Ibuprofen Extrudate, a Novel, Rapidly Dissolving Ibuprofen Formulation: Relative Bioavailability Compared to Ibuprofen Lysinate and Regular Ibuprofen, and Food Effect on All Formulations

Matthias Klueglich, MD, Arne Ring, PhD, Stefan Scheuerer, PhD, Dirk Trommeshauser, PhD, Chris Schuijt, PhD, Bernd Liepold, PhD, and Gunther Berndl, PhD

Journal of Clinical Pharmacology, 2005;45:1055-1061

Keywords: *Ibuprofen; bioequivalence; bioavailability; rate of absorption; food effect*

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, have been used for decades in the management of a multitude of pain conditions and rheumatic diseases. Their effects include inhibition of prostaglandin synthesis resulting in analgesic, anti-inflammatory, and antipyretic efficacy. Because of a longstanding and favorable safety record as well as proven efficacy in many different populations and indications, the popularity of ibuprofen is ever increasing.[1,2]

The vast majority of indications for pain treatment requires an onset of action as quickly as possible. For an oral administration drug, the time to onset of a desired pharmacological effect depends on many successive steps: dissolution of the formulation, passage to the site of absorption (usually the jejunal parts of the small intestine), permeation through physiological membranes, entry into the portal vein circulation (with potential enteric or hepatic first-pass metabolism), distribution from plasma to the site of action, and interaction with the receptor, which then causes a cascade of events leading to the targeted pharmacological modification. Distribution to other tissues, metabolism, and excretion of the active principle may also affect early availability of the drug at the effector site. For many compounds, the initial rise of the plasma concentration, following oral administration, is critical with regard to time to onset of the desired pharmacological effect.[3]

Ibuprofen shows low solubility in aqueous acidic media but is highly permeable through physiological membranes.[4] Bioavailability is close to 100% because of almost complete absorption, but the onset of absorption strongly depends on dissolution and thus on the administered formulation. Different approaches have been made to improve solubility of the active ingredient, such as transferring the substance to a salt (lysinate) or designing a pharmaceutical dosage form that favors a quick release of ibuprofen in the gastrointestinal tract.[5,6]

In the manufacture of ibuprofen extrudate tablets, a special extrusion technology is applied to provide the

From the Human Pharmacology Centre Ingelheim (Dr Klueglich), the Department of Medical Data Services and Biostatistics (Dr Ring), and the Department of Pharmacokinetics and Drug Metabolism (Dr Scheuerer, Dr Trommeshauser) Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany; the Corporate Department Medicine, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany (Dr Schuijt); the Analytical Development of SOLIQS, the Drug Delivery Business Unit of Abbott GmbH & Co KG, Ludwigshafen am Rhein, Germany (Dr Liepold); and the Pharmaceutical Development of SOLIQS, the Drug Delivery Business Unit of Abbott GmbH & Co KG, Ludwigshafen am Rhein, Germany (Dr Berndl). Submitted for publication January 24, 2005; revised version accepted June 10, 2005. Address for reprints: Matthias Klueglich, Boehringer Ingelheim Pharma GmbH & Co KG, Department of Project Management and R&D, D-88397 Biberach an der Riss, Germany. This article was presented as a poster at the 33rd Annual Meeting of the American College of Clinical Pharmacology, Phoenix, Arizona, in September 2004.
DOI: 10.1177/0091270005279579

active ingredient in a readily soluble form. The extrudate is produced by mixing ibuprofen with polyvidone and further excipients widely used in the manufacture of pharmaceutical products. Upon extrusion, the mixture is heated and plasticized to form a homogeneous mass. The plasticized product strand emerging at the extruder is conveyed to the calender and is shaped into granules. These extrudate granules are milled, mixed with further excipients and compressed on a usual tablet machine, and film coated. In the resulting tablet, the active ingredient ibuprofen is molecularly dispersed in the hydrophilic polymer matrix. Drug release thus becomes dependent on the disintegration time of the formulation and the dissolution of the polymer and is no longer determined by the solubility of ibuprofen itself.[7]

The purpose of this study was to demonstrate bioequivalence between a 400-mg ibuprofen extrudate and lysinate formulation, and to evaluate the relative bioavailability of the extrudate tablet compared to a regular ibuprofen tablet, based on C_{max} and $AUC_{0-\infty}$. The t_{max} and AUC_{trunc} (the area under the curve for the plasma analyte from zero until t_{max}) were determined to describe the early segments of the plasma concentration-time curve. In addition, the study was intended to evaluate the effect of food on the pharmacokinetics of all 3 different ibuprofen formulations. The overall aim of this study was to show that the novel formulation—the ibuprofen extrudate tablet—is rapidly absorbed, while exhibiting the same bioavailability (total exposure to ibuprofen) as the lysinate and regular ibuprofen formulations, both in fasted and fed conditions.

METHODS

The study was conducted at the Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma GmbH & Co KG, Germany, in compliance with the principles of the Good Clinical Practice (GCP), Declaration of Helsinki, October 1996 version. The trial was only initiated after the protocol and the informed consent and subject information forms had been reviewed and had received approval from the Independent Ethics Committee of the local Medical Council in Mainz, Germany, on February 27, 2002. It was planned and conducted according to an open-label, randomized, 12-sequence, 4-period, single-center, single-dose, crossover design in healthy male and female subjects 21 to 50 years old. Prior to the screening examination, all subjects provided written informed consent.

At the screening visit, a medical history was taken, a complete physical examination was performed, vital signs (blood pressure and pulse, at rest) were measured, an electrocardiogram (ECG) was recorded, and a complete laboratory screen (hematology, chemistry, urinalysis) was performed. If a subject was eligible for the study, he/she was randomized to a sequence of 4 out of 6 possible treatments with 400 mg ibuprofen single dose (ibuprofen extrudate, ibuprofen lysinate, and regular ibuprofen, in fed or fasted state), according to a partially balanced incomplete block design.[8] The ibuprofen extrudate tablets used were manufactured using the Meltrex technology (SOLIQS, the Drug Delivery Business Unit of Abbott GmbH & Co KG, Ludwigshafen am Rhein, Germany).

On the fed-state treatment days, subjects received a standardized continental breakfast 30 minutes before drug administration. The meal had to be completely ingested within 25 minutes; it consisted of 25 g jam, 20 g butter, 30 g cheese, 30 g ham, 2 bread rolls (70 g), and 200 mL orange juice. The total energy content was 2728 kJ (21.2 g protein, 29.7 g fat, 69.1 g carbohydrates, and 2.9 g fiber). Subjects were allowed to drink 2 cups of decaffeinated coffee. The treatment (tablet) was administered with 150 mL of nonsparkling water, under the supervision of the investigator and the study nurse.

Ethylenediaminetetraacetic acid (EDTA) blood samples for quantification of drug plasma concentrations were taken from a forearm vein. Five mL of blood were drawn for each of the 4 periods at the following time points: before drug administration, 0:15, 0:30, 0:45, 1:00, 1:15, 1:30, 1:45, 2:00, 2:30, 3:00, 4:00, 5:00, 6:00, 8:00, 10:00, 12:00, and 24:00 hours following drug administration. Blood samples were centrifuged immediately after collection for 10 minutes (at 2100*g*) at 4° to 8°C.

Ibuprofen plasma concentrations were quantified by a specific high-performance liquid chromatography (HPLC) method using ultraviolet detection (injection volume, 25 µL; mobile phase, 1100 g water, 850 g acetonitrile, 20 g KH2PO4, 20 g H3PO4 isocratic mode; flow, 1.0 mL/min; wavelength, 220 nm). The assay was validated from 0.25 µg/mL to 50 µg/mL. Assay precision and accuracy during sample assay for this trial was determined by the analysis of daily quality controls. Precision was within ±2.9% and accuracy was within ±2.7%. As internal standard, 4-tert-butylbenzoic acid (Lot No. 351360/1, purity >98%; Fluka, Buchs, Switzerland) was used.

Bioequivalence, relative bioavailability, and food effect were primarily determined on the basis of the parameters $AUC_{0-\infty}$ and C_{max}. $AUC_{0-\infty}$ was calculated by using the mixed log-linear trapezoidal rule and extrapolation from the last quantifiable concentration to infinity; t_{max} was defined as the time to reach C_{max}; AUC_{trunc} was evaluated as a measure of early exposure.[5]

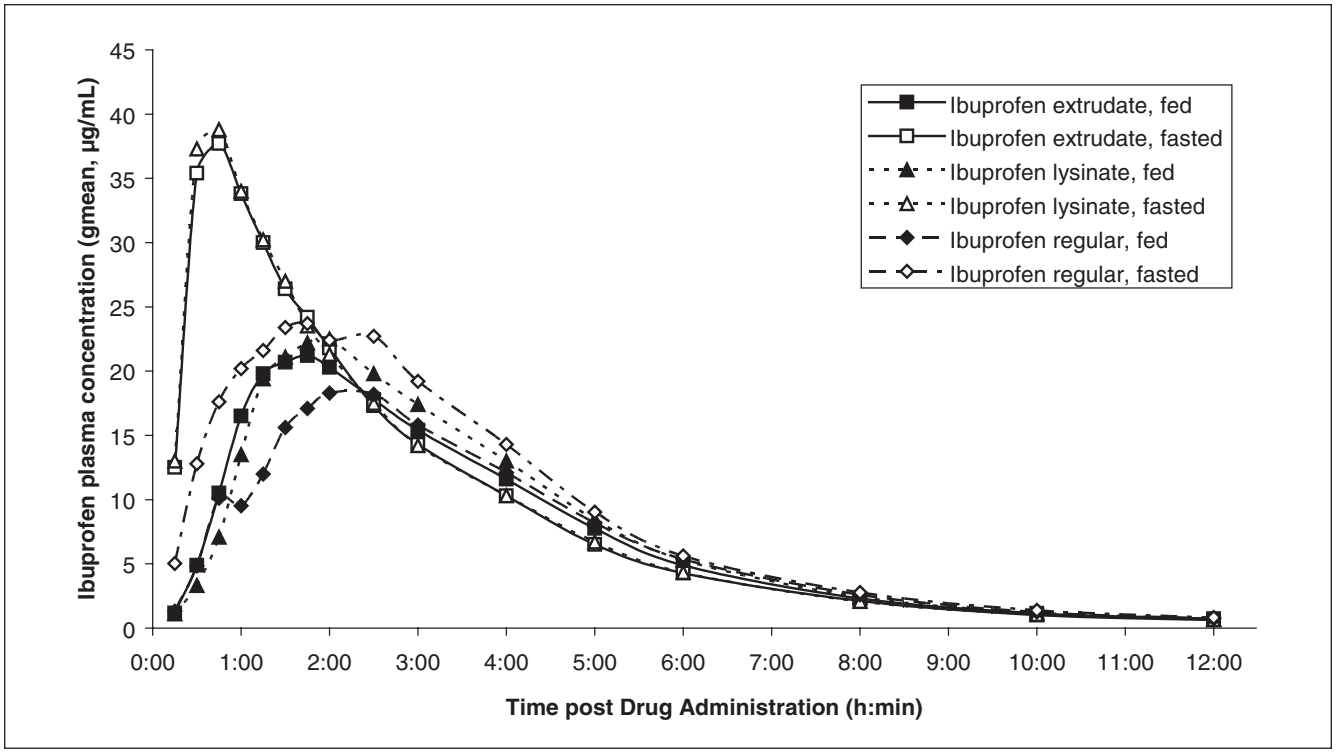

Figure 1. Geometric mean ibuprofen plasma concentrations following single oral administration of a 400-mg ibuprofen extrudate (square), lysinate (triangle), and regular (diamond) tablet under fed (filled) and fasted (open) conditions, respectively.

The statistical model used for the analysis of $AUC_{0-\infty}$ and C_{max} was an analysis of variance model on the logarithmic scale. This model included effects accounting for sequence, subject within sequence, period, and treatment. The subject within sequence effect was treated as random, whereas the other effects were considered as fixed. For tests on subject, period, and treatment effects, the denominator sum of squares was the sum of squares for error.

Confirmatory hypothesis testing was to be performed for the ratio of $AUC_{0-\infty}$ and C_{max} of the ibuprofen extrudate tablet (test) compared to the ibuprofen lysinate tablet (reference), both in a fasted state. It was tested according to the average bioequivalence criterion, whether the 90% confidence interval of these ratios falls completely into the interval 0.8 to 1.25.[9] In addition, the nonparametric 90% confidence intervals of the median differences in t_{max} were determined according to Hauschke et al[10], based on the Committee for Proprietary Medicinal Products (CPMP) requirements for demonstrating bioequivalence.[11] For the respective differences of additional ratios, no hypothesis was planned to be tested in a strict statistical sense; rather, they were to be interpreted in an exploratory manner. The planned sample size of the study was 36 subjects, according to the published and expected variability of ibuprofen tablet formulation.[12]

RESULTS

Thirty-eight subjects were randomized and treated. Thirty-five treated subjects completed the trial as planned per protocol. Three treated subjects discontinued prematurely because of unrelated adverse events. Thirty-seven subjects were included in the statistical evaluation of pharmacokinetic parameters. One subject was omitted from analysis because data were available for one treatment period only. The mean age of the treated subjects was 32.3 years (minimum, 23 years; maximum, 46 years; SD, 5.5 years). All subjects were of Caucasian ethnicity; 20 were male and 18 were female. The mean body mass index was 23.48 (SD, 2.17).

Tolerability of ibuprofen was good with all treatments. No relevant changes in vital signs, ECGs, laboratory results, or physical examinations were noticed. One subject experienced an acute gastritis 4 days after administration of ibuprofen lysinate.

Geometric mean plasma concentrations of ibuprofen, per time point, for the 6 different treatments are presented in Figure 1.

Table I Relative Bioavailability of Ibuprofen Extrudate, Compared to Ibuprofen Lysinate and Regular Ibuprofen, Under Fasted and Fed Conditions (Adjusted Treatment Rations of C_{max} and $AUC_{0-\infty}$ and Adjusted Treatment Differences of t_{max} With Their 90% Confidence Intervals)

	C_{max}			$AUC_{0-\infty}$			t_{max}		
		2-Sided 90% CI, %			2-Sided 90% CI, %			2-Sided 90% CI, h	
Treatment, Test/Reference	Adjusted gMean Ratio, %	Lower Limit	Upper Limit	Adjusted gMean Ratio, %	Lower Limit	Upper Limit	Adjusted Mean Difference, h	Lower Limit	Upper Limit
Ib-ex (fasted)/Ib-lys (fasted)	96.54[a]	88.61	105.19	98.27[a]	93.39	103.41	0.000	–0.125	0.125
Ib-ex (fasted)/Ib-reg (fasted)	129.13	118.51	140.70	99.43[a]	94.48	104.63	–0.875	–1.500	–0.125
Ib-ex (fed)/Ib-lys (fed)	95.62[a]	87.87	104.04	97.02[a]	92.27	102.02	–0.125	–0.375	0.250
Ib-ex (fed)/Ib-reg (fed)	104.64[a]	95.96	114.12	98.46[a]	93.52	103.67	–0.188	–0.875	0.375
Ib-ex (fed)/Ib-ex (fasted)	66.11	60.62	72.09	81.81	77.71	86.14	0.625	0.500	2.375
Ib-lys (fed)/Ib-lys (fasted)	66.75	61.30	72.68	82.87	78.78	87.17	1.000	0.625	1.375
Ib-reg (fed)/Ib-reg (fasted)	81.58	74.87	88.89	82.62	78.51	86.94	0.063	–1.000	1.000

CI, confidence interval; Ib-ex, ibuprofen extrudate; Ib-lys, ibuprofen lysinate; Ib-reg, ibuprofen regular.

a. Confidence interval of the ratio completely within bioequivalence range of 80% to 125%.

The geometric mean of C_{max}(gCV [gmean and gCV for log-transformed data]) was 26.2 µg/mL (26.0%) and 41.1 µg/mL (21.3%) for ibuprofen extrudate (fed and fasted), 29.6 µg/mL (17.4%) and 41.2 µg/mL (16.0%) for ibuprofen lysinate (fed and fasted), and 26.0 µg/mL (27.6%) and 33.5 µg/mL (17.8%) for ibuprofen regular (fed and fasted). The geometric mean of $AUC_{0-\infty}$(gCV [gmean and gCV for log-transformed data]) was 91.9 µg•h/mL (18.9%) and 111 µg•h/mL (19.1%) for ibuprofen extrudate (fed and fasted), 97.9 µg•h/mL (18.0%) and 112 µg•h/mL (17.8%) for ibuprofen lysinate (fed and fasted), and 92.1 µg•h/mL (17.0%) and 117 µg•h/mL (17.8%) for ibuprofen regular (fed and fasted). The median and range for t_{max} was 1.25 hours (1.00-5.00 hours) and 0.75 hours (0.50-1.50 hours) for ibuprofen extrudate (fed and fasted), 1.50 hours (1.00-3.00 hours) and 0.75 hours (0.50-1.50 hours) for ibuprofen lysinate (fed and fasted), and 1.63 hours (0.75-4.00 hours) and 1.38 hours (0.50-4.00 hours) for ibuprofen regular (fed and fasted).

Confidence intervals for the ratio of C_{max} and $AUC_{0-\infty}$ were completely included in the acceptance range 80% to 125% for the treatments extrudate (fasted) versus lysinate (fasted), and also for the treatments ibuprofen extrudate (fed) versus ibuprofen lysinate (fed) (Table I). Point estimators were 96.54% and 98.27%, and 95.62% and 97.02%, respectively.

The 90% confidence interval of the median t_{max} between ibuprofen extrudate and ibuprofen lysinate was –0.125 hours and 0.125 hours (adjusted mean difference, 0 hours) for the comparison fasted/fasted, and –0.375 hours and 0.250 hours (adjusted mean difference, –0.125 hours) for the comparison fed/fed (Table I).

The results for relative bioavailability (ratio of C_{max} and $AUC_{0-\infty}$) of ibuprofen extrudate, compared to both ibuprofen lysinate and regular ibuprofen under fasted and fed conditions, are shown in Table I.

Comparison of geometric mean AUC_{trunc} values between the ibuprofen extrudate and the ibuprofen lysinate formulations revealed almost no difference under fasted or fed conditions (fasted, 17.0 µg•h/mL vs 17.9 µg•h/mL; fed, 16.3 µg•h/mL vs 14.6 µg•h/mL). Under fasting conditions, early exposure for the extrudate formulation was higher compared to regular ibuprofen (37.9 µg•h/mL vs 19.6 µg•h/mL), whereas this difference was absent if both formulations were given after food (19.2 µg•h/mL vs 13.6 µg•h/mL). Food slowed down ibuprofen absorption for all 3 ibuprofen preparations, which was apparent by the reduction of AUC_{trunc} values (ibuprofen extrudate, 2.89 µg•h/mL vs 17.0 µg•h/mL—ie, 83%; ibuprofen lysinate, 1.79 µg•h/mL vs 17.9 µg•h/mL—ie, 90%; regular ibuprofen, 9.01 µg•h/mL vs 19.6 µg•h/mL—ie, 54%).

Food ingestion delayed C_{max} for approximately 0.50 to 0.75 hours compared to fasted treatment for the ibuprofen extrudate (median t_{max}, 0.75 hours [fasted] vs 1.25 hours [fed]) and the ibuprofen lysinate (median t_{max}, 0.75 hours [fasted] vs 1.50 hours [fed]), respectively. For the regular ibuprofen, the delay on t_{max} for the fed treatment was only about 0.25 hours (median t_{max}, 1.38 hours [fasted] vs 1.63 hours [fed]).

DISCUSSION

Ibuprofen serum concentrations and its analgesic effect have been shown to correlate.[13] Consequently, rapid ibuprofen absorption is a prerequisite for quick onset of action. Because of high membrane permeability,[4] extent of ibuprofen absorption approaches 100% and is independent from the formulation used. Dissolution thus becomes the limiting step for the rate of absorption.

Lysinate formulations have successfully been developed to improve solubility. They demonstrated an increased rate of absorption compared to regular ibuprofen (ie, ibuprofen acid) preparation.[5] Pharmacodynamically, ibuprofen lysinate has been shown to provide quicker relief of pain than has conventional ibuprofen formulations.[14]

The development of an extrudate formulation represents a novel approach to improve solubility of ibuprofen. The extrudate tablet can be regarded as "solid dispersion" of ibuprofen. The active ingredient is molecularly dispersed in a hydrophilic polymer matrix. Thus, ibuprofen is already available in a kind of soluble form and is ready for absorption as soon as the formulation has disintegrated. The release of the active ingredient depends on the disintegration time of the formulation and the dissolution of the polymer but is no longer determined by the (poor) solubility of the active substance itself, as is the case for the regular ibuprofen acid formulations. Although in our study we did not measure the desired pharmacodynamic effect (pain relief or reduction of pain perception), it can be reasonably assumed that quicker availability of ibuprofen in plasma, as shown for ibuprofen lysinate, will also provide quicker analgesic efficacy.[14]

The results of this study demonstrate bioequivalence between ibuprofen lysinate and the novel ibuprofen extrudate on the basis of $AUC_{0-\infty}$, C_{max}, and t_{max}. The pharmacokinetic profile of the test formulation (extrudate tablet) was different from that of regular ibuprofen when given fasted. C_{max} for the extrudate was approximately 20% higher, and t_{max} was almost 1 hour

earlier than for regular ibuprofen, while average total exposure ($AUC_{0-\infty}$) was almost identical. Thus, the extent of absorption was equivalent for the ibuprofen extrudate and regular ibuprofen, but—as would be expected—the formulations were not equivalent with regard to peak and early exposure (rate of absorption).

The analysis of t_{max} shows that the novel ibuprofen extrudate, like ibuprofen lysinate, is available in plasma more rapidly than regular ibuprofen, which is also reflected by a higher AUC_{trunc} for these formulations. The range of t_{max} within treatment groups was moderate to low.

We did not differentiate between the 2 ibuprofen enantiomers (S-ibuprofen and R-ibuprofen) for several reasons. The FDA guidance for bioequivalence studies generally recommends measurement of the racemate, using an achiral assay. The main objective of our study, indeed, was to provide evidence of bioequivalence between the ibuprofen lysinate and extrudate. For ibuprofen, measurement and interpretation of enantiomers is complex because of the in vivo unidirectional conversion of the (inactive) R-ibuprofen to the (active) S-ibuprofen. Because of the (partial) crossover design of the study, each volunteer acted as his/her own reference for the 4 treatments he/she received, and it is thus fair to assume that the chiral inversion was identical at least for these individual crossovers.

A further objective of this trial was to investigate the effect of food on ibuprofen pharmacokinetics. The results indicate that C_{max} for all 3 ibuprofen formulations was consistently lower and appeared later when the dose was administered following a standardized breakfast. These findings are in excellent agreement with published evidence, describing a delayed absorption and lower peak plasma concentrations of ibuprofen caused by food intake.[5] In contrast to fasting conditions, where drug dissolution is the rate-limiting step for drug absorption, gastric emptying becomes obviously more important at fed state. Following food ingestion, gastric emptying time can be prolonged up to 5 hours, compared to fasting conditions, where it usually takes place within 15 to 30 minutes. Thus, not surprisingly, a food effect could be demonstrated for all 3 ibuprofen formulations.

However, not only rate but also extent of ibuprofen absorption was reduced by food for all 3 formulations, as reflected by a decrease of AUC values. Elevation of gastric pH by administration of food might be expected to increase dissolution and absorption of the acidic ibuprofen. However, the main absorption site for ibuprofen is the upper small intestine rather than the stomach. With concomitant food, ibuprofen could be "trapped" into the chyme when passing this region. Earlier investigations indicated that an elevation of the viscosity of the contents in the upper gastrointestinal tract—such as caused by food ingestion—can reduce drug absorption.[15] The presence of a viscous chyme generated by a solid meal might act as a physical barrier and thereby reduce drug access to the absorptive surface of the upper intestinal tract. In addition, food-stimulated intestinal motility will reduce the residence time at the main absorption site.[16] These facts, taken together, might explain the lower extent of ibuprofen absorption at fed state compared to fasted treatments.

CONCLUSION

Bioequivalence between the 400-mg ibuprofen extrudate tablet and the 400-mg ibuprofen lysinate tablet was confirmed at fasted state and was also evident with concomitant food. The rate of absorption at fasted state was considerably faster following administration of the ibuprofen extrudate and the ibuprofen lysinate tablet than for regular ibuprofen. However, the overall extent of absorption was not different, and a food effect could be demonstrated for all 3 formulations.

The authors express special thanks to the project assistants (clinical study team: K Saar, H Wölfel, G Zander; pharmacokinetic evaluation: U Bloching-Knöll, J Rudzitis). This study was financed by Boehringer Ingelheim GmbH.

REFERENCES

1. Moore N. Forty years of ibuprofen use. *Int J Clin Pract Suppl.* 2003;135:28-31.

2. Rainsford KD. Discovery, mechanisms of action and safety of ibuprofen. *Int J Clin Pract Suppl.* 2003;135:3-8.

3. Martinez MN, Amidon GL. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. *J Clin Pharmacol.* 2002;42:620-643.

4. Levis KA, Lane ME, Corrigan OI. Effect of buffer media composition on the solubility and effective permeability coefficient of ibuprofen. *Int J Pharm.* 2003;6:49-59.

5. Geisslinger G, Dietzel K, Bezler H, Nuernberg B, Brune K. Therapeutically relevant differences in the pharmacokinetical and pharmceutical behavior of ibuprofen lysinate as compared to ibuprofen acid. *Int J Clin Pharmacol Ther Toxicol.* 1989;27:324-328.

6. Beaver WT. Review of the analgesic efficacy of ibuprofen. *Int J Clin Pract.* 2003;135:13-17.

7. Breitenbach J, Mägerlein M. Melt-extruded molecular dispersion. In: Ghebre Sellassie I, Martin C. *Pharmaceutical Extrusion Technology.* New York, NY: Marcel Dekker; 2003:245-260.

8. Patterson HD, Lucas HL. Change-over designs. *North Carolina Agricultural Experiment Station Technical Bulletin.* 1962;147:3-53.

9. Food and Drug Administration. *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered*

Drug Products—General Considerations. Rockville, Md: US Department of Health and Human Services; October, 2000. Available at: http://www.fda.gov/cder/guidance/4964dft.pdf.

10. Hauschke D, Steinijans VW, Diletti E. A distribution-free procedure for the statistical analysis of bioequivalence studies. *Int J Clin Pharmacol Ther Toxicol*. 1990;28:72-78.

11. Committee for Proprietary Medicinal Products (CPMP). *Note for Guidance on the Investigation of Bioavailability and Bioequivalence*. London, UK: The European Agency for the Evaluation of Medicinal Products, Evaluation of Medicines for Human Use CPMP/EWP/QWP/1401/98; July 26, 2001. Available at: http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf.

12. Davies NM. Clinical pharmacokinetics of ibuprofen: the first 30 years. *Clin Pharmacokinet*. 1998;34:101-154.

13. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinical analgesic response. *Clin Pharmacol Ther*. 1986;40:1-7.

14. Seibel K, Schaffler K, Reeh P, Reitmeir P. Comparison of two different preparations of ibuprofen with regard to the time course of their analgesic effect: a randomised, placebo-controlled, double-blind cross-over study using laser somatosensory evoked potentials obtained from UV-irritated skin in healthy volunteers. *Arzneimittelforschung*. 2004;54:444-451.

15. Singh BN. Effects of food on clinical pharmacokinetics. *Clin Pharmacokinet*. 1999;37:213-255.

16. Welling PG. Effects of food on drug absorption. *Pharmacol Ther*. 1989;43:425-441.