

IN VITRO DISSOLUTION AND PILOT PHARMACOKINETIC STUDIES OF ACETYLSALICYLIC ACID FROM AN ORALLY DISINTEGRATING TABLET FORMULATION OF LOW-DOSE ASPIRIN

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Received: November 21, 2011; Accepted: December 01, 2011

Abstract- Purpose: Low-dose aspirin (acetylsalicylic acid; ASA) is in routine use today in preventing myocardial infarction and cardiovascular events. Fasprin® (ASA, 81 mg) is a new orally disintegrating tablet formulation of low-dose ASA (ODA) that was designed as a fast-acting, quick-dissolving solid dosage form. The purpose of this work was to (1) evaluate, comparatively, the *in vitro* dissolution, and (2) evaluate the absorption kinetics of ASA in healthy adults following oral administration of the ODA product.

Methods: USP type II dissolution apparatus was implemented in the dissolution studies. For the pharmacokinetic studies, a single ODA dose was administered and blood samples were collected and analyzed for ASA content using a validated HPLC method. Absorption-related pharmacokinetic parameters were estimated using WinNonlin®.

Results: Dissolution rate and extent of ASA from the ODA formulation were either higher than or similar to those from leading aspirin-containing products. Noncompartmental pharmacokinetic analysis of ASA plasma profiles from the ODA product revealed a lag-time of at least three minutes. The maximum concentration (C_{max}) of ASA was 0.61 µg/mL and the time of C_{max} (t_{max}) ranged from 15 - 75 minutes. The elimination rate constant of ASA was 0.0245 min⁻¹, corresponding to a terminal $t_{1/2}$ of 28.3 minutes.

Conclusion: The ODA product demonstrated favorable dissolution compared to some leading ASA-containing products. It also provided systemic concentration of ASA at a relatively early time. While the overall absorption kinetics of the ODA product was generally comparable to those from other low-dose ASA-containing products, a direct product comparison is warranted.

Keywords- low-dose aspirin, Fasprin®, ASA, dissolution, pharmacokinetics, absorption

Introduction

In 1988, the United States Food and Drug Administration moved forward on approving the use of aspirin (acetylsalicylic acid; ASA) for reduction of the risk of a second or subsequent myocardial infarction, and prevention of an initial incidence of myocardial infarction (Bayer HealthCare LLC 2008; Food and Drug Administration 2008). This along with the approval of ASA as an agent to prevent transient ischemic attacks and stroke in men moved aspirin beyond its anti-inflammatory indication. Since that time, ASA has been shown time and time again to be effective in preventing myocardial infarction in a number of patient populations. A decade later, the results of studies further supported the effectiveness of ASA, this time in prevention of cardiovascular events in patients at risk [1]. In 2005, the benefits of ASA use in women with respect to lowering the risk of stroke were documented [2]. To this day, ASA is recommended by the American Heart Association and

the U.S. Preventive Services Task Force for patients at moderate risk for cardiovascular events (American Heart Association 2008; United States Department of Health and Human Services).

The mechanism of action of ASA involved permanent inhibition of cyclooxygenase1 - dependent platelet aggregation [3]. Specifically, ASA irreversibly acetylates the cyclooxygenase1 enzyme at a serine side chain [4, 5]. This acetylation of the enzyme inhibits the synthesis of thromboxane A₂, a key mediator in platelet activation, from arachidonic acid [5]. Owing to its irreversible effect on platelets aggregation, small doses of ASA administered chronically should be as effective as much larger doses [6].

In addition to its protective indications within the cardiovascular system, use of daily ASA for about 5 years has been shown to be effective in primary prevention of colorectal cancer in randomized controlled trials, with a latency of about 10 years [7]. While doses

required to produce those preventive effects in colorectal cancer were relatively high (300 – 500 mg), more recent studies on ASA taken at lower doses (75 – 300 mg) daily for several years has been shown to reduce long-term incidence and mortality due to colorectal cancer. Benefit was greatest for cancers of the proximal colon, which are not otherwise prevented effectively by screening with sigmoidoscopy or colonoscopy [8]. These recent finding could open the door for yet another indication to be added to the indications list for ASA, a molecule which is over a 100 years old.

Fasprin® (ASA, 81 mg) is a new orally disintegrating tablet formulation of low-dose ASA (ODA) that was introduced to the market in recent years. The purpose of the product was to present a fast-acting, quick-dissolving solid dosage form of ASA that might be especially valuable in situations when a fast onset of action is desirable. Therefore, the purposes of this study were to (1) evaluate the dissolution characteristics, *in vitro*, of various leading ASA-containing products relative to those from the ODA product, and (2) evaluate the absorption kinetics of ASA in healthy adult subjects following oral administration of Fasprin® (ODA product), with emphasis on determining the time of the earliest systemic exposure of ASA. The plasma-concentration versus time data for ASA were constructed and examined to determine the pharmacokinetic parameter estimates of ASA provided by the ODA product. As of today, this is the first attempt to characterize the dissolution properties or pharmacokinetics of this dosage form.

Methods

In Vitro Dissolution Studies

United States Pharmacopeia (USP) Dissolution apparatus type II was employed in the *in vitro* dissolution studies. Each dosage form ($n = 5 - 7$) of either the ODA product, 81 mg; Aspirin, 325 mg (Bayer); chewable Aspirin, 81 mg (Bayer) or enteric-coated Aspirin, 81 mg (Bayer) tablets were placed in 500 ml of 0.1 N HCl as the dissolution medium. The temperature was maintained at $37 \pm 1^\circ\text{C}$ with a circulating water-bath. The dissolution medium was continuously stirred with paddles at 50 rpm. One milliliter sample aliquots were withdrawn at pre-determined time points up to 120 min, filtered through 0.45 μm syringe filters, adequately diluted and analyzed by HPLC for ASA concentrations. Each withdrawn sample was replaced by an equal volume of temperature-equilibrated fresh dissolution medium. This procedure was slightly modified for the enteric-coated tablets, as described by Gjellan et al. [9]. Briefly, each tablet was placed in a volume of 375 ml of 0.1 N HCl for 2 hours. Then, 125 ml of 0.2 M Na_3PO_4 was added. The resulting pH of 7.1 – 7.2 was adjusted with 2 M HCl to a pH of 6.8. No ASA was released during the first 2 hours as evidenced by samples collected every 30 min within this period. Data reported for ASA dissolution from this dosage form represent those collected 5 minutes after the medium switch and up to 120 minutes.

The Rate and extent of ASA dissolution from all tablets, upon normalizing by the dose, were calculated and the dissolution profiles were constructed. The label strengths of the products were assumed to be 100%.

The statistical significance of differences in the rate and extent of dissolution from the various dosage forms was evaluated by ANOVA and Tukey's post-hoc test at P value of < 0.05 , using Minitab (v.15, Minitab Inc., State College, Pennsylvania).

Pharmacokinetic Studies

The pharmacokinetics of ASA from the ODA product was studied in healthy volunteers. The study was approved by the Ohio Northern University Institutional Review Board as a single-center, open-label, single-dose pharmacokinetic study. Thirteen healthy adult subjects were enrolled into the study; however, three subjects did not receive the study drug as venous blood access was not achieved. Of the ten subjects completing the study, three were male subjects and seven were females. The average age of the subjects was 28.2 ± 11.9 years (mean \pm standard deviation), ranging from 21 – 54 years (Table 1).

Each subject underwent screening and was defined as healthy based on medical/laboratory history and physical examination. Female subjects had a negative pregnancy test on study day. Subjects were not taking any medications and had not received any ASA or ASA-containing products within 14 days of the study day. All subjects were non-smokers. Five subjects fasted for at least eight hour prior to administration of the ODA product.

On the scheduled study day, each subject reported to the research center. Each subject was placed in the supine position and the upper torso was inclined to 30 to 45 degrees. Venous access was gained through the insertion of an 18- or 20-gauge venous catheter into an antecubital vein.

The ODA product was supplied by Improvita Inc., Cleveland, Ohio, while the other aspirin-containing dosage forms were purchased from a local community Pharmacy. Each subject received a single 81 mg dose of the ODA product. The dose was administered as directed by the product labeling. Specifically, each subject placed a single tablet on the tongue and allowed saliva to dissolve the tablet. Subjects indicated to the investigators the time at which the drug had completely disintegrated (no "grittiness"). Access to food or water was not allowed during the blood collection period of 120 minutes.

Plasma Analysis and HPLC Method

Four milliliters of blood were collected through the venous catheter prior to the ODA product administration and at 1, 3, 5, 7, 10, 15, 20, 25, 30, 35, 40, 45, 60, 75, 90, and 120 minutes after administration. Blood was collected in tubes containing sodium heparin. The blood was centrifuged within 15 minutes of collection at 3,500 rpm for ten minutes. Plasma was then transferred to

storage tubes and stored at -80°C until analysis for ASA was performed (within 21 days of collection).

A high performance liquid chromatography (HPLC) assay for quantification of ASA in human plasma was developed based on the method of Benedek et al. [10], with slight modification. An internal standard of *o*-anisic acid ($0.25\ \mu\text{g/mL}$) was mixed with samples containing ASA in 1:1 ratio (v:v). Base-line resolution was achieved and peak height ratios were plotted against the corresponding analyte concentrations. The slopes of the curves and the y-intercepts were determined by linear regression. The assay linearity was established over the full concentration range for ASA. Calibration curves of ASA were prepared in human plasma. Briefly, $160\ \mu\text{L}$ of blank human plasma, obtained from the healthy volunteers, was mixed with $40\ \mu\text{L}$ of ASA ($0.125, 0.25, 0.5, 2.5$ and $5\ \mu\text{g/mL}$) containing solutions. To that, $400\ \mu\text{L}$ of acetonitrile was added to precipitate the plasma proteins. The mixture was first mixed for 20 seconds then centrifuged at $13,000\ \text{rpm}$ for one minute. Three hundred μL of the clear supernatant was withdrawn and evaporated to dryness by blowing nitrogen gas at 50 psi. The residue was reconstituted with $100\ \mu\text{L}$ of the mobile phase and mixed with an equal volume of the internal standard and injected into the HPLC. For preparation of drug-containing samples for HPLC analysis, $200\ \mu\text{L}$ of plasma was mixed with $400\ \mu\text{L}$ of acetonitrile. The remainder of the procedure was similar to that of preparation of the calibration curve samples described above. The coefficient of variation for the assay was defined within and between days with 1.92% and 5.18% intra-day ($n = 3$) and inter-day ($n = 9$) variability, respectively. Variability of less than 10% was generally considered acceptable.

Pharmacokinetic Data Analysis

Noncompartmental pharmacokinetic analysis of the plasma-concentration versus time data for ASA was performed using WinNonlin® (v.2.1; Pharsight Corporation, Mountain View, California). For pharmacokinetic analysis of individual patient data, the labeled strength of the ODA product was assumed to be 100%. In this analysis, the observed maximum concentration (C_{max}) and the time of the maximum concentration (t_{max}) were the observed values from the plasma concentration–time profiles. The elimination rate constant (λ_z) was estimated using linear regression of the terminal \ln (concentration) versus time data (minimum of three data points). The terminal $t_{1/2}$ was calculated as $0.693/\lambda_z$. The pharmacokinetic analyses for ASA included calculation of the area under the plasma-concentration versus time curve from time zero until the time of the last measurable plasma concentration (C_{last} ; $\text{AUC}_{0 \rightarrow t}$) using the linear trapezoidal rule. The area under the plasma-concentration versus time curve from the time of the last measurable ASA concentration to infinite time ($\text{AUC}_{t \rightarrow \infty}$) was calculated as $C_{\text{last}}/\lambda_z$, and the area under the curve from zero to infinity ($\text{AUC}_{0 \rightarrow \infty}$) was calculated as the sum of $\text{AUC}_{0 \rightarrow t}$ and $\text{AUC}_{t \rightarrow \infty}$. The

clearance of ASA (CL/F) was calculated as the administered dose divided by $\text{AUC}_{0 \rightarrow \infty}$.

As this was a single-drug, non-comparative study, the pharmacokinetic parameter estimates for ASA were summarized using descriptive statistics. The C_{max} was presented as the mean \pm S.D. (standard deviation), while the t_{max} was summarized by presenting the median value and the minimum and maximum values (range). The terminal elimination rate constant (λ_z) was presented as the mean \pm S.D. and the terminal $t_{1/2}$ was presented as the harmonic mean value. The $\text{AUC}_{0 \rightarrow \infty}$ and CL/F were presented as the mean \pm S.D.

Results

Dissolution Studies:

The Rate of ASA dissolution of $3.53 \pm 0.29\ \%/min$ from the ODA formulation was significantly higher than those from Bayer's Chewable Aspirin 81 mg, Bayer's Enteric-Coated Aspirin 81 mg and Bayer's Aspirin 325 mg of $2.71 \pm 0.42, 2.49 \pm 0.46$ and $2.07 \pm 0.25\ \%/min$, respectively (Fig. (1) and Table 2). The extent of ASA dissolution from the ODA formulation was $92.03 \pm 6.05\ \%$, comparable to that from Bayer's Enteric-Coated tablet, $88.05 \pm 5.68\ \%$, but significantly higher than that from Bayer's Aspirin 325 mg and Bayer's Chewable Aspirin 81 mg of 82.24 ± 3.57 and $76.08 \pm 10.19\ \%$, respectively (Fig. (1) and Table 2). Over the sampling period, the extent of ASA dissolved from all formulations started to reach a plateau after 30 minutes from the beginning of the dissolution process.

Pharmacokinetic Studies:

Subjects were requested to indicate to the investigators when they perceived that the dose of the ODA product had completely disintegrated on their tongue. The average time for complete disintegration of the ODA product (Fasprin®) was 111.2 ± 65.2 seconds. The time of disintegration ranged from 45 to 235 seconds (Table 3). The ODA product began to disintegrate immediately upon administration.

In all subject, there was at least a three-minute lag-time before absorption of ASA was noted. Five of ten subjects had quantifiable ASA concentrations at five minutes, while seven of ten subjects had quantifiable ASA concentrations at seven minutes. By 15 minutes, all subjects had quantifiable ASA concentrations (Fig. (2)). In general, the concentrations of ASA increased with time as expected from extravascular dosing, with a maximum concentration occurring typically between 20 and 40 minutes, followed by concentrations decreasing with time in a monoexponential fashion. Fig. (2) presents the ASA concentration versus time data for all but one subject. Data from this subject was excluded from analysis as an outlier (Dixon's test) due to an abnormal absorption profile (data not shown) [11]. The time of the maximum concentration (t_{max}) of ASA ranged from 25 to 75 minutes, with a corresponding C_{max} of $0.61 \pm 0.34\ \mu\text{g/mL}$ (Table 4). The terminal (elimination) rate constant of ASA was $0.0245 \pm 0.0078\ \text{min}^{-1}$ and the harmonic mean $t_{1/2}$ of ASA in the subjects averaged 28.3 minutes.

The clearance of ASA with the bioavailability (F) unknown (CL/F) was 2282.4 ± 636 mL/minute (Table 4). The area under the ASA concentration versus time curve from time zero to infinity, $AUC_{0 \rightarrow \infty}$, was 37.9 ± 10.1 $\mu\text{g/mL} \times \text{min}$. The measured ASA concentration versus time data covered 86.4% of the $AUC_{0 \rightarrow \infty}$.

Discussion

The objective of this study was to characterize the *in vitro* dissolution as well as the absorption kinetics of ASA from a new orally disintegrating tablet formulation of low-dose ASA (ODA), Fasprin[®], with focus on the time of the earliest systemic exposure of ASA. Since the ODA product was designed to disintegrate rapidly in the mouth, it was not surprising that it demonstrated higher dissolution rate of ASA relative to the other leading ASA-containing products tested in this study. With time, though, the extent of dissolution from enteric-coated aspirin started to catch up with that from Fasprin[®]. While the differences in the dissolution rate data in this study might not bear clinical significance, it is reasonable to assume that Fasprin[®] can provide ASA levels at a faster rate compared to the other aspirin-containing products evaluated in this study, which could be valuable when a fast onset of ASA action is desirable.

The ODA product provided quantifiable concentrations of ASA to the systemic circulation in all subjects. While the time for the ODA formulation to disintegrate was variable, in this study, the dosage form completely disintegrated within four minutes, with seven of ten subjects reporting complete disintegration in less than two minutes. Although there was a lag-time prior to systemic exposure to ASA in all subjects, 50% percent of the subjects had quantifiable ASA plasma concentrations by 5 minutes and 100% of the subjects had ASA in the plasma by 15 minutes. This short time for the first quantifiable concentration of ASA can be attributed, at least in part, to the rapid disintegration and subsequent dissolution of the dosage form.

It is worth mentioning, though, that if the ODA product is to be administered chronically, for example, for its beneficial cardiovascular effects, rapid dissolution in the mouth might not be a clear advantage over other conventional ASA-containing products designed for oral administration for this purpose.

The plasma concentrations of ASA increased steadily in individual subjects after dosing until approximately 35 to 45 minutes when concentrations began to "level off" briefly prior to decreasing within the terminal elimination phase. A potential reason for this absorption pattern is that ASA from the ODA product started to get absorbed from the oral cavity soon after disintegration and then as the product, which is now in solution form or fine particles, started moving down the gastrointestinal tract, it continued to be absorbed from there as expected. The process of swallowing more and more of the product over time seems to be responsible for the observed slight "leveling off" of plasma levels of ASA, as well as the appearance of a blunt, instead of a sharp, C_{max} . Continued swallowing of portions of the product would be

anticipated as natural swallowing occurs relatively frequently until the oral cavity is depleted from any ASA. One study noted spontaneous swallowing occurred at a rate of 1.32 swallows per minute [12].

The median t_{max} , 30 minutes, was similar to values reported for other immediate-release solid dosage forms of aspirin [10, 14]. The median t_{max} for those subjects who fasted was 30 minutes and for those who did not fast, the value was 40 minutes. No significance can be applied to the difference as the small sample size precludes formal statistical analysis. The overall mean C_{max} value was 0.61 ± 0.34 $\mu\text{g/mL}$, corresponding to a variability of 55.7 % as represented by C.V.; the coefficient of variation. When looking at the subpopulations, the variability was 21.3 and 86.9% for fasting and non-fasting groups, respectively. While a large sample population is required to confirm this observation, there appears to be greater variability in C_{max} in the non-fasting sub-population suggestive of food effect impacting the absorption of ASA from the ODA product.

Charman WN et al. [13] evaluated the absorption kinetics of another low-dose (75 mg) controlled-release formulation of ASA. While the two formulations differ in their design, the extent of ASA absorption from both dosage forms, represented by $AUC_{0 \rightarrow \infty}$, was similar, 32.0 ± 7.5 and 37.9 ± 10.1 $\mu\text{g/mL} \times \text{min}$ for the controlled-release formulation and the ODA product, respectively, upon dose normalization. The CL/F values in four subjects were similar to values reported earlier [10]. In the remaining five subjects, in whom pharmacokinetic parameters could be calculated, the CL/F values were somewhat higher than reported earlier [10]. The terminal $t_{1/2}$ of ASA averaged 28.3 minutes. This value is slightly longer than reported for most other immediate-release ASA dosage forms [10, 14]. Whether clinically significant or not, this prolonged $t_{1/2}$ of 17.5 – 34.3% may be a consequence of the dosage form design of the ODA product and/or repetitive swallowing of some of the disintegrated tablet particles over time, such that the input of the dose continued, even in slight proportions, for some time throughout the sampling period and possibly within the early portion of the elimination phase.

Conclusion

The orally disintegrating tablet formulation of low-dose aspirin (ODA) under investigation, known as Fasprin[®], provided systemic concentrations of ASA at a relatively early time. The fact that the ODA disintegrates rapidly in the oral cavity is significant. This is because the formed ASA-containing solution/suspension will start getting absorbed from the oral cavity first, resulting in quantifiable levels in plasma early on, and then continue to the major site of absorption in the gastrointestinal tract. The faster ASA goes into the solution/suspension state, as with an orally disintegrating formulation, the more likely absorption will occur sooner. Overall, the absorption-related pharmacokinetic parameters of the ODA product were generally comparable to those from

other low-dose ASA-containing products. While the main objective of this study was to evaluate the *in vitro* dissolution characteristics and the absorption kinetics of ASA from the ODA product, a direct multi-dosage form, cross-over design study would be appropriate for comparative absorption characterization of ASA from this ODA product in relation to other ASA-containing oral dosage forms.

Acknowledgement

We would like to acknowledge the contributions of Matt Tupps, PharmD and Kate Turkaly, PharmD in the collection, analysis and reporting of data for the dissolution as well as the pharmacokinetic studies. Their assistance was valuable and highly appreciated.

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Table 1 - Subject demographics

Subjects* (n = 10) (3 M / 7 F) ^a	Age (years)	Height (inches)	Weight (kilograms)
Mean	28.2	66.5	70.1
S.D. ^b	11.9	3.8	16.2
Minimum	21	61	52.3
Maximum	54	73	100

*Five subjects fasted at least eight hours prior to dosing. ^a M: Male; F: Female ^b S.D.: Standard deviation

Table 2 - *In vitro* dissolution parameters of ASA from the different ASA-containing products

Dosage Form	Dissolution Rate (%/min)	Extent of Dissolution (%)
Fasprin® 81 mg	**3.53 ± 0.29 ^a	*92.03 ± 6.05 ^a
Bayer® 81 mg Chewable	*2.71 ± 0.42	76.08 ± 10.19
Bayer® 81 mg Enteric-Coated	2.49 ± 0.46	*88.05 ± 5.68
Bayer® 325 mg	2.07 ± 0.25	82.24 ± 3.57

(* Significantly higher than unmarked values, (** significantly higher than values marked with (*): One-way ANOVA followed by Tukey's post-hoc analysis, P < 0.05 ^a Values represent mean ± S.D. (n = 5 - 7).

Table 3 - Disintegration time of the ODA product (Fasprin®) on the tongue

Subjects* n = 10	Disintegration Time (seconds)
Mean	111.2
S.D.	65.2
Minimum	45
Maximum	239

*Five subjects fasted at least eight hours prior to dosing.

Table 4 - Pharmacokinetic parameter estimates for ASA upon single oral dose of the ODA product (Fasprin®)

Subjects* n = 9	Tmax (minutes)	Cmax (µg/mL)	λz (minutes ⁻¹)	t _{1/2} (minutes)	AUC _{0→∞} (µg/mL x min)	CL/F (mL/minute)
Mean	30 ^a	0.61	0.0245	28.3 ^c	37.9	2282
S.D.	(25, 75) ^{b†}	0.34	0.0078		10.1	636
C.V. (%) ^d		55.7	31.8		26.6	27.9

*Five subjects fasted at least eight hours prior to dosing.

^a Median; ^b Range; ^c Harmonic mean

^d C.V. (%): Coefficient of variation % = (mean / S.D.) x 100%

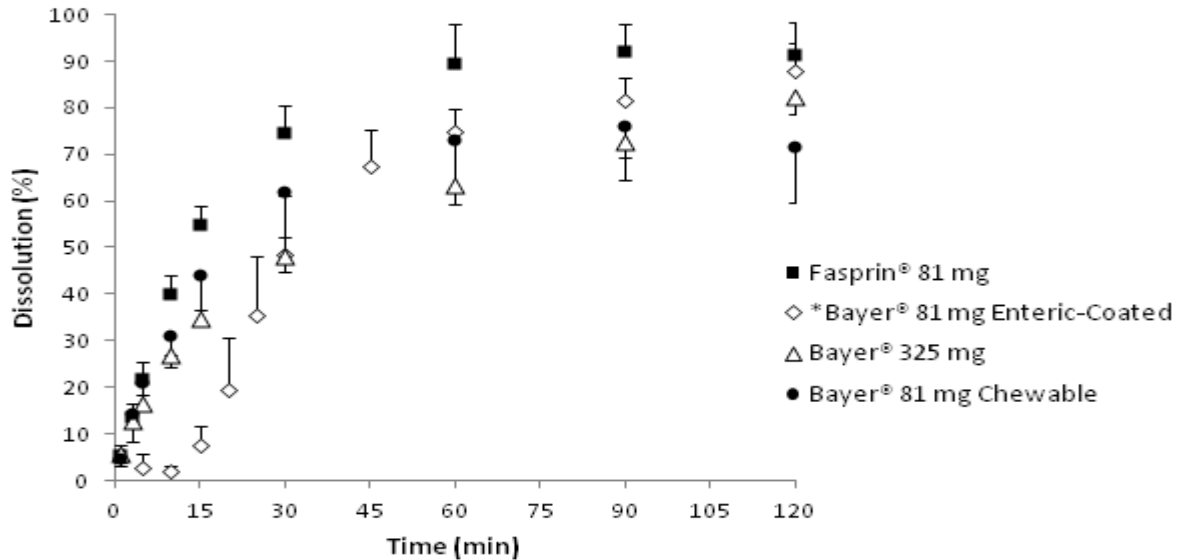


Fig. 1-*In vitro* dissolution profiles of ASA from the different ASA-containing products

*Data for Bayer® 81 mg enteric-coated tablets represent those collected after the switch in the dissolution medium as per the methods section.

Bars denote S.D.

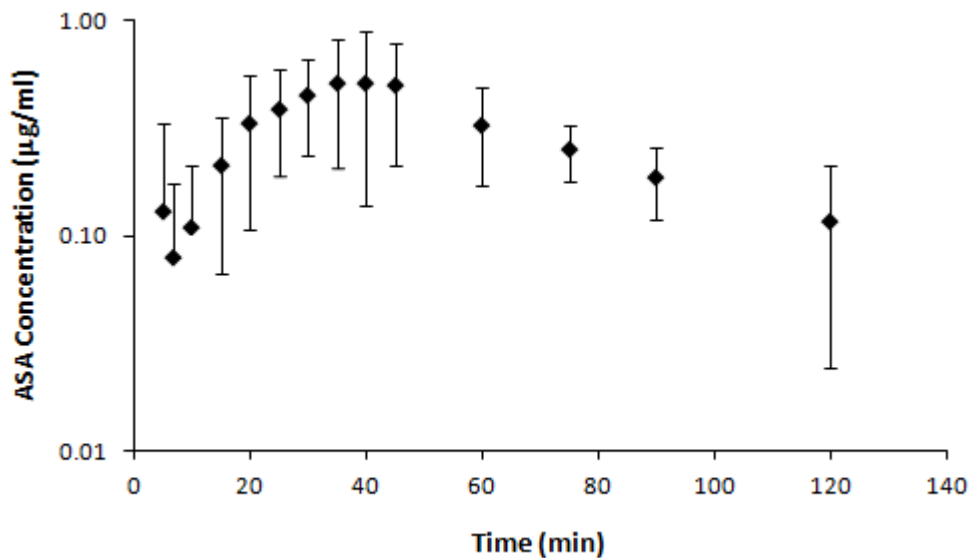


Fig. 2-Plasma concentration vs. time profile of ASA upon single oral dose of the ODA product (Fasprin®), (n = 9)