

The Relative Bioavailability of Ibuprofen After Administration With a Novel Soft Chewable Drug Formulation

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Abstract

The first aim of the present study was to evaluate the bioavailability of ibuprofen dispersed in a novel soft chewable formulation compared with a traditional ibuprofen tablet; its second was to map the quality of taste masking and patient product satisfaction. In a phase I, single-center, open-label, randomized, crossover study, healthy subjects received a soft-chew formulation or a hard tablet (reference), both containing 100 mg ibuprofen. Serial blood samples were collected over 24 hours to assess ibuprofen bioavailability. Taste and satisfaction after chewing the novel formulation 3 or 8 times were evaluated with a questionnaire. The soft-chew formulation showed comparable bioavailability to the reference tablet. The highest peak plasma concentration was observed after 3 chews, and the relative bioavailability was approximately 8% higher compared to 8 chews. The overall flavor was well appreciated, and chewing 3 times was significantly preferred ($P = .043$) over chewing 8 times. Soft chewable drug formulations may improve compliance and potentially benefit several subpopulations who experience dysphagia.

Keywords

soft-chew formulation, ibuprofen, bioavailability, taste masking, dysphagia

Patient compliance is important for clinical efficacy and successful treatment outcomes in patients.¹ Both dysphagia and off-taste may give rise to noncompliance and often occur when active pharmaceutical ingredients (APIs) for oral administration are formulated as hard tablets.² To ease swallowing, patients often tend to break, chew, or crush hard tablets and mix them with food or water even though this may change the release profile of the API and affect the rate or extent of drug absorption and subsequently also bioavailability.^{2,3} Crushing of tablets also enhances the off-taste of APIs and increases the risk of inaccurate dosing.³ It is known that modification of tablets hampers clinical efficacy and dosing accuracy, which increase health care costs, for example, through hospitalization.²

The need for improving drug dose acceptance and compliance is high, in particular for the pediatric and geriatric subpopulations, who will benefit from more user-friendly dosing forms that are easy to swallow and exhibit negligible API off-taste.² Dosing formulations have been developed such as elixirs, chewable tablets, and suspensions that facilitate swallowing.² Suspension-based formulations provide

acceptable taste-masking properties and chemical stability by reducing the solubility of the API in the formulation to a minimum.^{1,4} However, suspension formulations may suffer from different types of destabilization processes, such as sedimentation and flocculation of the suspended particles.⁵ In addition, the packing of API particles after sedimentation may provide a hard layer at the bottom of the container, also known as caking, which will counteract dosing

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Table I. Composition of Novel Chewable Formulation Containing Ibuprofen 100 mg

Ingredients	Composition per Chewable Tablet		Function
	%	Dose (mg)	
Ibuprofen (SN grade)	10.00	100	Drug substance
Water for injection	25.57	255.7	Solvent
Gelatin 150 bloom (type B, bovine)	9.640	96.40	Gelling agent
Xylitol	28.49	284.9	Sweetener
DL-Malic acid	2.800	28.00	Acidity modifier
Trisodium citrate dihydrate	5.510	55.10	Acidity modifier
Sorbitol	17.09	170.9	Sweetener
Sucralose	0.9000	9.000	Sweetener
Fractionated coconut oil <i>a</i>	qs	qs	Lubricant
Total	100.0	1000.0	

accuracy. Such destabilization processes may hence cause heterogeneous suspension formulations and could lead to the patient being unable to follow a uniform dosage regimen.⁶

A novel drug formulation has been developed that allows administration of APIs as a suspension embedded in a dispersed form within a unit dose that has a chewable gel matrix. The API particles are structurally arrested in the gel matrix, which eliminates time-dependent destabilization.^{7,8}

The novel drug formulation is designed as a uniform soft-chew dose with taste-masking properties using the well-known API ibuprofen as a model substance. Ibuprofen is a commonly used nonsteroidal anti-inflammatory drug and is rapidly and completely absorbed in the gastrointestinal tract after oral administration. Maximum serum concentration is typically achieved between 1 and 2 hours for dry tablet formulations, but a faster absorption can be expected if ibuprofen is delivered as a solution. Ibuprofen is an optically active molecule that can exist as both R(-) and S(+) enantiomers, and studies have shown differences in the pharmacokinetics and anti-inflammatory properties between these isomers.⁹ However, racemic ibuprofen is usually preferred in drug formulations, as it is the least expensive form, and there is little clinical benefit of using a single enantiomer.¹⁰ In the solubilized state ibuprofen has a strong pungent taste¹¹ and should therefore preferably be administered in the nondissolved state. In the investigated drug formulation the solubility of the ibuprofen is kept at a minimum in the soft-chew delivery unit by using a buffering system with a pH below the pKa of the carboxyl group of the ibuprofen (pKa of 4.9). This ensures nondissolution and improves taste-masking properties because very little of the API is released/solubilized in the oral cavity during mastication.

The aim of the present study was to evaluate the overall bioavailability of ibuprofen formulated as a soft, chewable tablet relative to a traditional hard ibuprofen tablet. For the approval of a novel formulation containing a generic API, a comparable bioavailability is a critical measure for regulatory approval. Two different levels of chewing were compared with respect to bioavailability, the quality of taste masking, and overall satisfaction.

Methods

Product Technical Background

The novel drug formulation was manufactured as a soft, chewable tablet containing 100 mg of ibuprofen aggregates (European Pharmacopoeia, SN Grade, racemic mixture, 60 to 130 μm ; Shasun Pharmaceuticals, Chennai, India) and was provided by ConCordix Pharma AS (Oslo, Norway). The exact composition of the novel soft-chew ibuprofen (batch LRN13-094) formulation is described in Table 1.

A gelatin solution was prepared by mixing and dissolving gelatin (150 Bloom bovine type B, Gelita, Eberbach, Germany) in water at 55°C. Xylitol, DL-malic acid, and trisodium citrate dihydrate (provided by Covance Laboratories Ltd, Alnwick, UK) were added to the sample vessel and mixed until completely dissolved, and thereafter a homogeneous dispersion of sorbitol, sucralose, and ibuprofen was added. The sample was stirred until all constituents were dissolved or dispersed, and excess air was removed by using a vacuum. The formulation mixture was transferred to molds and allowed to gel at room temperature before being packaged. The production process was conducted in accordance with good manufacturing practice guidelines at Covance Laboratories (Alnwick, UK).

The comparator was a hard tablet that was commercially available ibuprofen (Advil[®] 100 mg), which was

provided by Eurofins Optimed (Gières, France). The hard tablet was stored as recommended by the manufacturer instructions.

All labeling was in accordance with local regulatory specifications and requirements.

Study Design and Dosing Regime

This was a phase 1, single-center, open-label, randomized, crossover study, conducted in 20 healthy male volunteers (21 to 41 years old) at the laboratory of Eurofins Optimed (Gières, France). Prior to enrollment, a 21-day screening phase was conducted to determine subject eligibility, with the following inclusion criteria: signing informed consent, not smoking more than 5 cigarettes per day, and normal reference values for body mass index (between 18 and 27 kg/m²), blood pressure, electrocardiogram, laboratory parameters, and diet habits. Subjects who did not fulfill the inclusion criteria or had a history of current gastrointestinal, hepatic, renal, or hematological disease and/or hypersensitivity to any of the study products were excluded from participation.

After inclusion, subjects were randomized into one of 5 crossover sequences (A-B-C, A-C-B, B-A-C, B-C-A, C-A-B), with 4 subjects for each sequence. Study periods A and B are chewable formulation chewed 3 and 8 times, respectively, and study period C is the hard tablet. Each study period comprised 3 clinic days, followed by a washout phase of at least 3 days between different periods.

For each study period, subjects arrived at the clinic at day -1. On day 1 at T0 (08:00) after an overnight fast, blood was collected before and after drug administration. Subjects in a sitting position received the novel soft-chew formulation and were instructed to chew 3 (period A) or 8 (period B) times followed by swallowing and subsequent drinking 200 mL of water or to ingest the hard tablet (period C) with 200 mL of water. A mouth check was done to ensure the study drug had been taken.

According to the Eurofins ibuprofen analytical method (see later) a dosage of 100-mg ibuprofen gave rise to sufficient ibuprofen blood levels to allow determination of the relative bioavailability of the novel soft-chew formulation and the comparator tablet as well as to determine if the degree of mastication of the soft-chew resulted in an altered bioavailability. A higher dose (the clinically relevant dose of, e.g., 200 mg) was therefore deemed unnecessary for the evaluation of bioavailability.

Within 5 minutes after oral administration, subjects completed a questionnaire to evaluate taste and satisfaction of the chewable formulation. The questionnaire included items for appearance, texture, and taste. Blood was collected at 12 different time points as described

below (pharmacokinetic parameters). After blood sampling collection at 10 hours, the subjects were discharged and returned on day 2 for a blood draw, allowing evaluation of safety parameters and to check vital signs. Only after the last dose (third dose), the subjects underwent an additional laboratory safety evaluation including hematology, biochemistry, and urinalysis. On study days the subjects received a standardized breakfast and lunch. From day -1 to day 2 subjects were restricted to indoor activities (no exercise) and ordered to refrain from smoking and consumption of alcohol and xanthine-based beverages.

The final study protocol was approved by the independent ethics committee Comité de Protection des Personnes Sud-Est III (Groupement Hospitalier Edouard Herriot, Lyon, France) and was in accordance with the Declaration of Helsinki and the laws and regulations for clinical research in France. This study has been registered in EuDract (no. 2013-004252).

Pharmacokinetic Assessments

Pharmacokinetic parameters of interest were maximum plasma concentration (C_{\max} [ng/mL]); time passed since administration at which the maximum plasma concentration occurred (hours); area under the plasma concentration curve from administration to last observed concentration at time T measured by trapezoidal rules (AUC_{24t} [h·ng/mL]); area under the plasma concentration-time curve from administration up to infinity with extrapolation of the terminal phase (AUC_{∞} [h·ng/mL]). Half-life ($t_{1/2}$ [hours]) of ibuprofen was calculated by $\ln 2/k_{el}$.

In order to assess the pharmacokinetic properties of 100-mg ibuprofen aggregates in the novel soft-chew formulation, blood samples (180 mL in total) were collected at 15, 20, 30, and 45 minutes, 1, 1.5, 2, 4, 5, 6, 10, and 24 hours with an authorized time window of $\pm 10\%$ without exceeding 15 minutes. At each time point 5 mL of blood was drawn into lithium heparinized Vacutainer tubes. The blood samples were gently inverted a few times to ensure complete mixing with the anticoagulant. The exact time of sample collection was recorded on the electronic case report form. Within 30 minutes of blood collection, each blood sample was centrifuged at 1500g for 10 minutes at 4°C. Immediately after the centrifugation, plasma was transferred into 2 prelabeled polypropylene tubes frozen in an upright position at approximately -80°C for storage.

For each sample 800 μ L 0.1% formic acid in water was added to 25 μ L of blood plasma and vortex mixed for 30 seconds before centrifugation. Samples for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analyses were prepared using an OASIS HLB 1-cc cartridge, conditioned first with 1 mL of methanol, then with 1 mL of water. The supernatant

from the centrifuged samples was then applied to the cartridge, followed by washing with 1 mL 5% acetonitrile (ACN), 2% NH_4OH in water, and 1 mL 30% ACN, 0.1% FA in water. Finally, the sample was eluted with 2×0.5 mL 80% ACN, 0.1% FA in water into 96-well plates, and dried under nitrogen at 60°C . The samples were reconstituted with 100 μL ACN, followed with 100 μL 20 mM NH_4OAc in water, centrifuged, and injected onto the LC-MS/MS system. The LC-MS/MS analytical method was validated by ADME Bioanalyses (Vergèze, France) according to the Food and Drug Administration¹² using $^{13}\text{C}_2\text{H}_3$ -ibuprofen as an internal standard. High-performance liquid chromatography was performed using an ACE 5 C18 50×3 mm, $5\text{-}\mu\text{m}$ column at 30°C . The mobile phase in channel A consisted of 10 mM NH_4OAc (20% methanol in water), and that in channel B consisted of 10 mM NH_4OAc (methanol/ACN 80/20) with a sample injection volume of 10 μL and a flow rate of 0.5 mL/min for 8 minutes. Wash solvent was ACN/water 70/30. The detector used was an Applied Biosystems API 4000 (Foster City, California). It was operated in MRM mode, and the transitions monitored were 205 $m/z \rightarrow 161.1$ m/z for ibuprofen and 209 $m/z \rightarrow 165.1$ m/z for the internal standard, both with collision energies of 11 eV. Electrospray ionization was used at an ion spray voltage of 4200 V and a temperature of 500°C . The declustering potential, collision cell exit potential, and entrance potential were set at 48 V, 11 V, and 10 V, respectively, and the dwell time was 400 milliseconds. For processing of data, Analyst software 1.5.1 (Sciex, Framingham, Massachusetts) was used.

Validation showed that this method could be used to assay ibuprofen in human plasma between 50 ng/mL (lower limit of quantification) to 2500 ng/mL (upper limit of quantification), using linear regression and $1/x^2$ weighting. Repeatability was tested at 50, 150, 1250, and 2000 ng/mL and found to be within limits ($\pm 15\%$ above the lower limit of quantification and $\pm 20\%$ at the lower limit of quantification). In addition no carryover effects, run length effects, sample stability effects, or interference from human plasma was found.

Measurements of Taste and Satisfaction of the Chewable Formulation

Uniquely developed questionnaires were used to evaluate taste and satisfaction of the novel formulation. These assessments were performed in a nonblinded manner. The items for overall appearance and flavor/taste (overall favored/disfavored) were based on 9 scores: 1 = extremely disfavored to 9 = extremely favored. Texture evaluation consisted of 4 items including: mouth feel (9 scores: 1 = extremely disfavored to

9 = extremely favored), hardness (5 scores: 1 = too soft to 5 = too hard), chewing resistance (5 scores: 1 = much too easy to 5 = much too chewy), and ibuprofen particle size (5 scores: 1 = much too small to 5 = much too large). The scales were not validated, and the assessments were hence based on each participant's impression within the first 5 minutes after intake.

Safety Assessments

Clinical parameters included blood pressure, physical examination, electrocardiogram, and laboratory measurements obtained from blood samples (hematology, biochemistry, urinalysis, and serology). An independent investigator and/or laboratory performed all tests. Adverse events were recorded from baseline until the end of the study.

Statistical Analysis

Individual plasma concentrations and pharmacokinetic parameters, as well as the nominal sampling times, were tabulated for each subject and each period (A, B, C) together with descriptive statistics. If ibuprofen plasma concentrations were below the limit of detection, these values were replaced by zero for calculation of the descriptive statistics. Descriptive statistics for quantitative parameters were provided using mean and SD. Descriptive statistics for qualitative parameters were provided using frequencies (n) and percentage frequencies (%).

Relative bioavailability was calculated by comparing the ibuprofen plasma concentrations (AUC_{inf}) of each subject per period (A, B, C) and calculating the average (arithmetic mean). Bioequivalence was based on the ratios of 2 degrees of chewing of the soft-chew and the hard tablet and applied to the pharmacokinetic parameters C_{max} , $\text{AUC}_{24\text{h}}$, and AUC_{inf} with a CI of 90% and a range of 0.8 to 1.25, as established by the US Food and Drug Administration.

The pharmacokinetic interpretation was carried out by ADME bioanalyses (Vergèze, France) using Kinetica (Version 4.3, Thermo Electron Corporation, Waltham, Massachusetts). An independent model method was chosen.

Satisfaction and taste evaluation were analyzed by comparing the difference between chewing 3 and 8 times using SAS (release 9.3, SAS Institute, Cary, North Carolina) with a Wilcoxon Signed Rank test and a p-value of 0.05. Statistical analyses were carried out using OPTIMED SAS (release 9.3, SAS Institute).

Safety assessments were descriptively analyzed by the change between baseline and the end-of study visit values.

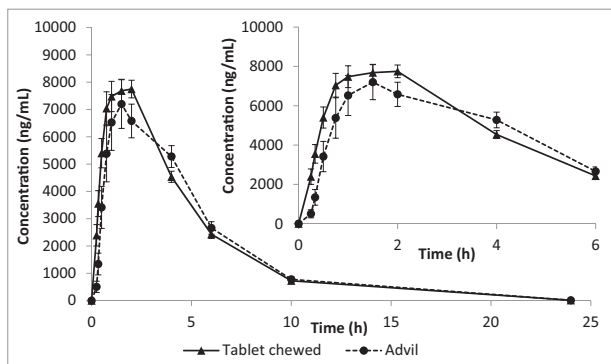


Figure 1. Overall mean (\pm SE) plasma ibuprofen concentrations over time after oral administration of 100 mg ibuprofen dispersed in the novel soft-chew formulation chewed 3 and 8 times combined compared with a 100-mg Advil[®] hard tablet.

Results

Demographics

In total, 28 healthy male subjects were screened of whom 20 subjects were found eligible, enrolled, and completed the study. Demographic results showed a mean age of 29.0 ± 7.8 years, a mean weight of 69.32 ± 8.60 kg, and a mean height of 177.05 ± 5.40 cm. All eligible subjects had a body mass index between 18.3 to 26.4 kg/m^2 (mean: $22.1 \pm 2.7 \text{ kg/m}^2$).

Pharmacokinetics

Overall results obtained for the soft-chew formulation and the comparator hard tablet are depicted in Figure 1. The mean C_{max} for the soft-chew formulation (3+8 times chewed combined) was slightly higher than

that for the hard tablet, but the mean $AUC_{24\text{h}}$ values showed the opposite trend.

Results obtained for each period—chewing 3 times (period A), chewing 8 times (period B), and the hard tablet (period C)—are depicted in Table 2 and Figure 2. Chewing 3 times showed the highest values for C_{max} , $AUC_{24\text{h}}$, and AUC_{inf} , followed by the hard tablet and chewing 8 times. The observed differences were small, and only the difference in C_{max} between 3 chews and 8 chews was statistically significant ($P < .05$).

The time to reach a maximum concentration of ibuprofen in serum was the shortest after chewing 3 times, with a median time of 1.25 hours, ranging from 0.50 to 2.00 hours. Median time from administration to peak concentration for chewing 8 times and the hard tablet were 1.75 hours (0.50–6.00) and 1.50 hours (0.75–4.00), respectively. Mean (arithmetic) values for time from administration to peak concentration are shown in Table 2.

The mean relative bioavailability was based on detectable values, with measurements below the lower limit of quantification considered as 0. The relative bioavailability ratios were calculated as previously described, and are shown in Table 3. As can be seen, all ratios were within 90% to 110%. Bioequivalence was met for all pharmacokinetic parameters and lay entirely within the predefined range of 0.8 to 1.25 (CI90%), except for the C_{max} ratios of 3:8 times chewing and 3 times chewing:hard tablet where the upper limit of the CI exceeded 1.25.

Evaluation of Satisfaction and Taste of the Tablet

The mean score of the overall appearance after chewing 3 times (period A) was similar to that of chewing

Table 2. Mean Ibuprofen Pharmacokinetic Parameters per Period (A, B, C)

	Statistics	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{24\text{h}}$ (h·ng/mL ^a)	AUC_{inf} (h·ng/mL ^a)	% AUC_{extra}	$T_{1/2}$ (hours)
Period A	N	20	20	20	20	20	20
	Mean	10,657 ^a	1.25 ^a	41,003	42,597	3.79	2.32
	SD	1939	0.61	11,450	11,551	2.34	0.5
	%CV	18.2	48.6	27.9	27.1	61.70	21.8
Period B	N	20	20	20	18	18	18
	Mean	9047 ^a	1.79	38343	39,543	3.98	2.24
	SD	2861	1.27	10,059	10674	2.25	0.49
	%CV	31.6	71.1	26.2	27.0	56.6	22.03
Period C	N	20	20	20	16	16	16
	Mean	9455	1.93 ^a	38,267	41,462	3.89	2.26
	SD	2442	1.29	10,990	11,065	2.16	0.53
	%CV	26.0	66.8	28.7	26.7	55.6	23.30

Period A: 100 mg ibuprofen dispersed in the novel chewable formulation chewed 3 times. Period B: 100 mg ibuprofen dispersed in the novel chewable formulation chewed 8 times. Period C: Advil[®] hard tablet containing 100 mg ibuprofen. Results obtained from serum. N, Number of subjects; SD, standard deviation; %CV, coefficient of variation; % AUC_{extra} , percentage of extrapolated AUC (average of $1 - [AUC_{24\text{h}}/AUC_{\text{inf}}]$); C_{max} , peak plasma concentration; T_{max} , time to reach C_{max} ; $T_{1/2}$, half-life.

^aIndicates values that are statistically different between periods ($P < .05$).

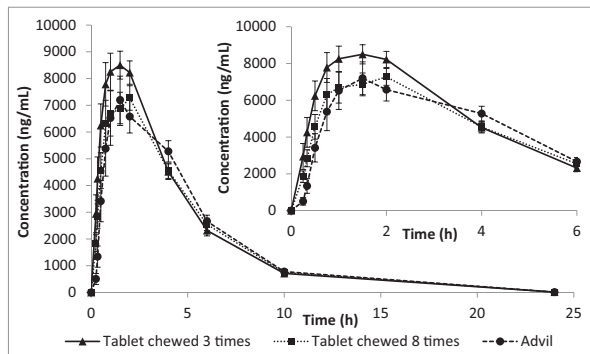


Figure 2. Mean (\pm SE) plasma ibuprofen concentration-time profiles after oral administration of 100 mg ibuprofen dispersed in the novel soft-chew formulation chewed 3 or 8 times and 100-mg Advil[®] hard tablet.

8 times (period B), and most subjects neither favored nor disfavored the soft-chew formulation (50% and 75% of subjects, respectively). The size of the product (\sim 0.8 mL volume) was found to be “just right” according to 75% of subjects who chewed 3 times and was even higher after 8 times chewing (80% of subjects), but these results were not statistically different (Table 4).

In both groups a plurality of subjects (30%) neither favored nor disfavored the mouth feel, followed by 25% of subjects who moderately preferred the mouth feel of the chewable formulation.

The majority of subjects who chewed 3 times evaluated the hardness, chewing resistance, and particle size of the chewable tablet as “just right” (80%, 60%, and 65% of subjects, respectively). Similar results were obtained after chewing 8 times for hardness (70% of subjects), chewing resistance (75% of subjects), and particle size (65% of subjects), and most evaluated the chewable formulation according to the item “just right.” No statistical differences were observed for any of the texture items.

The overall favor/disfavor was statistically similar between the 2 groups and evaluated as “favor moderately” by 45% of subjects who chewed 3 times and 35% of subjects who chewed 8 times.

A significant difference was observed for the overall flavor item, where chewing 3 times was preferred over chewing 8 times ($P = .0430$).

Safety Evaluation

No adverse events were reported during the study. No clinically relevant findings were observed in laboratory parameters or vital signs. All subjects who were included completed the study.

Discussion

This study evaluated the overall bioavailability of ibuprofen in a novel soft-chew dosing formulation compared to a traditional hard ibuprofen tablet. The results show that the relative bioavailability (AUC_{inf}) ratios of the novel formulation (chewed 3 or 8 times separately, and combined) compared with the hard tablet were within 90% to 110%. Chewing 8 times showed bioequivalence with the hard tablet, with all CIs within the predefined range of 0.8 to 1.25. On the other hand, for chewing 3 times compared to 8 times, and chewing 3 times compared to the hard tablet, the CIs for C_{max} have an upper range exceeding 1.25, which means that no conclusion on bioequivalence can be reached for these. The reason for the higher C_{max} for chewing 3 times compared to 8 times and the hard tablet is unexpected and yet unexplained. Although a slight buccal loss in one form or another resulting from extended chewing cannot be ruled out, a repeated trial with larger groups will be necessary to confirm or invalidate the effect of chewing on bioequivalence.

It is known that ibuprofen is almost completely absorbed, allowing for nearly 100% bioavailability.^{7,8} However, the rate of absorption depends on its

Table 3. Relative Bioavailability and Bioequivalence of Ibuprofen

Statistic	Relative Bioavailability Chewing 3 Times Compared With Chewing 8 Times	Relative Bioavailability Chewing 3 Times Compared With Hard Tablet	Relative Bioavailability Chewing 8 Times Compared With Hard Tablet
N	18	16	14
Mean \pm SD (%)	108.24 \pm 5.54	103.30 \pm 5.22	94.84 \pm 6.53
Median (%)	107.71	104.82	96.01
CI (90%) C_{max}	1.066–1.391*	1.033–1.277*	0.817–1.089
CI (90%) AUC_{24t}	1.039–1.098	1.029–1.120	0.959–1.054
CI (90%) AUC_{inf}	1.059–1.104	1.009–1.055	0.916–1.104

Ibuprofen (100 mg) dispersed in the novel chewable formulation chewed 3 or 8 times. Hard tablet (Advil[®]) containing 100 mg ibuprofen. Confidence interval (CI) of 90% was used with a range of 0.8 to 1.25 as per US Food and Drug Administration; CIs not fully within this range marked with *. Results obtained from calculations as described in Methods. C_{max} , peak plasma concentration; N, Number of subjects; SD, standard deviation.

Table 4. Evaluation of Satisfaction and Taste of the Chewable Formulation (100 mg Ibuprofen) Chewed 3 and 8 Times

Statistics	Chewed 3 Times	Chewed 8 Times
Size of the product ^a	3.1 ± 0.5	3.0 ± 0.4
Hardness ^a	2.7 ± 0.7	2.7 ± 0.6
Chewing resistance ^a	2.7 ± 0.8	2.7 ± 0.7
Particle size ^a	3.1 ± 0.6	2.8 ± 0.7
Overall appearance ^b	5.3 ± 1.0	4.9 ± 0.6
Mouth feel ^b	5.3 ± 1.5	5.1 ± 1.6
Overall favor/disfavor ^b	6.3 ± 1.2	5.7 ± 1.5
Overall favor/disfavor flavor ^{b,c}	6.4 ± 1.2	5.8 ± 1.5

Numbers shown as arithmetic mean ± standard deviation, based on scores given by 20 subjects. Mean (arithmetic) is based on the scores per category per item.

^aItems with scores ranging from 1 (too small/soft) to 3 (just right) to 5 (too large/hard).

^bItems with scores ranging from 1 ("disfavor extremely") to 5 ("neither favor nor disfavor") to 9 ("favor extremely").

^cSignificant difference between 3 and 8 times chewed ($P < .05$, analyzed with Wilcoxon signed-rank test).

solubility in the aqueous phase of the stomach. Ibuprofen has a pK_a of 4.91 with a very low solubility below this value and is solubilized and absorbed in the intestine at higher pH levels.⁸ In vitro studies have confirmed promising dissolution rates for ibuprofen aggregates incorporated in the novel drug formulation very similar to those of traditional tablets.¹³ In the present study the highest peak plasma concentration was observed after chewing 3 times and was reached in 1.25 hours, whereas the C_{max} of the hard tablet was 1202 ng/mL lower and took 1.93 hours to be reached. In addition, the relative bioavailability after chewing 3 times was approximately 8% higher compared with chewing 8 times. These differences, albeit small, would as outlined above have benefited from a repeated trial applying a larger study group and a higher frequency of initial sampling to evaluate their overall importance.

Clinical efficacy is related to good patient compliance and drug acceptance. A crucial factor to comply with oral drug administration is the size of the dosing formulation. In many cases people tend to modify hard tablets to ease administration, which may lead to a changed bioavailability, toxicity, and stability of APIs.⁵ For the current soft-chew formulation most of the subjects seemed to approve the size of the dosage, which is a pivotal attribute for user acceptance. However, the dosage in this study was only 100 mg, whereas typical adult dosages of ibuprofen are at least 200 mg. As the size of the 100-mg dosage novel formulation is small (~0.8 mL volume), a doubling in size is not anticipated to cause significant issues, but to conclude this, another survey is necessary. The hardness and chewing resistance were also approved, although additional preference studies should be performed here as well because the subjects were not able to compare samples with different textures (hardness and chewing resistance).

Various dosing formulations have been developed to provide pediatric- and geriatric-friendly dosage forms, such as elixirs, chewable tablets, and suspensions.¹ In particular pediatric and geriatric populations seem to be noncompliant to oral drugs due to swallowing and off-taste issues.^{3,14} It has been estimated that 70% to 90% of the older population experience some degree of dysphagia. The prevalence of dysphagia is particularly high in patients with age-related diseases such as Parkinson disease (80%), Alzheimer disease (40% to 70%), and acute stroke (50%).^{3,15,16}

However, issues with swallowing tablets occur in the whole population. A recent survey demonstrated that half of the participants (33 to 77 years) reported to have experienced difficulties when taking hard tablets, with 10% expressing that such pills should never have been made or used.¹⁷ Seven percent even refused to ever take hard-to-swallow pills, and 4% reported to have health complications because they could not comply with the oral treatment.¹⁷ Another survey asked people of all ages (1 to 70+ years) and found that an average of 26% had at least some difficulty with swallowing hard tablets. This percentage was larger among women than men and among the younger age groups (<14 years).¹⁸

The gel matrix of the soft-chew formulation used in this study has a sol-gel transition temperature that correlates well with physiological conditions and causes rapid disintegration/dissolution during mastication, thereby easing the process of swallowing. By a careful selection of the type of gelatin, the hardness as well as the sol/gel transition temperature of the gel matrix can be modified to optimize the mouth feel of the API formulation.^{19,20} However, and as reported in the present study, only minor modifications may be necessary, as the current formulation received positive feedback regarding texture.

A low-pH buffering system was applied to keep ibuprofen in the nondissolved state in the gelled matrix and during mastication. This method has been shown to provide good stability of the API while masking the pungent ibuprofen taste as well as offering microbial stability.¹³ In addition, the malic acid/citrate buffering system combined with sweeteners provides a pleasant acidulous flavor, which was well appreciated by most subjects. As shown in Table 4, chewing 3 times was significantly preferred ($P = .043$) over chewing 8 times. This observed difference is likely to be caused by a higher level of ibuprofen release in saliva, and hence also in the oral cavity, due to the prolonged 8-times chewing. In turn, this will reduce the overall palatability of the chewable formulation. However, in real-life situations the type of dose used in this study will most likely be chewed considerably less than 8 times, as the soft gelatin matrix rapidly disintegrates/dissolves on mastication and can normally be easily swallowed after 3 chews.

In conclusion, mastication did not significantly influence the relative bioavailability (AUC_{inf}) of ibuprofen aggregates in the novel formulation, even after chewing 8 times. The novel formulation chewed 8 times showed bioequivalence with the hard tablet, but when chewed 3 times no conclusion on bioequivalence could be reached due to differences in C_{max} . Further clinical studies with larger study groups may be required to obtain a conclusion on this matter.

The results indicate that bioequivalence with traditional ibuprofen tablets may be within reach, which for all types of generics is a requirement to avoid performing full clinical trials.

The novel soft-chew formulation has the potential to benefit several populations who have difficulties complying with their oral drug treatment. The size and texture of the chewable test formulation were well appreciated. In addition, the taste-masking properties disguised the off-taste of ibuprofen well, and the majority of subjects in this study were fairly positive about the overall appearance and flavor.

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Declaration of Conflicting Interests

Vitux Pharma AS and Vitux AS are fully owned subsidiaries of Vitux Group AS. M.N.H. is a full-time employee of Vitux AS, whereas T.E. and K.I.D. hold part-time engagements

in Vitux Pharma AS. T.S. and M.J.D. declare no competing interests.

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