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In-vivo disintegration and absorption of two fast acting aspirin tablet formulations compared to ibuprofen tablets using pharmacoscintigraphy

H. Stevens[a], M. Voelker[b,*], L. Gow[a], F. MacDougall[a], G. Bieri[c]

[a] BDD Pharma, Glasgow, United Kingdom
[b] Bayer AG, Leverkusen, Germany
[c] Bayer AG, Basel, Switzerland

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ABSTRACT

Introduction: Aspirin is widely used to relieve acute pain and reduce fever and inflammation. New 500 mg and 1000 mg aspirin rapid disintegrating tablets with small active ingredient particle size and sodium carbonate excipient were developed to replace regular 500 mg aspirin tablet formulation containing starch and cellulose. The rapid disintegrating aspirin tablets have been proven to show faster in-vitro dissolution and a shorter time to Cmax (Voelker 2012) resulting in faster pain relief (Cooper 2012). The current study correlates the site and time to complete tablet disintegration with the plasma concentration time profile, using γ-scintigraphy imaging technique. Two 400 mg ibuprofen tablet formulations (ibuprofen acid and ibuprofen lysine salt) have also been analyzed in this study.

Methods: Open label, randomized and four-way crossover trial in 12 healthy fasted males. Scintigraphy images and blood sampling were taken up to 4 h post dose. Tablets were radiolabelled with 4 MBq technetium (99mTc)-labelled DTPA using a drill and fill method (Wilson 2003). Site and time to complete tablet disintegration were derived from the scintigraphy images. Validated bioassays were used to measure plasma concentration.

Results: In all subjects the aspirin formulations disintegrated rapidly and completely in the stomach (500 mg Aspirin: 9.0 min, 1000 mg Aspirin: 5.0 min). Complete disintegration of the ibuprofen tablets occurred in 5 and 4 out of 12 subjects in the small intestine. Time to complete disintegration was longer (acid: 37.5 min, lysine-salt: 37.5 min) than with the aspirin formulations. This correlates with pharmacokinetics: a substantial difference in T_{max} between the two aspirin formulations (500 mg Aspirin: 20 min, 1000 mg Aspirin: 23 min) and the two ibuprofen formulations (acid: 68 min, lysine-salt: 42 min) was observed.

Conclusions: The gastrointestinal disintegration and systemic absorption of the aspirin formulations is faster compared to the ibuprofen formulations.

1. Introduction

Aspirin (acetylsalicylic acid, ASA) is a commonly used non-prescription medicinal drug for relief of pain and reduction of fever having high level of evidence. It's efficacy in acute pain [1,2], symptoms of common cold [2,3] and fever [2,4] has been shown in many randomized controlled clinical studies.

Aspirin is available in several pharmaceutical forms, including tablets, rapidly disintegrating tablets, chewable tablets, effervescent tablets and granules. These formulations have an impact on pharmacokinetic parameters [5] and consequently on pharmacodynamic properties. Rapidly disintegrating tablets have been demonstrated to show fast dissolution *in vitro* [6,7], fast bioavailability *in vivo* [6] and consequently early onset of action in different pain models [8,9]. Compared to conventional aspirin tablets an improvement of time to meaningful pain relief by the factor of 2 has been demonstrated (49 min vs. 99 min) [8].

Due to its chemical structure acetylsalicylic acid shows a pH-dependent equilibrium of the ionized (hydrophilic) and the non-ionized (lipophilic) form of the salicylate. Consequently its solubility is strongly dependent on the pH. Solubility is low at an acidic pH and increases with an increase in pH. The solubility in aqueous media is highest after conversion of the acid into a sodium salt [10]. On the other side the lipophilic properties of the non-ionized salicylic acid supports its transport through cell membranes.

The *in vitro* dissolution behaviour and the *in vivo* pharmacokinetic and pharmacodynamic properties of a fast disintegrating aspirin formulation has previously been shown [6,8,9]. This unique aspirin

* Corresponding author. Bayer AG, Building K56, 51368, Leverkusen, Germany.
E-mail address: michael.voelker@bayer.com (M. Voelker).

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formulation contains sodium carbonate as a disintegrant and very small particles of the active ingredient resulting in a favourable surface-to-volume ratio supporting solubility. Mean peak plasma concentrations of acetylsalicylic acid of 13–14 μg/mL of a dose of 500 mg are obtained within 17–20 min [6].

The rate and speed of absorption of a medicinal drug is limited by the process of tablet disintegration and dissolution in the stomach and the rate of gastric emptying into the upper small intestine [11]. Scintigraphy is an established method to determine disintegration of a pharmaceutical product, release of the active ingredient into the stomach and the rate of gastric emptying into the upper small intestine [11–13].

The current combined scintigraphy and pharmacokinetic study investigates the gastrointestinal disintegrating and absorption of two fast disintegrating aspirin formulations and compared with two commercial ibuprofen products. We have chosen the drug substance ibuprofen, because it is common practice to use ibuprofen formulations and aspirin formulations in self-medication for acute pain [1,14]. Ibuprofen is widely available as tablets containing ibuprofen acid or the more water soluble salts of ibuprofen, e.g. ibuprofen lysinate which dissolves and is absorbed more rapidly [15]. The scintigraphy study is aimed to provide visualization and localization of the disintegration, time to complete tablet disintegration and the rate and time of gastric emptying and to bring into context with bioavailability.

2. Material and methods

2.1. Materials

Non-radiolabeled product was supplied by Bayer. For Aspirin® 500 mg, Nurofen® 400 mg and Dolormin® Extra 400 mg marketed batches has been used. For Aspirin® 1000 mg a batch has been produced for this study. Technetium-99 m diethylenetriaminepentaacetic acid (^{99m}TcDTPA) was provided by the West Scotland Radionuclide Dispensary.

Tablets were radiolabeled by drilling a hole and filling with ^{99m}Tc-DTPA. The remaining space of the hole was filled with non-radiolabeled lactose then sealed with bone cement ensuring the packed hole was completely sealed.

Validation of the radiolabelling 'drill and fill' procedure via scintigraphic monitoring of radiolabelled tablets during *in vitro* dissolution testing confirmed that the radiolabelling procedure does not impact the tablet disintegration properties of the four formulations and the radiolabel acts as an appropriate marker for tablet disintegration. As disintegration of the formulation into primary particles is generally required in order for the active pharmaceutical ingredient to be released, the release of radiolabel as the tablet disintegrates was considered a surrogate for release. The dissolutions were conducted as per the USP methods for aspirin (pH 4.5 buffer, 50 rpm, 500 mL) and ibuprofen tablets (pH 7.2 buffer, 50 rpm, 900 mL). The dissolution profiles from the radiolabelled Aspirin® 500 mg and 1000 mg tablets were comparable to dissolution profiles provided by Bayer. The radiolabelled Nurofen® and Dolormin® Extra tablets provided similar dissolution profiles to the non-radiolabelled tablets.

2.2. Methods

The study was conducted as a single centre, randomized, open label, four-treatment, four period and four sequence study in fasted healthy male subjects. The study followed the Declaration of Helsinki, was approved by the Scotland A Research Ethics Committee and the Administration of Radioactive Substances Advisory Committee (ARSAC) and was conducted according to Good Clinical Practice.

The study consisted of a screening phase, a treatment phase with four treatment periods (Period 1, Period 2, Period 3, and Period 4) and a follow-up phase. All subjects were healthy as defined by assessment of routine clinical, laboratory, and instrumental examinations, and were non-smokers. Exclusion criteria included excessive xanthine consumption, more than moderate alcohol consumption, metabolic disease, history of hypersensitivity to the active substances and a history of hypersensitivity reactions such as asthma or allergic reactions.

Eligible subjects were selected within a period of approximately 28 days prior to the first dose of the radiolabelled study drug on Day 1 of Period 1. Subjects were discharged from the site after completion of the blood sampling and scintigraphic imaging and review of any adverse events at Day 1 of each treatment period. All four periods were separated by at least a seven-day wash-out phase. The following products were studied:

Treatment 1: 500 mg acetylsalicylic acid (Aspirin®, Bayer)
Treatment 2: 1000 mg acetylsalicylic acid (Aspirin®, Bayer)
Treatment 3: 400 mg ibuprofen (Nurofen®, Reckitt Benckiser Deutschland GmbH)
Treatment 4: 683 mg ibuprofen DL-lysin = 400 mg ibuprofen (Dolormin® Extra, Johnson & Johnson Deutschland GmbH)

Twelve healthy male volunteers were entered into the study. All volunteers gave written informed consent and underwent a medical examination to ensure compliance with the study criteria. Volunteers were required to be aged 18 to 65, BMI of 18.5 to ≤ 30 kg/m^2 and non-smokers. Subjects were dosed standing up and instructed to swallow the dosages together with 240 mL of non-carbonated water.

Following dosing sequential scintigraphic images, each lasting 25 s, were taken of the abdominal area (anterior only) in a standing position with the Gamma camera at the following time points: Pre-dose, at time of dose (0 min) and 2, 4, 6, 8, 10, 12, 15, 20, 25 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 135, 150, 165, 180, 195, 210, 225 and 240 min post-dose or until complete disintegration of the tablet and gastric emptying of the radiolabelled material, whatever was earlier. Pharmacokinetic samples were collected in a labelled 2.7 mL heparinized potassium fluoride collection tube for ASA and salicylic acid (SA) analysis or in a 2.0 mL K2 EDTA collection tube for ibuprofen total analysis prior to dosing, and at 5, 9, 13, 18, 23, 28, 33, 38, 48, 58, 68, 78, 88, 118, 178 and 238 min post-dose.

Subjects were discharged from the site after completion of the blood sampling and scintigraphic imaging, and review of any adverse events (AEs), at Day 1 of each treatment Period. All four Periods were separated by at least a seven-day wash-out phase.

2.3. Scintigraphy data analysis

The scintigraphy images and quantitative data were analyzed using the WebLink® image analysis program. Each image was qualitatively analyzed with regards to the position of the tablet (stomach, small intestine, ascending colon, transverse colon, descending colon). For each subject the images were identified where the tablet first entered the small intestine, the disintegration of the tablet started, the disintegration of the tablet was complete. Precise times could not be determined due to the intervals between acquisitions of images. The times presented represent the midpoint between the time of the image and the time of the previous image.

Based on the above analysis the following variables were obtained for the tablet core as applicable: gastric empty time, time of onset of release and site of onset, time of completion of release and site of completion, position at each time point. Gastric emptying kinetics of the dispersed radiolabelled material ($t_{50\%}$ and $t_{90\%}$) and the disintegration rate ($t_{50\%}$) of each formulation were determined quantitatively.

For the estimation of gastric emptying a region of interest (ROI) was drawn around the stomach for each subject, ashe shape of the stomach may vary between subjects. The radioactive counts within this ROI were determined, using the WebLink software, for each subsequent

Table 1
Scintigraphic parameters of Aspirin® 500 mg, Aspirin® 1000 mg, Nurofen® and Dolormin® Extra: tablet disintegration and gastric emptying (S = stomach, SI = small intestine).

Endpoint		Aspirin® 500 mg	Aspirin® 1000 mg	Nurofen®	Dolormin® Extra
Onset of release (N)	S	12	12	7	8
	SI	0	0	5	4
Completion of release (N)	S	12	12	7	8
	SI	0	0	5	4
Time to complete radiolabel release (min)	N	12	12	12	12
	Mean	8.5	5.8	47.7	41.7
	SD	0.99	2.97	30.42	17.35
	CV	11.6	51.3	63.8	41.6
	Median	9.0	5.0	37.5	37.5
	Min - Max	7.0–10.0	3.0–13.5	17.5–127.5	17.5–75.0
Time to $t_{50\%}$ tablet disintegration (min)	N	12	12	12	12
	Mean	7.4	4.0	40.9	36.5
	SD	1.25	1.16	20.90	14.75
	CV	17.0	29.4	51.2	40.4
	Median	7.4	4.1	34.9	33.3
	Min - Max	5.4–9.0	1.5–6.0	16.3–91.1	16.3–68.9
Time to $t_{50\%}$ gastric emptying (min)	N	12	12	7	8
	Mean	19.9	17.6	46.3	56.3
	SD	11.36	16.49	31.82	17.84
	CV	57.2	93.9	68.7	31.7
	Median	16.7	11.8	34.6	50.9
	Min - Max	10.9–53.9	8.7–66.6	20.0–114.3	37.3–88.3
Time to $t_{90\%}$ gastric emptying (min)	N	12	12	7	8
	Mean	46.4	40.8	75.8	81.4
	SD	37.96	38.19	43.42	25.58
	CV	81.8	93.6	57.3	31.4
	Median	28.9	26.6	64.1	78.1
	Min - Max	12.6–138.1	14.9–151.1	28.4–143.1	53.0–126.3

image and a time-activity curve determined. The data was then entered into validated spreadsheets designed to calculate $t_{50\%}$ and $t_{90\%}$ values. The radioactive counts were corrected for background radiation and radioactive decay and the results expressed as gastric emptying time curves. Completion of gastric emptying was determined visually by an image with negligible gastric activity.

For the calculation of disintegration rate a ROI was drawn around the tablet core (hot spot) in each individual anterior image. The radioactive counts within this ROI were determined and a time activity curve determined, using the WebLink software and the data entered into validated spreadsheets. The radioactive counts were corrected for background radiation and radioactive decay and the results expressed as disintegration time curves.

Based on the above analysis the following variables could be obtained: disintegration rate of the tablet; 50% disintegration of the tablet; % of disintegration at each time point. Complete disintegration was determined visually by an image with no visible radiolabel 'hot spot' remaining.

For graphical presentation the radioactivity was presented in a colour code which shows increasing radioactivity levels: black > blue > green > yellow > orange > red > white. The colours are a visual representation of where radioactive counts are distributed throughout a scintigraphic image. Black areas are background where little/no radioactivity is observed and red/white areas reflect where the highest levels of radioactivity are seen.

2.4. Pharmacokinetic data analysis

Pharmacokinetic parameters were calculated for ASA, SA and total ibuprofen from the plasma concentration data using standard, non-compartmental methods using actual sampling times. A high performance liquid chromatographic method (column: ACE 3C18, 30 × 4.6 mm, 3 µm; column temperature: 25 °C; mobile phase A and B: milli-Q type water/acetonitrile and acetic acid; chromatographic mode: isocratic) for the determination of ASA and SA in human heparinized/potassium fluoride and ibuprofen in human EDTA K2 plasma using LC-MS/MS detection was validated by the Bioanalytical Division of inVentiv Health Clinique according to the guidance for Industry entitled "Bioanalytical Method Validation" (May 2001) of the Food and Drug Administration, and the Guideline on Bioanalytical Method Validation (2011) by the European Medicines Agency. For validation calibration curves, between-run accuracy and precision and within-run accuracy and precision was determined.

Based on the concentration time data, the following pharmacokinetic parameters were calculated from the estimated plasma concentration of ASA, SA, and ibuprofen: $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $t_{½}$.

2.5. Statistics

As an exploratory study and considering variability of ASA measurement, a sample size of 12 in this cross-over design study is considered appropriate to evaluate the time to complete tablet disintegration with scintigraphy measurement for the new disintegrating aspirin tablets, as well as to show pharmacokinetic profiles of the four different formulations. Scintigraphy and pharmacokinetic data were summarized by treatment and parameter presented as descriptive statistics. All summaries and statistical analyses were generated using SAS version 9.4 or higher within the environment Windows 8. Continuous parameters were summarized by descriptive statistics (number of observations (n), arithmetic mean (mean), arithmetic standard deviation (SD), arithmetic coefficient of variation (CV), minimum, median and maximum). Categorical parameters will be summarized by frequency distributions (n, %), where n is the actual number of subjects with data within a category for the particular summary statistic.

3. Results

Twelve healthy male subjects were randomized, received at least one dose of study treatment and were included in the safety, scintigraphy and pharmacokinetic analysis. The mean age was 32.6 years (range 24–42 years). The mean body mass index of the individuals was 26.4 (± 3.36) kg/m^2. All subjects were white. Overall, the sequence

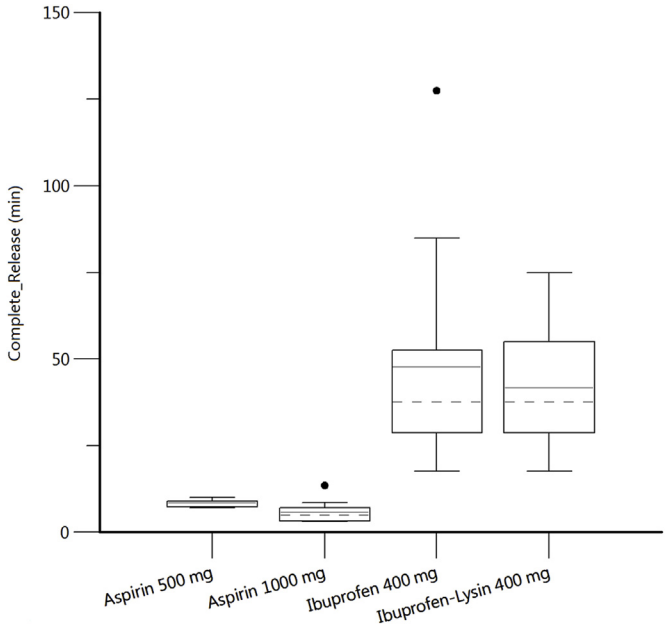

Fig. 1. Time to completion of tablet disintegration of Aspirin® 500 mg, Aspirin® 1000 mg, Nurofen® and Dolormin® Extra presented as box-whisker plot (horizontal lines represent (from the top) the maximum, the third quartile, the median, the first quartile and the minimum. The framed box represents the middle 50% of the distribution (between the first and third quartiles), outliers are represented by the black dot.

groups were well balanced with regards to the demographic data at baseline.

3.1. Scintigraphy

The *in vivo* disintegration behaviour of the tablets was determined scintigraphically and is described quantitatively in Table 1. The median time to complete disintegration was 9.0 min and 5.0 min for the 500 mg and 1000 mg Aspirin formulations respectively. This is faster than for the ibuprofen formulations (37.5 and 37.5 min, respectively). Generally, the variability of time to complete disintegration was much lower for the two aspirin formulations compared to the two ibuprofen formulations with a very narrow range for Aspirin 500 mg and Aspirin 1000 mg (Fig. 1). The aspirin formulations disintegrate between five and eight times faster than the ibuprofen formulations. The onset and completion of disintegration of both aspirin tablets occurred for all subjects in the stomach, whereas for ibuprofen 5 and 4 subjects, respectively, had onset and completion in the small intestine. The faster disintegration of the aspirin products compared to the ibuprofen products is demonstrated in representative scintigraphic images for one individual (Fig. 2).

The images in Fig. 2 show further differences between the behaviour of the aspirin and ibuprofen formulations, with the aspirin formulations exhibiting flotation prior to rapid dispersion, whereas the ibuprofen tablets remained located in the lower body region of the stomach for the duration of stomach residence. This effect is likely due to changes in buoyancy of the aspirin tablets as the carbonate excipient generates carbon dioxide on contact with stomach acid.

In instances where complete tablet disintegration was observed to occur in the stomach, the time to 50% ($t_{50\%}$) and 90% ($t_{90\%}$) gastric emptying of the dispersed tablet was calculated from the scintigraphic images (Table 1).

3.2. Pharmacokinetics

The plasma concentration vs. time curves for acetylsalicylic acid, salicylic acid and ibuprofen are presented in Fig. 3 A-C. Dose-dependency for ASA and SA is obvious. Lysinated ibuprofen differs substantially from ibuprofen. Descriptive pharmacokinetic summary statistics for the area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), half-life ($t_{1/2}$) and the mean residence time (MRT) are summarized in Table 2. Median ASA and SA T_{max} for the aspirin products are 20 min and 23 min, respectively, and 53 min and 57 min, respectively, with an overall small range. Median T_{max} for the ibuprofen products are 68 min and 42 min, respectively, with an overall wide range. The high variability of T_{max} of the ibuprofen-containing products compared to the aspirin-containing products is also presented in the box plot for ASA T_{max} and ibuprofen T_{max} (Fig. 4).

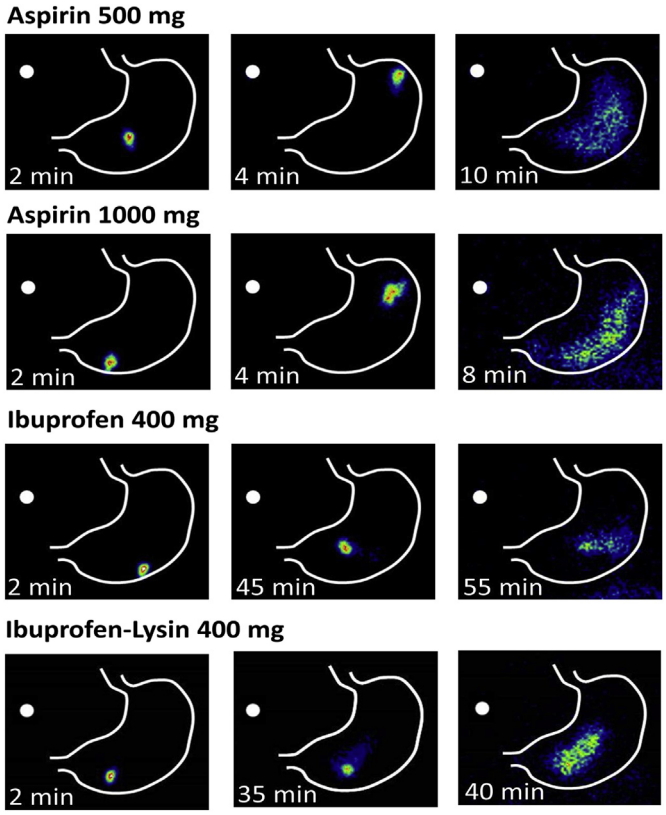

Fig. 2. Representative scintigraphy images of Aspirin® 500 mg, Aspirin® 1000 mg, Nurofen® and Dolormin® Extra at selected time points showing tablet disintegration over time. Colours are a visual representation of where radioactive counts are distributed throughout a scintigraphic image. Colours show increasing radioactivity levels: black (background, no radioactivity) > blue > green > yellow > orange > red > white. Intact tablets will appear to have a red/white centre as the radioactivity is contained in the centre of the tablet. As the tablets disintegrate and the radioactivity spreads over a wider area the colours will change from red/yellow to green/blue. The white dot represents an external marker to allow accurate alignment.

4. Discussion

The scintigraphic data gathered was able to demonstrate that in all subjects (n = 12) the aspirin formulations disintegrated quickly and completely in the stomach, with median times to complete release (min-max) of 9.0 min (7.0–10.0 min) and 5.0 min (3.0–13.5 min) for 500 mg and 1000 mg Aspirin tablets respectively. The observation that both aspirin tablets displayed onset and completion of disintegration in the stomach is reflective of the rapid rate of disintegration for these formulations. Interestingly, for both fast disintegrating aspirin tablets, the tablets were observed to float to the top of the contents of the stomach in each subject within minutes following dosing (Fig. 2). The tablets

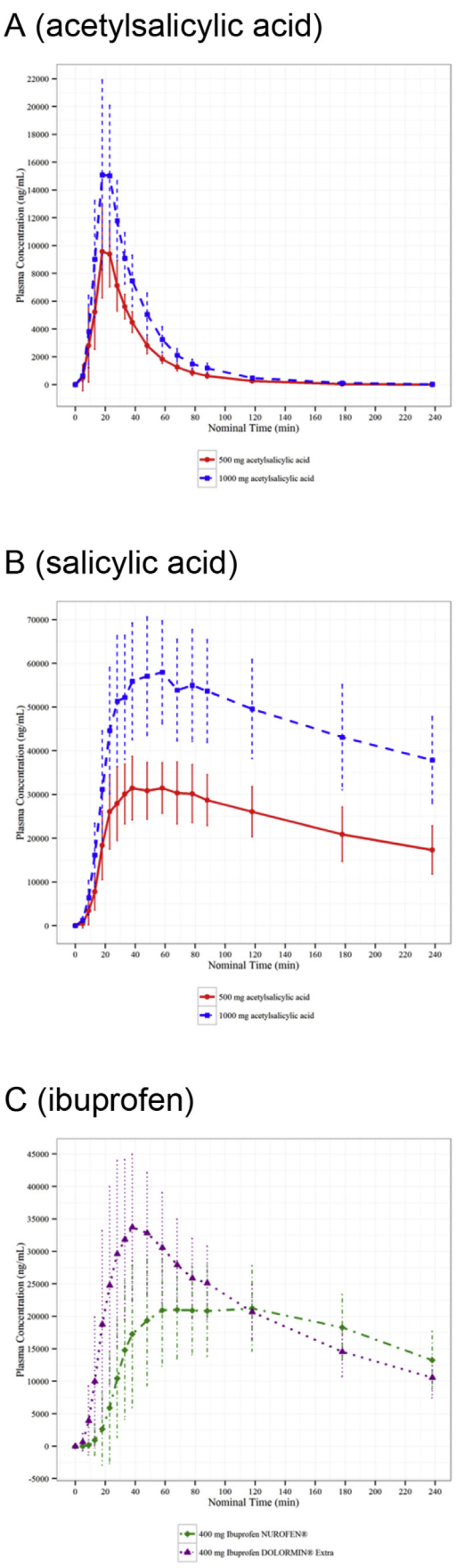

Fig. 3. Plasma concentration vs. time curves of acetylsalicylic acid (A), salicylic acid (B) and ibuprofen (C) of the treatments Aspirin® 500 mg (red curve), Aspirin® 1000 mg (blue curve), Nurofen® (green curve) and Dolormin® Extra (purple curve). Values are presented as mean (± SD).

remained in this position until full disintegration occurred. No floating was observed for the ibuprofen tablets. The observed floating behaviour for the aspirin formulations is thought likely to be a result of the disintegrant, sodium carbonate reacting with the local acid environment and resulting in the liberation of carbon dioxide.

Onset and complete disintegration was also observed in the stomach for 15 of 24 ibuprofen administrations, however in 9 of 24 administrations onset and complete disintegration was observed to occur in the small intestine (Table 1). It was also noted that the variability in time to complete disintegration was much lower for the aspirin formulations, as shown in Fig. 1. In the fasted state the stomach is subject to the Migrating Motor Complex (MMC) which recurs cyclically approximately every 2 h. The MMC begins with a quiescent period in Phase I, progresses into increasing smooth muscle contractions in Phase II, before stronger contractions in Phase III (also known as the housekeeper wave) act over a 5–10 min period to propel any larger particles of undigested material, including monolithic tablets, from the stomach into the small intestine. As this gastric emptying of monoliths is a time dependent process, it was more likely to occur for the more slowly disintegrating ibuprofen formulations than the fast disintegrating aspiring formulations. The ibuprofen formulations may then as a consequence have experienced further variability in disintegration rate due to differences in the hydrodynamic environment between the stomach and small intestine.

The mean $t_{50\%}$ tablet disintegration was less than 8 min for the two Aspirin® formulations (7.4 min and 4.0 min). This rapid disintegration rate *in vivo* confirms previously reported *in vitro* data where dissolution percentages of 92–100% within 15 min were observed [6], and shows that *in vivo* the formulation behaves as designed with sodium carbonate as a disintegrant. Furthermore, the enhanced disintegration behaviour of the sodium carbonate containing formulations in this study in comparison with non-sodium carbonate containing formulations is very similar to findings previously reported in the literature with acetaminophen preparations containing both sodium and calcium carbonate [13]. The slight difference in the disintegration rate of 500 mg and 1000 mg aspirin tablets may be a result of the larger physical size and therefore surface area of the 1000 mg tablet, which offers a greater area for fluid to access the tablet and allow the disintegration process to proceed. Such small differences in disintegration rate would not be expected to have any significant effect on biological absorption rate, when compared to larger differences in disintegration time.

The longer and more variable disintegration times observed for the ibuprofen tablets in the scintigraphic study (Fig. 1) is likely to be a significant factor in the greater T_{max} variability observed for these formulations when compared to the fast disintegrating aspirin formulations in Fig. 4. The ibuprofen in the tablets will not be available for dissolution and subsequent absorption *in vivo* until disintegration of the tablet has occurred, and as such the larger the degree of variability in this disintegration process the larger the expected variability in T_{max} would be.

The mean $t_{50\%}$ of tablet disintegration for the ibuprofen formulations was 40.9 min (range 16.3–91.1 min) for and 36.5 min (range 16.3–68.9 min). Following a similar trend, the time to complete disintegration was longer (mean time (range), ibuprofen acid: 47.7 min (17.5–127.5 min), ibuprofen lysine salt: 41.7 min (17.5–75 min)) than in the aspirin formulations. The rate and extent of ibuprofen absorption were 25% and 15% lower for the 400 mg ibuprofen Nurofen® tablet when compared to the 400 mg ibuprofen Dolormin® Extra tablet. There was no noticeable difference in the observed scintigraphic disintegration behaviour of the two ibuprofen formulations to explain this difference in absorption behaviour, nor was there any particular difference between the location of complete disintegration of the tablets, with complete disintegration of the ibuprofen tablets occurring in 5 (Nurofen®) and 4 (Dolormin® Extra) out of 12 subjects in the small intestine. This suggests that the difference in absorption rate and extent may be due to the different forms of ibuprofen contained within these

Table 2
Pharmacokinetic parameters (Mean/SD for AUC, C_{max}, $t_{1/2}$ and MRT (mean residence time)); Median/Min, Max for T_{max}).

Product	Aspirin® 500 mg		Aspirin® 1000 mg		Nurofen®	Dolormin® Extra
Active Ingredient	Acetylsalicylic acid	Salicylic acid	Acetylsalicylic acid	Salicylic acid	Ibuprofen	Ibuprofen-Lysin
AUC_{0-t} (min x ng/mL)	330,000/61,600	5,540,00/1,320,000	531,000/105,000	10,700,000/2,560,000	3,960,000/808,000	4,650,000/975,000
C_{max} (ng/mL)	10,000/2880	33,200/6330	17,300/6310	60,100/13,300	27,400/4360	36,900/9360
T_{max} (min)	20.0/18.0, 27.0	53.0/33.0, 78.0	23.0/18.0, 38.0	57.0/28.0, 78.0	68.0/33.0, 178	42.0/28.0/118
$t_{1/2}$ (min)	27.1/3.28	207/56.4	27.7/3.75	292/75.8	144/37.2	121/24.5
MRT (min)	39.2/4.09	318/78.6	42.0/5.95	441/106	239/51.0	194/46.7

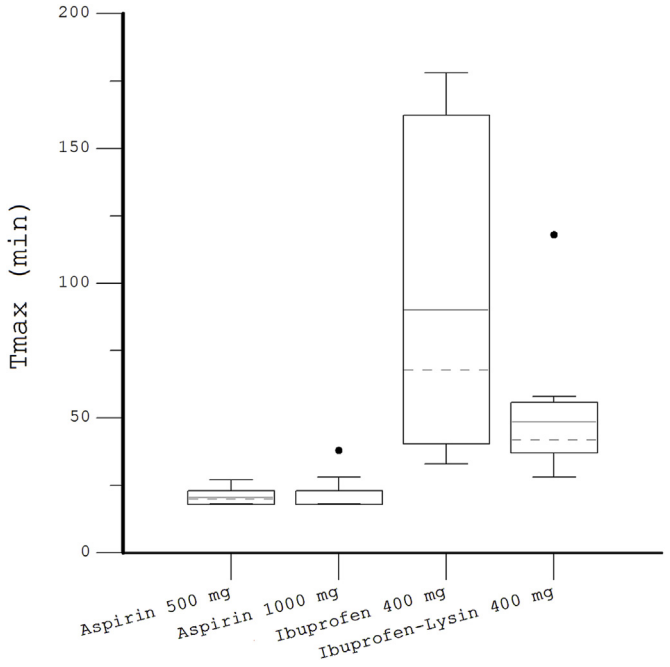

Fig. 4. Time to maximum plasma concentration (T_{max}) of Aspirin® 500 mg, Aspirin® 1000 mg, Nurofen® and Dolormin® Extra presented as box-whisker plot (horizontal lines represent (from the top) the maximum, the third quartile, the median, the first quartile and the minimum. The framed box represents the middle 50% of the distribution (between the first and third quartiles), outliers are represented by the black dot).

formulations, the acid (Nurofen®), and the more soluble lysine salt (Dolormin® Extra) which is generally considered to be faster acting.

The mean $t_{50\%}$ and $t_{90\%}$ gastric emptying times for dispersed radioactive material for all four treatments (Table 1) were within the expected ranges for fasted dosing conditions with mean $t_{50\%}$ ranging from 17.6 to 56.3 min and $t_{90\%}$ ranging from 40.8 to 81.4 min. While all gastric emptying data was within expected ranges, the mean $t_{50\%}$ and $t_{90\%}$ gastric emptying times displayed in Table 1 demonstrate a clear difference in behaviour between the aspirin and ibuprofen formulations. The mean $t_{50\%}$ values of 19.9 and 17.6 min for both aspirin formulations is noticeably faster than the ibuprofen tablets at 46.3 and 56.3 min. This pattern is also observed for $t_{90\%}$ gastric emptying values, and the min-max ranges reported for the gastric emptying data sets. This may be reflective of the earlier onset and faster rate of disintegration of the aspirin tablets resulting in dispersed material being available more rapidly for gastric emptying.

The 500 mg and 1000 mg acetylsalicylic acid disintegrating tablets were well absorbed following oral administration and rapidly metabolized to salicylic acid. The increase in the rate and extent of ASA absorption appears to be dose proportional for the 500 mg and 1000 mg acetylsalicylic acid disintegrating tablets, however this should not be considered conclusive as only two dosage data points were gathered.

Plasma ASA concentrations were detectable within 5 min of administration of the two aspirin formulations, with a peak observed 20 min post-dose, correlating well with previously reported *in vivo* data [6], and expected performance of the formulations utilizing the combined benefits of micronized drug and sodium carbonate disintegrant. The scintigraphic observations of rapid onset and completion of disintegration of these formulations, along with faster gastric emptying of dispersed material provides *in vivo* proof of the mechanism of the rapid absorption and clinical effect observed previously [8,9]. Peak plasma SA concentrations were attained within 1 h following administration with an estimated elimination half-life of approximately 4 h for both 500 mg and 1000 mg acetylsalicylic acid rapidly disintegrating tablets. The low variability of the peak plasma pharmacokinetic data observed for the aspirin formulations may also be linked to the rapid disintegration observed scintigraphically.

Aspirin is known to cause irritations to the gastric mucosa [16]. This may be caused by direct topical irritation of the gastric mucosa and - more established - by systemic cylcooxygenase-mediated inhibition of gastroprotective prostaglandins [17]. Quickly dispersible and dissolving aspirin formulations with fast systemic bioavailability may contribute to less aspirin particle adherence to the mucosa potentially resulting in an improved gastric tolerability. The floating effect described above may further contribute. Whether these characteristics effect aspirin's stomach tolerability needs to be proven in additional clinical research.

These data can be further used for scientific research by pharmacists and clinicians. The implications for onset of pain relief and tolerability of analgesic substances needs to be evaluated in further clinical research.

5. Conclusions

The pharmacoscintigraphic study successfully enabled visualization and quantification of the disintegration behaviour of different aspirin and ibuprofen formulations. The onset and rate of disintegration for the two aspirin formulations was substantially faster than for the ibuprofen tablets studied, which corresponded well with pharmacokinetic data. Rapid disintegration of the aspirin formulations which had previously been demonstrated *in vitro* have now been confirmed *in vivo*, providing confirmation of the mechanism of rapid absorption and clinical effect which has previously been demonstrated.

The gastrointestinal disintegration and the subsequent systemic absorption of the aspirin formulations was faster compared to the ibuprofen formulations, and differences noted between the two ibuprofen formulations in terms of absorption could not be explained through scintigraphic evaluation of their disintegration behaviour, suggesting the solubility of the salt form may have influenced absorption.

Study registration

The study was registered with ClinicalTrials.gov, registration number: NCT03225352, registration date: July 21, 2017.

Declaration of interests

The study was sponsored by Bayer AG, Leverkusen, Germany. MV and GB are employees of Bayer. HS, LG and FM are employees of BDD Pharma Ltd, Glasgow UK. BDD Pharma received fees from Bayer for planning and executing the study. The study protocol was jointly developed by MV, GB, LG and HS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2019.02.013.

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