BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 17, 511–519 (1996)

THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF IBUPROFEN AND FLURBIPROFEN FROM SUSTAINED RELEASE FORMULATIONS

ANISHA PARGAL*, MEDHA G. KELKAR AND P. JAGADEESH NAYAK

Research Division, Boots Pharmaceuticals Ltd., Sion, Bombay 400 022, India

ABSTRACT

The effect of food on the plasma concentration–time profile of sustained release dosage forms of ibuprofen and flurbiprofen has been investigated in healthy Asian Indian volunteers, in two separate studies. In study 1, 20 volunteers were administered a single 200 mg multiple-unit sustained release capsule of flurbiprofen (Froben SR®), after an overnight fast or a heavy vegetarian breakfast. Food produced a statistically significant increase in the mean ($\pm$SE) maximal plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC_{0-48}). C_{max} ($\pm$SE) increased from $9{\cdot}88 \pm 0{\cdot}48\,mg\,L^{-1}$ (fasting) to $11{\cdot}36 \pm 0{\cdot}88\,mg\,L^{-1}$ (postprandial) and AUC_{0-48} ($\pm$SE) increased from $120{\cdot}78 \pm 9{\cdot}64\,mg\,h\,L^{-1}$ (fasting) to $149{\cdot}73 \pm 12{\cdot}24\,mg\,h\,L^{-1}$ (postprandial). The mean ($\pm$SE) time to peak (t_{max}) was also significantly delayed from $3{\cdot}85 \pm 0{\cdot}27$ h to $8{\cdot}70 \pm 0{\cdot}89$ h. In study 2, 18 volunteers were administered a single 800 mg erodible sustained release matrix tablet of ibuprofen (Brufen Retard®), after an overnight fast or along with a heavy vegetarian breakfast. The formulation exhibited multiple peaks ($n \geqslant 2$) on the plasma concentration–time curve. Although food did not affect the bioavailability of this formulation, there was a statistically significant increase in the mean ($\pm$SE) concentration of the first peak (C_{peak1}) from $14{\cdot}21 \pm 1{\cdot}38\,mg\,L^{-1}$ (fasting) to $20{\cdot}14 \pm 1{\cdot}38\,mg\,L^{-1}$ (with food). The time at which C_{peak1} was reached was not influenced by the intake of food.

Results indicate that while qualitative changes in the plasma concentration versus time curves are primarily influenced by the nature of the formulation and the type of meal, bioavailability is influenced by the absorption characteristics of the drug as well. Thus, despite a significant increase in peak plasma concentrations of both drugs with a meal, the bioavailability of flurbiprofen alone was enhanced.

KEY WORDS: ibuprofen; flurbiprofen; sustained release; food effects; ethnic variation

INTRODUCTION

Flurbiprofen and ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs), with demonstrated effectiveness in the treatment of rheumatoid arthritis and osteoarthritis. They are currently marketed as sustained release

Address for correspondence: Dr. Anisha Pargal, B. V. Patel Pharmaceutical Education and Research Development Centre, Thaltej, Ahmedabad 380 054, Gujarat, India.

CCC 0142–2782/96/060511–09

Received 23 February 1995
Accepted 8 November 1995

dosage forms, for once-a-day dosing. The flurbiprofen sustained release formulation (Froben SR®, Boots Pharmaceuticals plc., Nottingham, U.K.), is formulated as a multi-unit capsule, based on bead technology,[1] while the ibuprofen sustained release formulation (Brufen Retard®, Boots Pharmaceuticals plc., Nottingham, U.K.), is designed as a single-unit erodible matrix tablet.[2] Both formulations have been evaluated for their sustained release characteristics in healthy Caucasian volunteers and patients.[1,3,4]

In recognition of the complexity of food–drug interactions, especially with respect to novel drug delivery systems for oral administration, regulatory authorities require that the bioavailability of sustained release formulations be evaluated for food effects.[5] This study was therefore designed to evaluate the effect of a heavy vegetarian breakfast on the bioavailability of Froben SR® and Brufen Retard®, in healthy Asian Indian volunteers.

MATERIALS AND METHODS

Subjects

Two separate studies have been reported in this paper. Both the studies were conducted as open, randomized, crossover studies, where a single dose of the specific formulation was administered to 20 (study 1) or 18 (study 2) healthy, male Asian Indian volunteers, after an overnight fast or with a standardized heavy breakfast, separated by a washout period of 1 week.

All the volunteers conformed to the exclusion criteria, provided written informed consent, and underwent a physical examination, urinalysis, and blood chemistry determinations. The subjects were instructed to refrain from all medications from 7 d prior to the study, and until the study was completed. Alcohol was not permitted from 24 h prior to, and during each treatment period.

The protocol was approved by the hospital's ethics committee.

Drugs and reagents

The sustained release formulations of Brufen Retard® and Froben SR®, and the internal standards (4-*n*-pentylphenyl)acetic acid and 2-(2′-chloro-4-biphenyl)propionic acid were provided by Boots Pharmaceuticals plc., Nottingham, U.K. Acetonitrile and methanol chromatographic grade were obtained from Merck (Bombay, India) and Glaxo Laboratories (Bombay, India), respectively. All other reagents were analytical grade.

Dose administration

Study 1. 20 volunteers were administered a single 200 mg sustained release capsule of flurbiprofen (Froben SR®, Boots Pharmaceuticals plc., Nottingham, U.K.). A cup of coffee or tea was permitted in the morning,

prior to dose administration. For treatments without food, the dose was administered with 4 oz of water. A standard breakfast (total caloric value, 3194 kJ) consisting of two slices of buttered bread, two *medhu vadas* (lentil-based, fried doughnut-shaped fritters), a banana, and 8 oz of milk was provided 2 h after dose administration. For treatments with food, the dose was administered immediately after the standard breakfast, with 4 oz of milk from the breakfast. Lunch was provided 4 h post-dose.

Study 2. 18 volunteers were administered a single 800 mg sustained release tablet of ibuprofen (Brufen Retard®, Boots Pharmaceuticals plc., Nottingham, U.K.). A cup of coffee or tea was permitted in the morning, prior to dose administration. For treatments without food, breakfast consisting of two slices of buttered bread and a cup of coffee was given 2 h post dose. For treatments with food, the dose was administered two-thirds of the way through a standard breakfast (total caloric value, 3039 kJ) consisting of two slices of buttered bread, two teaspoonsful of jam, two *medhu vadas*, a banana, and a cup of coffee. Two-thirds of this breakfast was demarcated as consisting of two slices of bread, one teaspoonful of jam and two *medhu vadas*. The tablet was taken with some coffee. Lunch was provided 4 h post dose.

Sample collection

Study 1. 5 mL blood samples were collected at 0 h and then at 0·5, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, 24, 30, and 48 h after dose administration. Plasma was separated by centrifugation and stored at −50 °C, until assayed for flurbiprofen.

Study 2. 5 mL blood samples were collected at 0 h and then at 0·5, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 30, and 48 h post-dose. Plasma was separated by centrifugation and stored at −50 °C, until assayed for ibuprofen.

In both the studies, the 0–8 h blood samples were drawn via an indwelling cannula, which was kept patent with saline and heparin (1000 units/mL solution). All the later samples were collected by direct venipuncture.

HPLC determination of flurbiprofen in plasma

Flurbiprofen plasma concentrations were determined by a high-performance liquid chromatographic method. 0·5 mL plasma samples were spiked with a methanolic solution of internal standard, containing 10 μg of 2-(2′-chloro-4-biphenyl)propionic acid in 50 μL. Samples were then acidified with 0·5 mL of 1 N HCl and extracted with 10 mL of dichloromethane. The organic layer was transferred to conical centrifuge tubes and evaporated until dry, at 30 °C, under a gentle nitrogen stream. The residue was redissolved in 0·5 mL of mobile phase and a 50 μL aliquot was injected onto a 10 μm particle size, C-18 μ Bondapak column (150 × 3.9 mm).

The mobile phase, consisting of a v/v mixture of 19% acetonitrile, 19% methanol, and 62% of 1% glacial acetic acid (pH 5·8), was pumped at a flow rate of 1·8 mL min^{-1}. The UV absorbance of the effluent was detected at 260 nm. The retention times for flurbiprofen and internal standard were 5·65 and 7·99 min, respectively.

Analysis of plasma controls, spiked with flurbiprofen to yield concentrations of 10 mg L^{-1} and 2 mg L^{-1}, gave mean ($n = 132$) assayed values of 10·28 mg L^{-1} and 2.01 mg L^{-1}, with between-days coefficients of variation of 2·73% and 3·40%, respectively.

The standard curve was linear in the concentration range of 30–0·5 mg L^{-1}. The minimum detection limit was 0·5 mg L^{-1}.

HPLC determination of ibuprofen in plasma

Ibuprofen plasma concentrations were determined by a high-performance liquid chromatographic method. 0·5 mL plasma samples were spiked with a methanolic solution of internal standard, containing 10 μg of (4-*n*-pentylphenyl)acetic acid in 50 μL. Samples were then acidified and extracted, as described for flurbiprofen, prior to injecting them onto a reverse phase, 4 μm particle size, C_{18} Novapak column (150 × 3.6 mm).

The mobile phase, consisting of a mixture of 25% acetonitrile and 75% 0·01 M dipotassium hydrogen orthophosphate (pH 6·05), was pumped at a flow rate of 1·4 mL min^{-1}. The UV absorbance of the effluent was detected at 225 mm. The retention times for ibuprofen and internal standard were 5·2 and 7·9 min, respectively.

Analysis of plasma controls, spiked with ibuprofen to yield concentrations of 20 mg L^{-1} and 2 mg L^{-1}, gave mean assayed values of 20·59 mg L^{-1} ($n = 130$) and 2·08 mg L^{-1} ($n = 132$), with between-days coefficients of variation of 3·38% and 5·22%, respectively. The assay was linear in the concentration range of 40–0·5 mg L^{-1}. The minimum detection limit was 0·5 mg L^{-1}.

Pharmacokinetic analysis and statistics

Maximal plasma concentration (C_{max}) and time to reach the maximal concentration (t_{max}) were directly determined from the plasma concentration versus time curves. The area under the curve from 0 to 48 h (AUC_{0-48}) was calculated by the trapezoidal rule. The Student paired *t*-test was used to statistically assess the effect of food on the formulation.

RESULTS

Study 1

The mean plasma concentration versus time curves for flurbiprofen, in the presence and absence of food, are illustrated in Figure 1, and individual

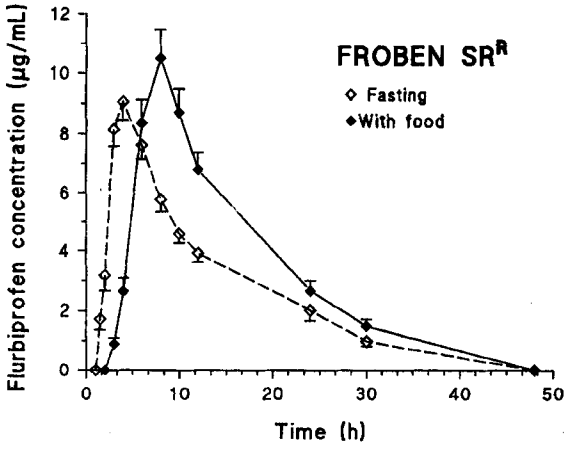

Figure 1. Mean (±SE) plasma flurbiprofen concentration versus time curves for Froben SR®, administered to 20 healthy volunteers, fasting and with food

pharmacokinetic parameters for the two treatments are detailed in Table 1. Food produced a significant increase in the extent of absorption as evinced by a statistically significant increase ($p<0{\cdot}001$) in $AUC_{0\text{-}48}$ from 120·78 mg h L^{-1} (fasting) to 149·73 mg h L^{-1} (with food), as well as a statistically significant increase ($p<0{\cdot}05$) in C_{max} from 9·88 mg L^{-1} (fasting) to 11·36 mg L^{-1} (with food). Absorption was delayed with a statistically significant increase ($p<0{\cdot}001$) in t_{max} from 3·85 h to 8·70 h.

Study 2

The mean plasma concentration versus time curves for ibuprofen, in the presence and absence of food, are illustrated in Figure 2, and the individual pharmacokinetic parameters are detailed in Table 2. The formulation exhibited multiple peaks ($n\geqslant 2$) on the plasma concentration versus time curve. The mean peak plasma concentrations under fasting conditions were 14·21 mg L^{-1} (C_{peak1}) and 15·14 mg L^{-1} (C_{peak2}), which increased to 20·14 mg L^{-1} (C_{peak1}) and 17·76 mg L^{-1} (C_{peak2}) after food administration. The corresponding times

Table 1. Pharmacokinetic parameters of flurbiprofen, after administration of Froben SR®, fasting and with food. Data are expressed as the mean of 20 volunteers ± SE

Pharmacokinetic parameter	Fasting	With food	*p* value
C_{max} (mg L^{-1})	9·88 ± 0·48	11·36 ± 0·88*	<0·05
t_{max} (h)	3·85 ± 0·27	8·70 ± 0·89***	<0·001
$AUC_{0\text{-}48}$ (mg h L^{-1})	120·78 ± 9·64	149·73 ± 12·24***	<0·001

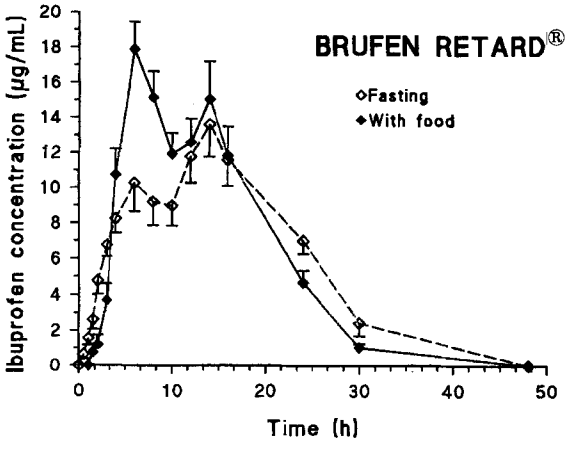

Figure 2. Mean (±SE) plasma ibuprofen concentration versus time curves for Brufen Retard®, administered to 18 healthy volunteers, fasting and with food

of occurrence of the peaks (t_{peak}) were 5·95 h (t_{peak1}) and 17·38 h (t_{peak2}) under fasting conditions, and 6·00 h (t_{peak1}) and 15·29 h (t_{peak2}) with food. A statistically significant effect of food ($p < 0{\cdot}02$) on an increase in the C_{peak1} value was detected. The AUC_{0-48} values did not demonstrate a statistically significant effect of food. The C_{max} value was slightly but not significantly increased from 18·07 mg L^{-1} to 20·93 mg L^{-1}.

DISCUSSION

The effect of food on the bioavailability of sustained release dosage forms is a complex function of the nature of the drug, sites of drug absorption, dosage form design, size and content of the meal, time at which the meal is administered with respect to medication, and concomitant changes in the drug release rate, gastric emptying rate, and gastrointestinal transit times.[6,7]

Multiparticulate sustained release preparations, when taken before a meal, result in rapid initial exponential gastric emptying, which may cause an early high peak blood level of the drug. However, when administered with food, the particles exhibit an approximately linear pattern of gastric emptying, and become intimately mixed with the solid components of the meal. Further, the meal size modulates the rate of entry of particles into the duodenum.[8] Pellet systems, when taken with or after a light meal (1000–2000 kJ), exhibit a short lag phase, before commencement of a linear emptying pattern.[9] The administration of an encapsulated pellet system, after a very heavy breakfast (5000 kJ), has been shown to markedly enhance gastric residence.[10] In our work it would therefore appear that Froben SR® exhibits the characteristics of a

Table 2. Pharmacokinetic parameters of ibuprofen, after administration of Brufen Retard®, fasting and with food. Data are expressed as the mean of 18 volunteers ± SE

Pharmacokinetic parameter	Fasting	With food
C_{max} ($mg\,L^{-1}$)	18·07 ± 1·34	20·93 ± 1·47
C_{peak1} ($mg\,L^{-1}$)	14·21 ± 1·38	20·14 ± 1·38**
C_{peak2} ($mg\,L^{-1}$)	15·14 ± 1·95	17·76 ± 2·18
t_{max} (h)	9·28 ± 1·18	8·67 ± 1·01
t_{peak1} (h)	5·95 ± 1·00	6·00 ± 0·32
t_{peak2} (h)	17·38 ± 1·31	15·29 ± 1·06
AUC_{0-48} ($mg\,h\,L^{-1}$)	268·79 ± 21·11	271·96 ± 22·27

**Significant difference in C_{peak1} values with food, at $p < 0{\cdot}02$.

multiparticulate system. Consequently, administration of food produces a significant delay in absorption (t_{max}), increased intestinal absorption (C_{max}), and a concomitant increase in bioavailability (AUC). Since the absorption of Froben SR® under fasting conditions is incomplete (the mean relative bioavailability (AUC_{0-48}) has been found to be only 72·8% (range, 43·45–105·07%), when compared with the area under the curve from 0 h to infinity ($AUC_{0-\infty} \times 2$) of a 100 mg conventional release tablet (unpublished observation)), the increase in bioavailability with food is probably the result of increased contact time with the absorptive surface of the intestine.

On the other hand, the bioavailability of Brufen Retard® in our experiments is not significantly altered with food, although it exhibits enhanced intestinal absorption, with a significant increase in the concentration of the first peak (C_{peak1}), and a food-induced lag time in absorption. This behaviour can be attributed to the fact that ibuprofen is well absorbed along the entire length of the gastrointestinal tract, and hence its bioavailability is a function of the total transit time, and independent of transit time changes in any one anatomical location.[11] This is also reflected in the mean relative bioavailability (AUC_{0-48}) of Brufen Retard® under fasting conditions, which was found to be approximately 99% (range, 18·64–157·17%), when compared with the area under the curve from 0 h to infinity ($AUC_{0-\infty} \times 4$) of a 200 mg conventional release tablet (unpublished observation).

Also, in our study, Brufen Retard® retains its bimodal release pattern, even after administration with a meal. This is in contrast to studies in British subjects,[3] where a light breakfast (646 kJ) caused a levelling of the two peaks to a plateau, whereas after a heavy breakfast (3327 kJ) only the secondary peak was evident. The differences in the content of the meal, as well as the dietary habits[12] of the study subjects, therefore appear to influence the gastrointestinal physiology sufficiently to alter the release pattern of Brufen Retard®.

CONCLUSION

The work presented here illustrates the contribution of (i) physicochemical characteristics of the drug, (ii) formulation characteristics (matrix and multiparticulate), and (iii) type of meal, to the plasma concentration versus time profiles and bioavailability of ibuprofen and flurbiprofen.

Although no specific statements on the exact mechanism of food effects *in vivo* can be made, the data suggest that (i) food–formulation interactions that increase residence time in the intestine could significantly increase the bioavailability of drugs whose major site of absorption appears to be the small intestine, *viz.* flurbiprofen, whereas, the same may not be true for drugs that are absorbed uniformly along the entire length of the gastrointestinal tract, *viz.* ibuprofen, and (ii) that the drug release pattern from the single-unit erodible matrix used in this work appears to be influenced by the type of meal administered, and, consequently, the magnitude of effect on the bioavailability of a drug in this formulation would be dependent on the absorption characteristics of the drug itself and the meal content.

The clinical consequences of the interactions reported herein would be expected to be minimal, as both ibuprofen and flurbiprofen have a wide therapeutic index. However, the results suggest that the occurrence of therapeutically significant interactions is a distinct possibility in the case of other drugs, studied under similar conditions.

In conclusion, this work re-emphasizes the complexity of food–drug–formulation interactions, and the importance of evaluating them on an individual basis and in different ethnic populations.

ACKNOWLEDGEMENTS

The authors wish to thank the Department of Clinical Pharmacology, K. E. M. Hospital, Bombay, for technical assistance; Research Division, Boots Pharmaceuticals plc., Nottingham, U.K., for technical guidance and for supplying the sustained release formulations and analytical standards; and Dr. C. L. Kaul for his moral and technical support.

REFERENCES

1. R. C. Hamdy, A. Bird, P. Le Gallez, J. Hill and I. D. Hind, A multiple dose pharmacokinetic and tolerance study of once daily 200 mg sustained-release flurbiprofen capsules in young and very elderly patients. *Eur. J. Clin. Pharmacol.*, **39**, 267–270 (1990).
2. K. A. Khan, J. F. Lampard, M. G. Pankhania, J. R. Bratty and C. G. Wilson, Pharmaceutical aspects and *in vivo* performance of Brufen Retard—An ibuprofen SR matrix tablet. *Proceedings of the International Symposium on the Controlled Release of Bioactive Materials*, vol 18, 1991, pp. 351–352.

3. C. G. Wilson, N. Washington, J. L. Greaves, F. Kamali, J. A. Rees, A. K. Sempik and J. F. Lampard, Bimodal release of ibuprofen in a sustained-release formulation: a scintigraphic and pharmacokinetic open study in healthy volunteers under different conditions of food intake. *Int. J. Pharm.*, **50**, 155–161 (1989).
4. M. J. Kendall, R. Jubb, H. A. Bird, P. le Gallez, J. Hill, A. J. Taggart and R. Rau, A pharmacokinetic comparison of ibuprofen sustained-release tablets given to young and elderly patients. *J. Clin. Pharm. Ther.*, **15**, 35–40 (1990).
5. J. P. Skelly, G. L. Amidon, W. H. Barr, L. Z. Benet, J. E. Carter, J. R. Robinson, V. P. Shah and A. Yacobi, *In vitro* and *in vivo* testing and correlation for oral controlled/modified-release dosage forms. *Pharm. Res.*, **7**, 975–982 (1990).
6. P. G. Welling, Effects of food on drug absorption. *Pharmacol. Ther.*, **43**, 425–441 (1989).
7. I. R. Wilding, A. J. Coupe and S. S. Davis, The role of γ-scintigraphy in oral drug delivery. *Adv. Drug Deliv. Rev.*, **7**, 87–117 (1991).
8. S. O'Reilly, C. G. Wilson and J. G. Hardy, The influence of food on the gastric emptying of multiparticulate dosage forms. *Int. J. Pharm.*, **34**, 213–216 (1987).
9. S. S. Davis, R. Khosla, C. G. Wilson and N. Washington, The gastrointestinal transit of a controlled release pellet formulation of tiaprofenic acid. *Int. J. Pharm.*, **35**, 253–258 (1987).
10. M. Marvola, A. Kannikoski, H. Aito and S. Nykanen, The effect of food on the gastrointestinal transit and drug absorption of a multiparticular sustained release verapamil formulation. *Int. J. Pharm.*, **53**, 145–155 (1989).
11. A. F. Parr, R. M. Beihn, R. M. Franz, G. J. Szpunar and M. Jay, Correlation of ibuprofen bioavailability with gastrointestinal transit by scintigraphic monitoring of ^{171}Er-labelled sustained-release tablets. *Pharm. Res.*, **4**, 486–489 (1987).
12. J. M. C. Price, S. S. Davis and I. R. Wilding, The effect of fibre on gastrointestinal transit times in vegetarians and omnivores. *Int. J. Pharm.*, **76**, 123–131 (1991).