out using either FaSSGF and $FaSSGF_{DIL}$ as the donor phase, followed by conversion to fasted state simulating intestinal fluid-version 1 (FaSSIF-V1) as the acceptor phase (*12*).

The second objective was to ascertain the impact of the IBU dose on its release under fasted state conditions. To this end, dissolution tests were conducted for Nurofen, Dolormin, and Spedifen at various doses corresponding to 200, 400, and 600 mg of IBU as the free acid.

The third objective was to study release from the three formulations under fed state conditions to determine whether release from the dosage form or gastric emptying would be the rate-limiting step to absorption. For this purpose, the recently introduced FEDGAS media were used to assess the IBU products under fed gastric conditions (*13*). Three FEDGAS versions have been developed to mimic the composition of the gastric contents after ingestion of a high-fat meal in the early, middle, and late phases of digestion. Their compositions are specially tailored to represent the composition of gastric contents in the fed state over time, making FEDGAS media a valuable tool for forecasting formulation performance in product development (e.g., bioequivalence to originator product) (*13*).

As a last step, the results of the various dissolution studies were compared with the results of clinical studies, which have reported different pharmacokinetic behavior among the three products studied.

METHODS

Materials

Nurofen (200 mg) orodispersible tablets (lot KY216) were purchased commercially from Reckitt Benckiser Deutschland GmbH (Heidelberg, Germany). Dolormin (200 mg) film-coated tablets (lot KJL4L01) were obtained from Johnson & Johnson GmbH (Neuss, Germany). Spedifen (600 mg) granules (lot 380063) were obtained from Zambon Switzerland Ltd (Cadempino, Switzerland). The excipients in these three formulations are listed in Table 1.

IBU Pharmaceutical Secondary Standard (lot LRAC0253) was purchased from Sigma Aldrich (Taufkirchen, Germany).

Hydrochloric acid (1N HCl) (lot 22G134004), 1N sodium hydroxide (lot 21D204022), and acetonitrile ([CAN] lot 21l142132) as well as 0.45-µm Chromafil filters and 0.45-µm PTFE ReZist filters were purchased from VWR International GmbH (Darmstadt, Germany). Polyethylene prefilters (10 µm) were obtained from Quality Lab Accessories (Telford, PA, USA), and glass microfiber filters (diameter 0.47 mm; pore size 0.7 µm) (lot 9850840) were purchased from GE Healthcare (Chicago, IL, USA). Sodium chloride (lot: 52318748) was obtained from Carl Roth GmbH + Co. KG (Karlsruhe, Germany).

Table 1. Excipients in Nurofen Orodispersible Tablets, Dolormin Film-Coated Tablets, and Spedifen Granules

	Nurofen (*7*)	Dolormin (*43*)	Spedifen (*25*)
IBU Dose (Form)	200 mg (free acid)	200 mg (lysinate salt)	600 mg (arginate salt)
Excipients	Ethyl cellulose Silicon dioxide Hypromellose Mannitol Aspartame Croscarmellose sodium Magnesium stearate Lemon aroma	Microcrystalline cellulose Povidone (K30) Magnesium stearate Titanium dioxide Hyprolose Hypromellose	Arginine Sodium bicarbonate Sucrose Apricot aroma Aspartame Saccharin sodium

IBU: Ibuprofen.

$FEDGAS_{early}$ (lot FEDBUF6-0422), $FEDGAS_{middle}$ (lot FEDBUF45-0422-A), and $FEDGAS_{late}$ stage buffer concentrate (lot FEDBUF3-0422-A) as well as FEDGAS gel (lot FEDGAS-1222-A), FaSSIF/FeSSIF/FaSSGF powder (lot FFF-0222), and FeSSIF-V2 powder (lot V2FES-0322-A) were all purchased from biorelevant.com Ltd. (London, UK).

MilliQ (deionized) water was freshly obtained from a Milli Q Reference A+ system (Serial no. F7EA11088B) purchased from Merck KGaA (Darmstadt, Germany). Anhydrous sodium dihydrogen phosphate (lot A0430090) was obtained from Thermo Fisher Scientific Inc. (Waltham, MA, USA). Maleic acid (lot 8608238003B1W) and sodium hydroxide pellets (lot B183516204B1W) manufactured by Merck KGaA were purchased from VWR International GmbH.

Preparation of Biorelevant Dissolution Media

Biorelevant dissolution media were prepared according to the instructions on the biorelevant.com website (*13*, *14*). $FaSSGF_{DIL}$ and FaSSIF-V1 double concentrate media (for two-stage experiments) were prepared using FaSSIF/FeSSIF/FaSSGF powder (3F). The compositions of the media are shown in Tables 2 and 3.

The preparation of each individual FEDGAS medium ($FEDGAS_{early/middle/late}$) was performed using the corresponding buffer concentrate, which was then mixed with the FEDGAS gel.

This study utilized three distinct dissolution media, each of which represents a specific gastric residence time after a meal, because the composition and volume of the gastric contents undergoes changes with time postprandially (*15*). Accordingly, the volume and pH of the test medium was successively reduced from 900 mL in $FaSSGF_{early}$ (pH 6.0) to 500 mL in $FaSSGF_{middle}$ (pH 4.5) and $FaSSGF_{late}$ (pH 3.0), thereby mimicking the fed state in the stomach. Based on the time frames for FeSSGF suggested by Markopoulos et al., $FEDGAS_{early}$ corresponds to the first 75 minutes after meal ingestion, $FEDGAS_{middle}$ corresponds to 75–165 minutes post-ingestion, and $FEDGAS_{late}$ represents the period beyond 165 minutes (*16*). The dissolution of IBU from each product was tested in single stage experiments using each of the FEDGAS media.

Table 2. Compositions of Biorelevant Media Representing the Fasted Gastric State

	FaSSGF	$FaSSGF_{DIL}$	FaSSIF-V1 (double concentrated for two-stage experiments)
NaCl (mg)	499.75	99.95	2093
1 N HCl (mg)	7275	1455	-
NaOH pellets (mg)	-	-	210.0
NaH_2PO_4 (anhydrous) (mg)	-	-	1719
FaSSIF/FeSSIF/ FaSSGF powder (mg)	15	3	1090
Medium volume used in dissolution experiments (mL)	250	250	250
pH	1.60	2.34	6.55 / 7.50*

**Depending on the pH of the gastric medium, double concentrated FaSSIF-V1 was adjusted to either 6.55 ($FaSSGF_{DIL}$) or 7.50 (FaSSGF), with the aim of generating a final pH of 6.50 in the acceptor medium (FaSSIF-V1) in two-stage tests.*
FaSSGF: fasted state simulated gastric fluid; $FaSSGF_{DIL}$: diluted FaSSGF; FaSSIF-V1: FaSSIF version 1; FaSSIF: fasted state simulated intestinal fluid; FeSSIF: fed state simulated intestinal fluid.

Table 3. Compositions of Biorelevant Media Representing the Fed Gastric State (FEDGAS)

	$FEDGAS_{early}$	$FEDGAS_{middle}$	$FEDGAS_{late}$
FEDGAS buffer concentrate (g)	36.40	19.67	19.06
MilliQ (g)	732.20	406.78	406.72
FEDGAS gel (g)	152.90	84.94	84.94
Medium volume used in dissolution experiments (mL)	900	500	500
pH	6.0	4.5	3.0

Single-Stage Dissolution Testing

Under fasted gastric conditions, all three products were studied at doses of 200, 400, and 600 mg using single-stage dissolution tests. Under fed gastric conditions, 200 mg of Nurofen and Dolormin and 600 mg of Spedifen were studied.

Single-stage dissolution tests were performed in a calibrated USP paddle apparatus (type 2, PTWS 120S dissolution tester, Pharma Test Apparatebau AG, Hainburg, Germany) using standard vessels and paddles. Single-stage tests using FaSSGF at pH 1.6 or $FaSSGF_{DIL}$ were performed in 250 mL of dissolution medium. Tests using FEDGAS were conducted with 900 mL of $FEDGAS_{early}$ or 500 mL of $FEDGAS_{middle}$ and $FEDGAS_{late}$. All media were freshly prepared and maintained at 37 ± 0.5 °C. The paddle speed was set to 75 rpm, and all experiments were conducted at least in triplicate.

Samples from FaSSGF, $FaSSGF_{DIL}$, and FaSSIF-V1 were withdrawn using a 5-mL syringe, prefiltered with a 10-µm polyethylene filter. The first 4 mL were returned to the vessel, and 1 mL was filtered through a 0.45-µm PTFE filter (ReZist filter unit; GE Healthcare, Whatman Inc., NJ, USA). The filtrate sample was promptly diluted appropriately with mobile phase. The pH of each sample was measured using a 766 Calimatic pH meter (Knick Elektronische Messgeräte GmbH & Co. KG Berlin, Germany) with an Inlab Micro pH electrode (Mettler Toledo Berlin, Germany). The loss of media due to sampling was accounted for in the calculations.

Samples from FEDGAS were withdrawn using a 5-mL syringe, returning the first 3 mL to the vessel. The remaining 2 mL were collected in an Eppendorf vial, and 1 mL was withdrawn and diluted with acetonitrile in a ratio of 3:2 (v:v). The sample was then promptly vortexed, followed by centrifugation (MicroCL 21R centrifuge, Thermo Fisher Scientific, Karlsruhe, Germany) at 14,000 rpm and 4 °C for 20 minutes. After centrifugation, the supernatant was diluted in a ratio of 3:10 (v:v) with mobile phase for Nurofen and Dolormin and 3:40 for Spedifen, resulting in final dilutions of 1:5 (v:v) and 1:20 (v:v), respectively. The loss of media due to sampling was compensated for by adding fresh media to the vessel.

Two-Stage Dissolution Testing

Two-stage dissolution testing was performed at 200 mg for Nurofen; 200, 400, and 600 mg for Dolormin, and 200 and 400 mg for Spedifen.

Two-stage dissolution tests are typically used to characterize the supersaturation and subsequent precipitation of weakly basic drugs resulting from the pH shift between gastric and intestinal conditions. Another application is evaluation of the behavior of salts of weakly acidic drugs, for which precipitation of the free acid gastric conditions may lead to slower dissolution in the small intestine.

In this study, two slightly different two-stage dissolution protocols were compared. The first method was based on the approach by Mann et al., as implemented in the OrBiTo project (*12*). The second method was developed more recently as part of a Product Quality Research Institute (PQRI) ring study and was designed to better simulate the pH conditions immediately after ingestion of the dosage form with a glass of water (240 mL) (*11*, *17*).

Mann et al. Protocol

For the Mann et al. protocol, in the first stage, 250 mL of FaSSGF (pH 1.6) was used to simulate average gastric conditions in the fasted state (*12*). Following a 30-minute period of dissolution testing in FaSSGF, the change in fluid composition due to gastric emptying was mimicked by adding 250 mL of prewarmed, double concentrated FaSSIF-V1 (pH 7.5). This resulted in a final pH of 6.5, which corresponds to the composition of FaSSIF-V1. Throughout the 3-hour test, the temperature was maintained at 37 ± 0.5 °C in the dissolution apparatus, and the paddle speed was set to 75 rpm. Sample preparation and analysis were conducted in the same manner as for the single-stage tests. Following filtration, the filtrates were promptly diluted with mobile phase in a ratio of 1:1, and the pH of each sample was measured. All studies were conducted at least in triplicate.

PQRI "More Restrictive" Protocol

For the PQRI ring study protocol, the gastric medium was $FaSSGF_{DIL}$, comprising 50 mL of FaSSGF (pH 1.60), to which 200 mL MilliQ water was added, yielding a final pH of 2.34 (*17*). The temperature was maintained at 37 ± 0.5 °C, and the paddle speed was set to 75 rpm. Following 30 minutes of dissolution testing in $FaSSGF_{DIL}$, a pH shift was induced by the introduction of 250 mL of prewarmed, double concentrated FaSSIF-V1 (pH 6.55) into the vessel. The utilization of a lower pH in the double concentrate was necessary, because $FaSSGF_{DIL}$ (pH 2.34) is less acidic than FaSSGF (pH 1.60). The preparation and analysis of the samples followed the same procedure as for the single-stage tests, and all studies were conducted at least in triplicate.

Analytical Methods

Quantitative analysis of samples using FaSSGF, $FaSSGF_{DIL}$, and FaSSIF-V1 (including samples from two-stage testing)

was carried out with an isocratic high-performance liquid chromatography (HPLC) method on a C18, 15-cm, 4.6-mm Purospher STAR, 5-µm LiChroCART column (Merck Millipore, Burlington, MA, USA) using a Hitachi Chromaster 5210 autosampler, 5110 pump, 5310 column oven, and 5410 ultraviolet (UV) detector (VWR Hitachi, Darmstadt, Germany). The mobile phase consisted of a mixture of ACN:MilliQ with 0.1% phosphoric acid (40:60) [v/v]. The column temperature was held at 30 °C, the injection volume was 20 µL, and the flow rate was set to 1.0 mL/min. The drug substance was quantified at 240 nm, with a retention time of 6.0 min. The calibration utilized the area under the curve (AUC) of IBU peaks over the concentration range 3–532 µg/mL and resulted in an $R^2 > 0.9999$, with a limit of detection (LOD) of 1.15 µg/mL and limit of quantification (LOQ) of 3.46 µg/mL.

Analysis of the FEDGAS samples was performed using a second HPLC-UV system, consisting of a VWR Hitachi Chromaster 5160 pump, 5310 oven, 5260 sampler, and a 5420 UV-Vis detector. An isocratic mobile phase consisting of a mixture of ACN:MilliQ with 0.1% trifluoroacetic acid (50:50) [v/v] was applied. A Gemini-NX 250 × 4.6 mm, 5-µm, 5 A column, equipped with a Gemini-NX 5-µm, 110-Å, 5 × 4.6-mm precolumn (Phenomenex, Aschaffenburg, Germany) was used. The temperature was set to 30 °C, the injection volume was 20 µL, and the flow rate was set to 1.0 mL/min. IBU achieved retention times of approximately 12.8 min using this method. The calibration utilized the AUC of IBU peaks over the concentration range 10–70 µg/mL and resulted in an $R^2 > 0.9999$, with an LOD of 1.18 µg/mL and a LOQ of 3.58 µg/mL.

Dissolution test results are expressed as mean ± SD percentage of cumulative release, along with the obtained pH of each sample.

RESULTS

Single-Stage Dissolution Testing Under Fasted Gastric Conditions

The results of single-stage dissolution testing under fasted state conditions are presented in Figures 1–3. The data underlying these figures are available from Zöller (*18*).

Nurofen Orodispersible Tablets

The dissolution profiles of Nurofen orodispersible tablets (free acid form of IBU) are presented in Figure 1. Using a single Nurofen orodispersible tablet (200 mg of IBU), slow and incomplete dissolution was observed in both FaSSGF and $FaSSGF_{DIL}$. After 50 minutes, a plateau concentration of approximately 53 µg/mL was attained in both media. The pH remained close to the initial pH throughout the tests. The dissolution profile was similar when higher doses were tested. For the 400 mg dose, concentrations reached a plateau of approximately 55 µg/mL after 40 minutes. For the 600 mg dose, a plateau of 53 µg/mL in FaSSGF and 56 µg/mL in $FaSSGF_{DIL}$ was reached after 20 minutes.

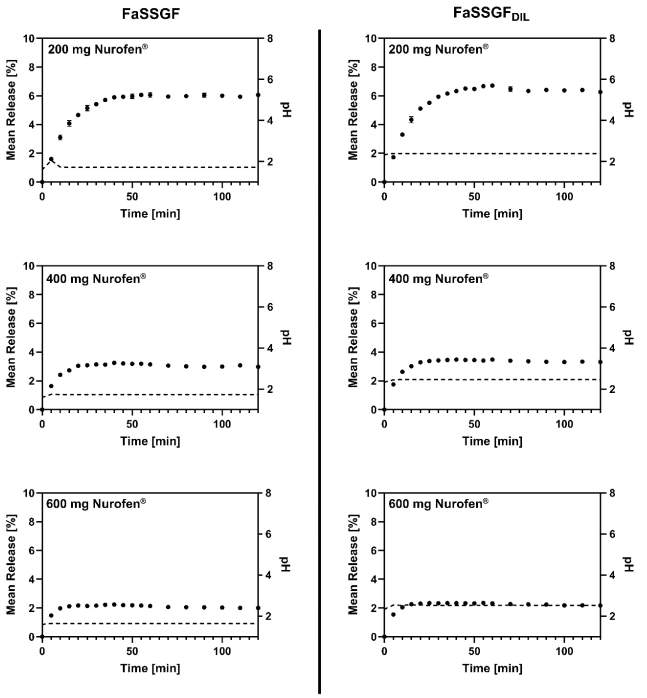

Figure 1. Mean ± SD percentage release of ibuprofen free acid from Nurofen orodispersible tablets (dots) and recorded pH values (dashed lines) in FaSSGF (left) and $FaSSGF_{DIL}$ (right). Most SD bars lie within the symbol. FaSSGF: fasted state simulated gastric fluid; $FaSSGF_{DIL}$: diluted FaSSGF.

Dolormin Film-Coated Tablets

The dissolution profiles of Dolormin film-coated tablets (lysinate salt form of IBU) are presented in Figure 2. The 200-mg single dose of Dolormin dissolved rapidly in both gastric media, initially reaching comparable concentrations of approximately 150 µg/mL. This resulted in supersaturation with respect to the free acid equilibrium solubility (25 µg/mL at pH 1.75 and 28 µg/mL at pH 3.51) (*19*). In FaSSGF, precipitation started after 50 minutes, whereas precipitation began after 25 minutes in $FaSSGF_{DIL}$. While only a marginal increase in pH was recorded for FaSSGF, an increase from 2.34 to 3.51 was measured in $FaSSGF_{DIL}$. However, in both media the final pH was still well below the pKa of IBU (4.5-4.6) (*20*).

More pronounced differences in release behavior of the formulation in the two gastric media were observed at higher doses. In FaSSGF, maximum concentrations of 159 µg/mL and 140 µg/mL were observed at 400 mg and 600 mg , respectively, which was similar to the behavior at 200 mg. Here, too, the maximum concentration was followed by precipitation to the free acid. In $FaSSGF_{DIL}$, by contrast,

the concentration of dissolved IBU reached 822 µg/mL at the 400-mg dose, followed by partial precipitation to a final concentration of 745 µg/mL after 60 minutes. No precipitation was observed for the 600-mg dose, which generated a concentration of 1674 µg/mL.

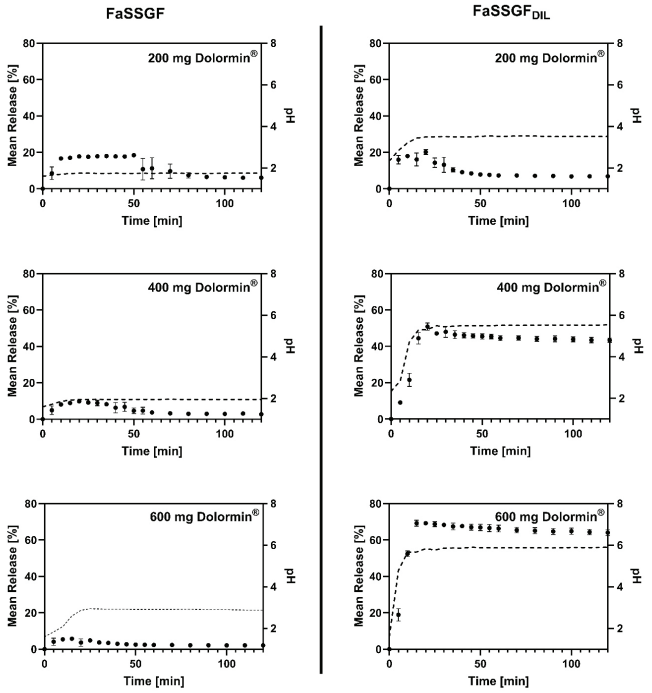

Figure 2. Mean ± SD percentage release of ibuprofen lysinate from Dolormin film-coated tablets (dots) and recorded pH values (dashed lines) in FaSSGF (left) and FaSSGF$_{DIL}$ (right). FaSSGF: fasted state simulated gastric fluid; FaSSGFDIL: diluted FaSSGF.

The differences in concentrations achieved in the two media align with the differences in the final pH of the medium. Final pH values averaged 3.51 for the 200-mg dose, 5.54 at the 400-mg dose and 5.90 at the 600-mg dose using FaSSGF$_{DIL}$. Only marginal increases in pH were observed in FaSSGF, in which final pH values were 1.75 at the 200-mg dose, 1.95 at the 400-mg dose, and 2.87 at the 600-mg dose.

Spedifen Granules

The dissolution profiles of IBU from the Spedifen granules (arginate salt form of IBU) are presented in Figure 3.

For Spedifen, significant variations in pH and the dissolution profile were observed between the two media, even at the lowest dose of 200 mg. Dissolution in FaSSGF reached only 14% release (111 µg/mL) of the dose, which was followed by precipitation to a plateau concentration of 10 µg/mL, and the pH increase was modest. In contrast, dissolution in FaSSGF$_{DIL}$ was almost complete within the first 10 minutes, with 92% release (787 µg/mL) and an increase in pH to nearly 8 by the end of the experiment. At the 400-mg dose, 36% (575 µg/mL) was released in FaSSGF after 15 minutes, with an attendant rise in pH to above 5. Some precipitation followed, to a plateau of around 31% release (533 µg/mL), during which the pH stabilized to a final value of 5.1. In contrast, the same dose in FaSSGF$_{DIL}$ 94% release (1611 µg/mL), comparable to the results with the 200-mg dose, and the final pH was 8.19.

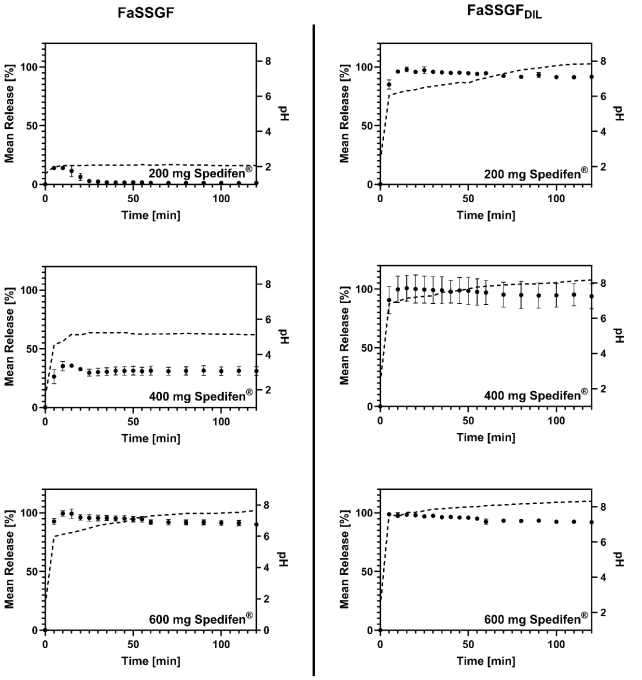

Figure 3. Mean ± SD percentage release of ibuprofen arginate from Spedifen granules (dots) and recorded pH values (dashed lines) in FaSSGF (left) and FaSSGF$_{DIL}$ (right). FaSSGF: fasted state simulated gastric fluid; FaSSGF$_{DIL}$: diluted FaSSGFin).

Interestingly, the dissolution profile for 600 mg of Spedifen was similar in both gastric media. In both cases, complete dissolution was achieved within the first 10 minutes of the test. The pH increased rapidly in the first 5 minutes of both tests to values of pH 5.98 in FaSSGF and pH 7.62 in FaSSGF$_{DIL}$, subsequently trending to a pH of around 8 by the end of the experiment.

Two-Stage Dissolution Testing

The results of two-stage dissolution testing under fasted state conditions using the Mann et al. and PQRI protocols are presented in Figures 4–6. The data underlying these figures are available from Zöller (*18*).

Nurofen Orodispersible Tablets

As shown in Figure 4, the dissolution profiles of the 200-mg Nurofen orodispersible tablets obtained with both protocols displayed a similar pattern. In the initial (gastric) phase, a maximum mean release of 6% (52 µg/mL) and 7% (58 µg/mL) was achieved after 30 minutes using the Mann et al. protocol and PQRI protocol, respectively.

These results were comparable to those in the single stage tests. The slightly higher pH of $FaSSGF_{DIL}$ had little effect on dissolution, as expected from the pKa of IBU (4.5–4.6) (*20*). Subsequent to the pH shift, induced by adding double concentrated FaSSIF-V1, complete dissolution was achieved in both cases. Due to the higher solubility of IBU in an almost pH-neutral environment (3172 µg/mL at pH 6.5), precipitation was neither expected nor observed in the intestinal phase of the two-stage tests (*19*).

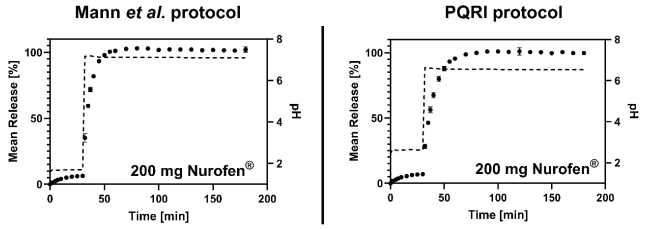

Figure 4. Mean ± SD percentage release of ibuprofen from Nurofen orodispersible tablets (dots) and recorded pH values (dashed lines) using FaSSGF (left) and $FaSSGF_{DIL}$ (right) in two-stage testing. Most SD bars lie within the symbols. PQRI: Product Quality Research Institute; FaSSGF: fasted state simulated gastric fluid; $FaSSGF_{DIL}$: diluted FaSSGF.

Dolormin Film-Coated Tablets

The changes observed in the single-stage tests for pH of the gastric medium were also observed in the gastric phase of the two-stage tests with Dolormin film-coated tablets (lysinate salt). As shown in Figure 5, at the 200-mg dose, the concentrations measured before initiating the intestinal stage were 141 µg/mL for FaSSGF and 164 µg/mL for $FaSSGF_{DIL}$. The pH in FaSSGF changed only marginally from 1.6 to 1.7, and the pH in $FaSSGF_{DIL}$ increased to an average value of pH 3.4.

Concentrations in the gastric phase using FaSSGF (Mann et al. protocol) at doses of 400- and 600 mg were also low, with only a minor increase in pH, in accordance with the results in single-stage testing. In contrast, using $FaSSGF_{DIL}$ (PQRI protocol) a pH of 5.13 and 5.41 were reached at the 400 and 600-mg doses, respectively, in the gastric phase. Higher pH values were associated with a much higher mean release of 52% and 62%, respectively.

After addition of double concentrated FaSSIF-V1, the pH increased to 6.4, resulting in instantaneous dissolution in both protocols at all three doses.

Spedifen Granules

Figure 6 shows that using the Mann et al protocol, during the gastric phase, the 200-mg dose of Spedifen had rapid initial dissolution during the gastric phase, resulting in a concentration of 370 µg/mL, followed by a decline in concentration, which was attended by a minor change in pH from 1.60 to 2.15. Conversely, following the PQRI protocol, dissolution of Spedifen in $FaSSGF_{DIL}$ reached 90% in the gastric phase, with a rapid increase to pH 6.7 at the start of the test. Carrying out the Mann et al. protocol with 400 mg of Spedifen resulted in a more pronounced pH increase to 5.33 in the gastric stage, with little precipitation. Using the PQRI protocol at the same dose, dissolution occurred rapidly without precipitation, with the pH climbing to an average value of 6.8 in the gastric phase. All results for the gastric phase were in concordance with the results of the single-stage tests of Spedifen.

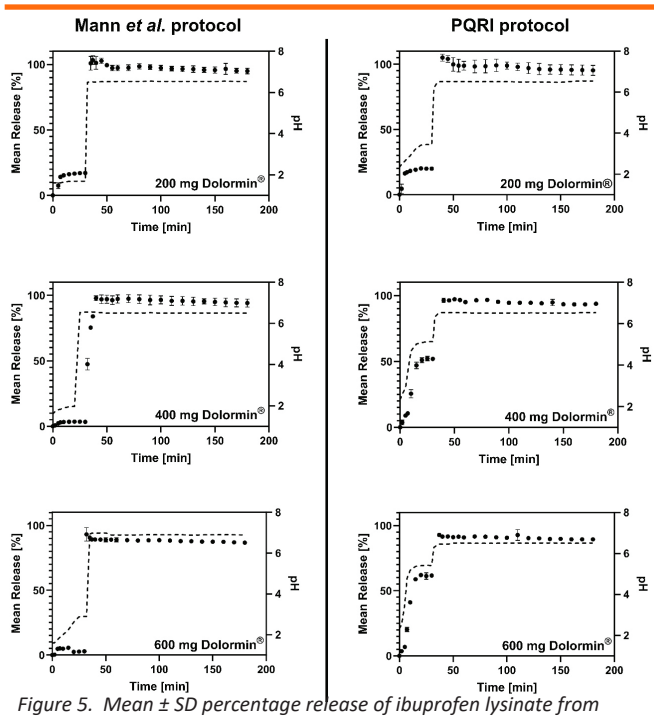

Figure 5. Mean ± SD percentage release of ibuprofen lysinate from Dolormin film-coated tablets (dots), and recorded pH values (dashed lines) using FaSSGF (left) and $FaSSGF_{DIL}$ (right) in two-stage testing. PQRI: Product Quality Research Institute; FaSSGF: fasted state simulated gastric fluid; $FaSSGF_{DIL}$: diluted FaSSGF.

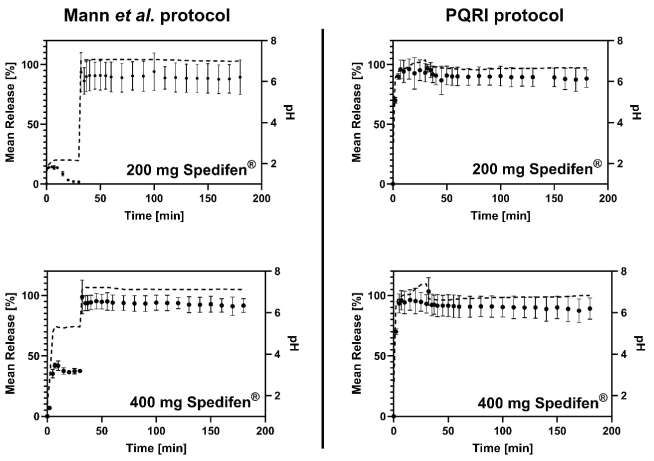

Figure 6. Mean ± SD percentage release of ibuprofen arginate from Spedifen granules (dots) and recorded pH values (dashed lines) using FaSSGF (left) and $FaSSGF_{DIL}$ (right) in two-stage testing. PQRI: Product Quality Research Institute; FaSSGF: fasted state simulated gastric fluid; $FaSSGF_{DIL}$: diluted FaSSGF.

A tendency for higher variability in the data for Spedifen compared to the Dolormin and Nurofen products was observed and may be attributable in part to the sample preparation. For Spedifen, only the appropriate mass of granules (corresponding to 200 or 400 mg of IBU) in each sachet was weighed out and used in the experiment.

Upon addition of FaSSIF-V1 double concentrate, dissolution was almost complete at both doses in both protocols, with final pH values ranging from 6.7–7.1.

Single-Stage Dissolution Testing Under Fed Gastric Conditions

The results of single-stage dissolution testing under fed gastric conditions are presented in Figure 7. The underlying data are available as supplemental material from the authors.

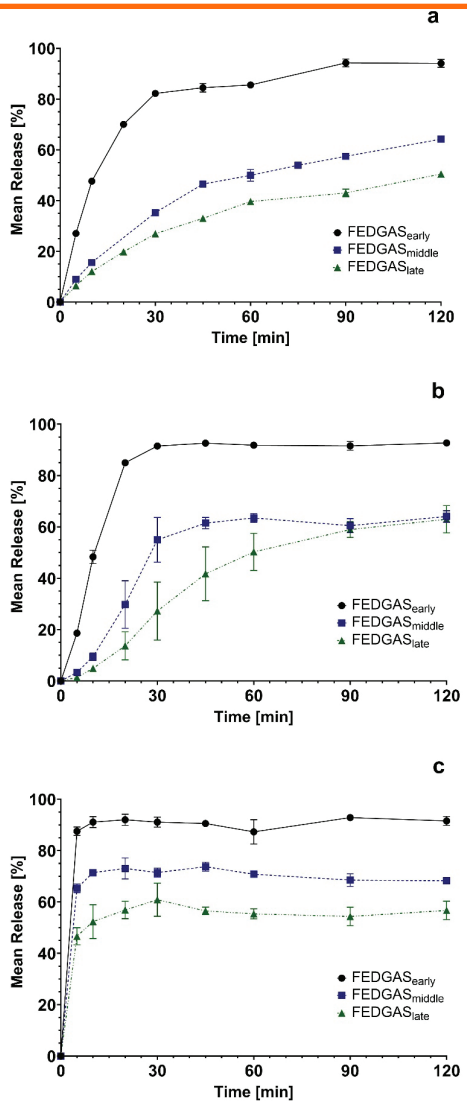

*Figure 7. Mean ± SD percentage release, under fed state simulated gastric conditions (FEDGAS), of (**a**) IBU free acid from 200-mg Nurofen orodispersible tablets, (**b**) IBU lysinate from 200-mg Dolormin film-coated tablets, and (**c**) IBU arginate from 600-mg Spedifen granules. Most SD bars lie within the symbols. IBU: ibuprofen.*

Nurofen Orodispersible Tablets

For Nurofen, the release of IBU was much faster in all three FEDGAS media than in FaSSGF, in which the percentage release was only about 2%; however, there were substantial differences in the release profiles using the fed state media. The highest release was observed in FEDGAS$_{early}$, in which almost 94% (209 µg/mL) of the dose was released within 120 minutes. In comparison, the release in FEDGAS$_{middle}$ was 64% (257 µg/mL), and just 50% (202 µg/mL) in FEDGAS$_{late}$ within the same period. The final pH was identical with the starting pH.

Dolormin Film-Coated Tablets

Here too, the release of IBU from the lysine salt formulation was much higher in FEDGAS media than in FaSSGF. Release was most rapid and extensive in FEDGAS$_{early}$, with 91% (203 µg/mL) of IBU released within 30 minutes, after which the release plateaued to 93% (206 µg/mL). More than 60% release was attained within 120 minutes in both FEDGAS$_{middle}$ and FEDGAS$_{late}$. The release was initially faster in FEDGAS$_{middle}$, with 55 % (220 µg/mL) in 30 minutes, compared to 27% (109 µg/mL) in FEDGAS$_{late}$. Again, the final pH was identical with the starting pH.

Spedifen Granules

Rapid IBU release from Spedifen was observed at the beginning of the dissolution test under fed gastric conditions. After just 5 minutes (first sampling time), a release of 88% (584 µg/mL) was measured in FEDGAS$_{early}$, with the concentration reaching 92% (610 µg/mL) by 120 min. In FEDGAS$_{middle}$ and FEDGAS$_{late}$, the release was lower, with 65% (784 µg/mL) and 47% (559 µg/mL) released within 5 minutes, respectively. By the end of the test, 68% IBU (819 µg/mL) had been released in FEDGAS$_{middle}$ and 57% (681 µg/mL) in FEDGAS$_{late}$. Here too, the final pH was identical with the starting pH.

DISCUSSION

Since the introduction of biorelevant media in 1998, they have become widely accepted to forecast drug performance in vivo (*16*, *21–24*). In this study, we investigated whether in vitro dissolution can be used to elucidate the clinical performance of three IBU products designed to facilitate fast release and thus fast absorption and a rapid onset of action of IBU: a) the free acid (Nurofen orodispersible tablets); b) the lysinate salt (Dolormin film-coated tablets); and c) the arginate salt (Spedifen granules). Three doses were tested under conditions simulating the fasted state, and selected doses were also tested in fed state media. As single-stage tests can be of limited predictive power, we also carried out two-stage

tests according to protocols suggested by Mann et al. and, more recently, by a PQRI working group (*11*, *12*, *17*).

Simulating Fasted State Administration

The higher solubility of the lysinate and arginate salts compared to the free acid, is expected to positively influence the dissolution behavior of their formulations (*19*, *25*). This was confirmed by our studies under fasted state conditions (single-stage tests in FaSSGF and $FaSSGF_{DIL}$), which showed more extensive dissolution of both salt formulations compared to the free acid. The positive effect of the salt form on IBU dissolution was especially pronounced at higher doses and in $FaSSGF_{DIL}$.

The higher solubility of the two salt forms initially leads to concentrations far higher than the solubility of the free acid. As the salt dissolves, the basic groups in the salt formers (lysine, containing a primary amino group with pKa 10, and arginine, containing a guanidium group with pKa 13.8) remain protonated, whereas the acidic group of IBU is initially deprotonated (*26*, *27*). During further dissolution in FaSSGF or $FaSSGF_{DIL}$, the protonated acidic group acts as a proton acceptor. IBU is therefore expected to precipitate as the more stable protonated (i.e., uncharged) form, as long as the pH of the medium remains below its pKa (*19*). As precipitation continues and more protons are removed from the medium by protonation of the IBU anion, the pH will shift to a higher value.

If the concentration of the salt former (i.e., the dose of the salt) is high enough, the buffer capacity of the dissolution medium can be exceeded. Thus, during dissolution of the salt and protonation of IBU, the pH may approach or even exceed the pKa of IBU, resulting in an attendant increase in its solubility (*28*).

For the lysinate salt (Dolormin), the choice of FaSSGF versus $FaSSGF_{DIL}$ does not impact dissolution at a 200-mg dose. Despite the low buffer capacity of FaSSGF, this dose is not sufficient to drive the pH over the pK_a of IBU (*29*). However, considering a more typical dosing for adults of 400-mg IBU, the choice of gastric simulating medium is crucial for dissolution from Dolormin (*30*). While the lower pH of FaSSGF suppressed the ability of the lysinate salt to shift the pH and thus led to low drug release, there was a marked increase in pH and thus faster and more extensive dissolution in $FaSSGF_{DIL}$. The results suggest that if Dolormin is ingested with a glass of water, dissolution in the stomach will be faster and more complete than if it is ingested away from water intake or with just a few sips.

For the arginate salt (Spedifen), the release was very fast and complete at all doses in $FaSSIF_{DIL}$. At a 600-mg dose, the salt also overwhelmed the pH of FaSSGF, driving the bulk pH up to a value of 8, resulting in fast and complete dissolution. As Spedifen is usually dosed at 600 mg, it is likely that it will facilitate fast dissolution in the stomach irrespective of the volume or timing of co-administered water. The difference in behavior between the two salt forms can be explained partly in terms of the salt formers' basicities. Compared to lysine with its primary amino group (pKa 10), the guanidinium group of arginine is more basic (pKa 13.8) and thus favors generation of a higher pH. A quantitative discussion of these effects can be found in Zöller et al. (*19*).

Comparison of the excipients in the two salt formulations (Table 1) suggests that these may also have an impact on dissolution. In Dolormin (lysinate salt), there are no excipients that could drive up the pH of the dissolution medium. In this case, the higher pH must therefore be attributed to the salt former. This finding is in line with the marked pH changes that have been observed when pure drug IBU sodium is dissolved in an HCl medium (*31*). On the other hand, Spedifen contains sodium bicarbonate and arginine in addition to the arginate salt of IBU. These two excipients are both basic and may partly explain the higher pH values observed during dissolution of Spedifen compared to Dolormin.

In contrast to the salt forms, dissolution of IBU from Nurofen orodispersible tablets containing the free acid form of IBU, was low in both fasted state gastric media. This was to be expected, given the pK_a of IBU of 4.5–4.6, as the acid group of IBU remains protonated at the pH of both media (pH 1.60 and 2.34) (*20*). Thus, little or no effect due to the volume or timing of water intake on dissolution in the stomach is expected.

In media simulating the intestinal fluids, release was (almost) complete for IBU formulations at all doses, with the free acid form taking slightly longer to achieve complete release.

Relationship Between In Vitro Dissolution and Pharmacokinetic Study Data - Fasted State

IBU free acid is poorly soluble in the fasted stomach. As a result, most of the dose is passed into the small intestine undissolved. As gastric emptying times for orodispersible tablets like Nurofen are short, (i.e., tablets disintegrate in the mouth and form a suspension-like mixture of gastric fluid and undissolved IBU particles in the stomach)

dissolution of the free acid in the small intestine becomes the rate-limiting step to absorption (*32*). For conventional tablets containing IBU free acid, this is also expected to be the case.

Administration of IBU as a salt formulation under fasted conditions has been shown to result in higher C_{max} and shorter t_{max} values compared to the free acid, which has been extensively studied for the lysinate salt (*33–36*). The faster onset of plasma concentrations represents a clinical advantage when rapid onset of drug concentrations and pain relief are desired. In a randomized cross-over study in healthy volunteers at a dose of 400 mg, the lysinate salt formulation achieved median C_{max} and t_{max} values of 44.9 µg/mL and 0.5 h, respectively, while the maximum plasma concentration for the free acid formulation was 31.8 µg/mL at 1.88 h. AUC values were similar to the free acid formulation. (*36*).

A 400-mg dose of IBU arginate oral formulation also resulted in a higher C_{max}, combined with shorter t_{max} values (0.25–0.5 h), while the AUC was similar to that of the free acid formulation (*37, 38*). Similarly, Shin et al. reported a rapid onset of IBU plasma levels under fasting conditions after ingestion of a 200-mg IBU arginate formulation, with a C_{max} of 30.2 µg/mL and a t_{max} of 0.42 h, compared with a C_{max} of 24.1 µg/mL at 1.25 h for the free acid formulation (39). Another clinical study of a 400-mg IBU arginate formulation reported a C_{max} of 56.4 µg/mL with a t_{max} of 0.4 h (*40*). Again, $AUC_{0-\infty}$ was similar for the salt and free acid formulations of IBU, indicating no differences in the extent of absorption (*39, 40*).

Comparing in vitro data with the clinical performance of the three products suggests that the pharmacokinetic data are closely tied to the gastric dissolution performance. Especially the results in $FaSSGF_{DIL}$ link well to the higher C_{max} and shorter t_{max} vales reported in the literature for both salts. Biorelevant dissolution testing combined with continual monitoring of pH revealed the mechanism behind the advantages of the salt forms in the fasted state. During dissolution of the salt forms, the bulk pH in the gastric media increases, especially at higher doses. This increase, which depends on the pK_a of the salt former, but may also be enhanced by basic excipients in the formulation, means that a greater amount of IBU is already present in the dissolved form when it leaves the stomach, leading to more rapid absorption.

The in vitro results for the free acid and pharmaceutical salt formulations of IBU line up well with the in vivo data: *IBU salts are particularly suitable for administration in the fasted state.*

Relationship Between In Vitro Dissolution and Pharmacokinetic Study Data - Fed State

The FEDGAS media were first introduced in 2021 (*13*). They were developed to simulate the composition of gastric contents after ingestion of a high-fat meal, representing different postprandial phases: $FEDGAS_{early}$ (pH 6.00), $FEDGAS_{middle}$ (pH 4.50) and $FEDGAS_{late}$ (pH 3.00) (*13*). Due to their specific composition and ability to reflect pH changes over time in the postprandial stomach, FEDGAS media serve as a valuable tool for predicting formulation performance during product development, including bioequivalence assessments (*13*).

The release of IBU in FEDGAS followed a pH-dependent trend in all the formulations investigated (Fig. 7). As expected for a weakly acidic compound, the highest release was observed at pH 6 in $FEDGAS_{early}$, followed by a lower release at pH 4.5 in $FEDGAS_{middle}$, and the lowest release at pH 3 in $FEDGAS_{late}$. In $FEDGAS_{early}$, all three formulations released 80% or more within 1 hour. So, if the dosage form is administered directly with a meal, dissolution in the stomach is expected to be comparable among formulations. A further consideration is the change in gut motility pattern that occurs upon feeding. Food ingestion disrupts the MMC cycle characteristic of fasted state gut motility, leading to a shift in the dynamics of gastric emptying (*32*). Previous studies have shown that, under fed conditions, gastric emptying is typically completed after more than 6 hours (*25*). During this time, the stomach contents are only gradually released into the small intestine. Thus, gastric emptying in the fed state is likely to be the rate-limiting step to absorption of IBU, irrespective of the formulation. Thus, for both dissolution and physiological reasons, any benefits of salt formulation with respect to fast onset of action will be attenuated if the dose is taken concordantly with a meal.

After oral administration of formulations containing the free acid form of IBU, relatively slow absorption has been reported in the literature (*37*). For the free acid, a negative effect of food on C_{max} and t_{max} has been reported in the literature (*41*). C_{max} was reduced from 33.5 µg/mL in the fasted state to 26.0 µg/mL in the fed state, while t_{max} was delayed by 0.25 h (1.38 h [fasted] to 1.63 h [fed]) (*41*). This limits the suitability of administering free acid formulations of IBU when a rapid onset of analgesia is required (*37*).

The in vitro dissolution profiles of the lysinate salt (Dolormin) and the free acid (Nurofen) in all three FEDGAS media were comparable. In accordance with the dissolution data, Weiser et al. reported that in the fed state, the plasma levels of the lysinate salt failed to show a significant improvement in C_{max} and t_{max} compared to the free acid at a dose of 400 mg (*36*). The C_{max} for the lysinate salt was 24.71 µg/mL compared to 27.34 µg/mL for the free acid, and the median t_{max} was reported to be 1.63 and 1.25 h, respectively (*36*).

According to the Swiss Prescribing Information for Spedifen, the absorption of IBU formulated as the arginate salt is also significantly slower in the fed state than in the fasted state, and lower plasma levels are achieved, despite its fast dissolution in $FEDGAS_{early}$ (*25*). Similarly, the results of the present study indicate that gastric emptying in the fed state is rate-limiting to IBU absorption.

In summary, the clinical results show that neither pharmaceutical salts nor free acid formulations of IBU are suitable for rapid pain relief if given with or after a meal. In general, IBU administered in fed state is more appropriate for the treatment of chronic conditions where prolonged pain relief is preferred to rapid onset of action. It is noted that for chronic therapy, it is considered advisable to take IBU in the fed state, as this may protect the stomach lining, so in this case it would be of little importance whether IBU is ingested as the free acid or in a pharmaceutical salt form (*42*).

CONCLUSION

Under fasted conditions, the improved dissolution behavior of IBU salts, compared to the free acid, is consistent with clinical performance. The faster onset of drug release observed in vivo appears to be dissolution-related and is mainly attributed to the ability of the salt form to increase gastric pH. The results highlight the need for biorelevant dissolution methods to investigate the role of dose, basiscity, and excipients in the behavior of pharmaceutical salts. Under fed state conditions, the dissolution of the lysinate salt showed no advantage over the free acid, which was confirmed by clinical studies. Although the arginate salt dissolves somewhat faster than the free acid in the fed state, this does not translate into clinical benefit, because slow gastric emptying of the meal becomes rate-limiting to absorption. Therefore, the benefits of pharmaceutical salt formulations of IBU with respect to rapid onset of action are primarily relevant for ingestion in the fasted state.

ACKNOWLEDGEMENT

This manuscript was derived in part from the Doctoral dissertation of Laurin Zöller (*18*).

DISCLOSURES

The authors received no financial support for this work and have no conflicting interests.

SUPPLEMENTAL MATERIAL

Supplemental material is available for this article and may be requested by contacting the corresponding author.

REFERENCES

1. Bushra, R.; Aslam, N. An overview of clinical pharmacology of Ibuprofen. *Oman Med. J.* **2010**, *25* (3), 155–1661. DOI: 10.5001/omj.2010.49.
2. Geisslinger, G.; Menzel, S.; Gudermann, T.; Hinz, B.; Ruth, P.; Mutschler, E. *Mutschler Arzneimittelwirkungen: Pharmakologie - Klinische Pharmakologie - Toxikologie*; 11th ed. Wissenschaftliche Verlagsgesellschaft Stuttgart, 2020.
3. Ho, K. Y.; Gwee, K. A.; Cheng, Y. K.; Yoon, K. H.; Hee, H. T.; Omar, A. R. Nonsteroidal anti-inflammatory drugs in chronic pain: implications of new data for clinical practice. *J. Pain Res*. **2018**, *11*, 1937–1948. DOI: 10.2147/JPR.S168188.
4. Phillips, W. J.; Currier, B. L. Analgesic pharmacology: II. Specific analgesics. *J. Am. Acad. Orthop. Surg*. **2004**, *12* (4), 221–233. DOI: 10.5435/00124635-200407000-00003.
5. Blondell, R. D.; Azadfard, M.; Wisniewski, A. M. Pharmacologic therapy for acute pain. *Am Fam Physician*. **2013**, *87* (11), 766–772.
6. Tighe, P.; Buckenmaier, C. C., III; Boezaart, A. P.; Carr, D. B.; Clark, L. L.; Herring, A. A.; Kent, M.; Mackey, S.; Mariano, E. R.; Polomano, R. C.; Reisfield, G. M. Acute pain medicine in the United States: a status report. *Pain Med*. **2015**, *16* (9), 1806–1826. DOI: 10.1111/pme.12760.
7. Nurofen 200 mg orodispersible tablets lemon - technical information. https://imedikament.de/nurofen-200-mg-schmelztabletten-lemon/fachinformation (2014, accessed Aug 8, 2025).
8. Bioavailability and Bioequivalence Studies submitted in NDAs or INDs - General Considerations; Guidance for Industry. U.S.. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, 2014.
9. Dressman, J. B.; Berardi, R. R.; Dermentzoglou, L. C.; Russell, T. L.; Schmaltz, S. P.; Barnett, J. L.; Jarvenpaa, K. M. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm. Res*. **1990**, *7* (7), 756–761. DOI: 10.1023/A:1015827908309.
10. Karamanolis, G.; Theofanidou, I.; Yiasemidou, M.; Giannoulis, E.; Triantafyllou, K.; Ladas, S. D. A glass of water immediately increases gastric pH in healthy subjects. *Dig. Dis. Sci*. **2008**, *53* (12), 3128–3132. DOI: 10.1007/s10620-008-0301-3.

11. Tsume, Y.; Ashworth, L.; Bermejo, M.; Cheng, J.; Cicale, V.; Dressman, J.; Fushimi, M.; Gonzalez-Alvarez, I.; Guo, Y.; Jankovsky, C.; Lu, X.; Matsui, K.; Patel, S.; Sanderson, N.; Sun, C. C.; Thakral, N. K.; Yamane, M.; Zöller, L. Harmonizing biopredictive methodologies through the Product Quality Research Institute (PQRI) part I: biopredictive dissolution of ibuprofen and dipyridamole tablets. *AAPS J*. **2023**, *25* (3), 45. DOI: 10.1208/s12248-023-00793-7.
12. Mann, J.; Dressman, J.; Rosenblatt, K.; Ashworth, L.; Muenster, U.; Frank, K.; Hutchins, P.; Williams, J.; Klumpp, L.; Wielockx, K.; et al. Validation of dissolution testing with biorelevant media: an OrBiTo study. *Mol. Pharm*. **2017**, *14* (12), 4192–4201. DOI: 10.1021/acs.molpharmaceut.7b00198.
13. What is FEDGAS? Biorelevant.com Ltd. https://biorelevant.com/learning_center/what-is-FEDGAS/ (accessed Nov 14, 2023).
14. Media prep tool. Biorelevant.com Ltd. https://biorelevant.com/#media_prep_tool_tab (accessed Nov 24, 2023).
15. Schiller, C.; Fröhlich, C.-P.; Giessmann, T.; Siegmund, W.; Mönnikes, H.; Hosten, N.; Weitschies, W. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment. Pharmacol. Ther*. **2005**, *22* (10), 971–979. DOI: 10.1111/j.1365-2036.2005.02683.x.
16. Markopoulos, C.; Andreas, C. J.; Vertzoni, M.; Dressman, J.; Reppas, C. In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media. *Eur. J. Pharm. Biopharm*. **2015**, *93*, 173–182. DOI: 10.1016/j.ejpb.2015.03.009.
17. Tsume, Y.; Ashworth, L.; Bermejo Sanz, M.; Cicale, V.; Dressman, J.; Fushimi, M.; Gonzalez-Alvarez, I.; Haung, P.-S.; Jankovsky, C.; Liu, X.; Lu, X.; Matsui, K.; Patel, S.; Ruiz-Picazo, A.; Sun, C. C.; Thakral, N.; Zöller, L. Advancing the harmonization of biopredictive methodologies through the Product Quality Research Institute (PQRI) Consortium: biopredictive dissolution of dipyridamole tablets. *Mol. Pharm*. **2024**, *21* (10), 5315–5325. DOI: 10.1021/acs.molpharmaceut.4c00878.
18. Zöller, L. Predicting the dissolution gains and precipitation risks of salt forms of drugs [Doctoral Thesis]. Universitätsbibliothek Johann Christian Senckenber, 2025. DOI: 10.21248/gups.90983.
19. Zöller, L.; Avdeef, A.; Karlsson, E.; Borde, A.; Carlert, S.; Saal, C.; Dressman, J. A comparison of USP 2 and µDISS Profiler™ apparatus for studying dissolution phenomena of ibuprofen and its salts. E*ur. J. Pharm. Sci*. **2024**, *193*, 106684. DOI: 10.1016/j.ejps.2023.106684.
20. Potthast, H.; Dressman, J. B.; Junginger, H. E.; Midha, K. K.; Oeser, H.; Shah, V. P.; Vogelpoel, H.; Barends, D. M. Biowaiver monographs for immediate release solid oral dosage forms: ibuprofen. *J. Pharm. Sci*. **2005**, *94* (10), 2121–2131. DOI: 10.1002/jps.20444.
21. Dressman, J. B.; Amidon, G. L.; Reppas, C.; Shah, V. P. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. *Pharm. Res*. **1998**, *15* (1), 11–22. DOI: 10.1023/A:1011984216775.
22. Galia, E.; Nicolaides, E.; Hörter, D.; Löbenberg, R.; Reppas, C.; Dressman, J. B. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. *Pharm. Res*. **1998**, *15* (5), 698–705. DOI: 10.1023/A:1011910801212.
23. Klein, S. The use of biorelevant dissolution media to forecast the in vivo performance of a drug. *AAPS J*. **2010**, *12* (3), 397–406. DOI: 10.1208/s12248-010-9203-3.
24. Jantratid, E.; Janssen, N.; Reppas, C.; Dressman, J. B. Dissolution media simulating conditions in the proximal human gastrointestinal tract: an update. *Pharm. Res*. **2008**, *25* (7), 1663–1676. DOI: 10.1007/s11095-008-9569-4.
25. Spedifen granules 600 mg. Compendium website; HCl Solutions AG. https://compendium.ch/product/16540-spedifen-gran-600-mg/mpro (accessed Dec 8, 2023).
26. Fitch, C. A.; Platzer, G.; Okon, M.; Garcia-Moreno, B. E.; McIntosh, L. P. Arginine: Its pKa value revisited. *Protein Sci*. **2015**, *24* (5), 752–761. DOI: 10.1002/pro.2647.
27. Matthew, J. B.; Gurd, F. R.; Garcia-Moreno, B.; Flanagan, M. A.; March, K. L.; Shire, S. J. pH-dependent processes in proteins. *CRC Crit. Rev. Biochem*. **1985**, *18* (2), 91–197. DOI: 10.3109/10409238509085133.
28. Skrdla, P. J. Estimating the maximal solubility advantage of drug salts. *Int. J. Pharm*. **2021**, *595*, 120228. DOI: 10.1016/j.ijpharm.2021.120228.
29. Jantratid, E.; Dressman, J. Biorelevant dissolution media simulating the proximal human gastrointestinal tract: an update. *Dissolut. Technol*. **2009**, *16* (3), 21–25. DOI: 10.14227/DT160309P21 (accessed 2024-04-25).
30. M, D. B. Ibuprofen - usage, dosage, side effects, drug warnings, and precautions. iCliniq website. https://www.icliniq.com/articles/drug-and-supplements/ibuprofen (updated 2024; accessed Apr 4, 2024).
31. Arbiol Enguita, A. M.; Zöller, L.; Tomberg, T.; Heikkilä, M. J.; Saarinen, J. K. S.; Wurr, L.; Konings, T.; Correia, A.; Saal, C.; Dressman, J.; Strachan, C. J. Chemically specific coherent raman imaging of liquid-liquid phase separation and Its sequelae. *Anal. Chem*. **2025**, *97* (6), 3242–3252. DOI: 10.1021/acs.analchem.4c03923.
32. Deloose, E.; Janssen, P.; Depoortere, I.; Tack, J. The migrating motor complex: control mechanisms and its role in health and disease. *Nat. Rev. Gastroenterol. Hepatol*. **2012**, *9* (5), 271–285. DOI: 10.1038/nrgastro.2012.57.
33. Legg, T. J.; Laurent, A. L.; Leyva, R.; Kellstein, D. Ibuprofen sodium is absorbed faster than standard Ibuprofen tablets: results of two open-label, randomized, crossover pharmacokinetic studies. *Drugs R D* **2014**, *14* (4), 283–290. DOI: 10.1007/s40268-014-0070-8.
34. Geisslinger, G.; Dietzel, K.; Bezler, H.; Nuernberg, B.; Brune, K. Therapeutically relevant differences in the pharmacokinetical and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid. *Int. J. Clin. Pharmacol. Ther. Toxicol*. **1989**, *27* (7), 324–328.

35. Luckow, V.; Krammer, R.; Traub, R. [Comparative biological availability of two different ibuprofen granules.] [Article in German]. *Arzneimittelforschung* **1992**, *42* (11), 1339–1342.
36. Weiser, T.; Schepers, C.; Mück, T.; Lange, R. Pharmacokinetic properties of ibuprofen (IBU) from the fixed-dose combination IBU/caffeine (400/100 mg; FDC) in comparison with 400 mg IBU as acid or lysinate under fasted and fed conditions-data from 2 single-center, single-dose, randomized crossover studies in healthy volunteers. *Clin. Pharmacol. Drug Dev*. **2019**, *8* (6), 742–753. DOI: 10.1002/cpdd.672.
37. Davies, N. M. Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin. Pharmacokinet*. **1998**, *34* (2), 101–154. DOI: 10.2165/00003088-199834020-00002.
38. Cajaraville, J. P. Ibuprofen arginate for rapid-onset pain relief in daily practice: a review of its use in different pain conditions. *J. Pain Res*. **2021**, *14*, 117–126. DOI: 10.2147/JPR.S280571.
39. Shin, D.; Lee, S. J.; Ha, Y.-M.; Choi, Y.-S.; Kim, J.-W.; Park, S.-R.; Park, M. K. Pharmacokinetic and pharmacodynamic evaluation according to absorption differences in three formulations of ibuprofen. *Drug Des. Devel. Ther*. **2017**, *11*, 135–141. DOI: 10.2147/DDDT.S121633.
40. Ceppi Monti, N.; Gazzaniga, A.; Gianesello, V.; Stroppolo, F.; Lodola, E. Activity and pharmacokinetics of a new oral dosage form of soluble ibuprofen. *Arzneimittelforschung* **1992**, *42* (4), 556–559.
41. Klueglich, M.; Ring, A.; Scheuerer, S.; Trommeshauser, D.; Schuijt, C.; Liepold, B.; Berndl, G. Ibuprofen extrudate, a novel, rapidly dissolving ibuprofen formulation: relative bioavailability compared to ibuprofen lysinate and regular ibuprofen, and food effect on all formulations. *J. Clin. Pharmacol*. **2005**, *45* (9), 1055–1061. DOI: 10.1177/0091270005279579.
42. Ibuprofen. MedlinePlus website; American Society of Health-System Pharmacists. https://medlineplus.gov/druginfo/meds/a682159.html (updated 2023, accessed Apr 25, 2024).
43. *Dolormin pain tablets - technical information*. https://imedikament.de/dolormin-schmerztabletten (2014, accessed Feb 15, 2025).