Pharmaceutical Research, Vol. 7, No. 10, 1990

Report

Application of Radiotelemetric Technique in Evaluating Diclofenac Sodium Absorption After Oral Administration of Various Dosage Forms in Healthy Volunteers

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Received November 13, 1989; accepted April 3, 1990

A radiotelemetric technique with the Heidelberg capsule (HC) was used to improve the quality of data generated in a bioavailability study involving an enteric-coated (EC) formulation. Further, changes in plasma levels of the drug from other dosage forms were related to changes in the pH environment as determined by the HC. Eight healthy male subjects received the following treatments, 15 min after a light breakfast, according to a randomized, four-way crossover design: (A) HC and 75 mg of a diclofenac sodium aqueous buffered solution; (B) HC and one 75-mg Voltaren EC tablet; (C) HC and one 100-mg Voltaren slow-release (SR) tablet; and (D) HC alone. Each treatment was separated by a 1-week washout period. Two additional subjects subsequently received Treatment B only. Multiple peaks were observed in the drug plasma level–time profiles for the buffered aqueous solution which, in all cases, occurred before gastric emptying of the HC. The multiple peaks were not observed for the Voltaren SR tablet, but a variable absorption lag time occurred which coincided with the gastric residence time of the SR tablet. For the EC tablet the variability of individual plasma level–time profiles was drastically reduced when the time after dosing was adjusted to coincide with gastric emptying of the HC. Finally, the lag time between gastric emptying of the EC tablet and the onset of drug absorption was consistently at 1 hr for all subjects. This lag time was longer than the *in vitro* disintegration or dissolution times measured under USP conditions.

KEY WORDS: radiotelemetric technique; diclofenac sodium; absorption; enteric-coated tablet; slow-release tablet; buffered aqueous solution; multiple peak behavior.

INTRODUCTION

Diclofenac sodium (Voltaren) is a nonsteroidal antiinflammatory drug used for the treatment of degenerative joint diseases and other arthritic conditions. Absorption of the drug after oral dosing is extremely rapid, with peak concentrations being reached within 5–10 min of administering a buffered aqueous solution (1). The drug is also rapidly cleared from plasma, with levels declining to roughly 10% of the peak value within 3 hr (2). When the drug is given as an unbuffered aqueous solution, rapid absorption and elimination also occur, but multiple peaks are frequently observed in the resulting plasma profiles (1,3).

The onset of absorption after administration of an enteric-coated (EC) tablet is dependent on gastric emptying, which is highly variable both within and between individuals (4,5). However, once absorption starts, the appearance of drug in the circulation is rapid reaching peak levels within 0.5 hr. These characteristics require frequent blood sampling over an extended time period to define accurately the plasma profile for the EC tablet. When using this tablet as the reference standard in diclofenac sodium bioavailability studies, a reliable method for detecting gastric emptying would permit the blood sampling schedule to be adjusted to the onset of drug absorption and, thus, obtain more accurate estimates for the relevant pharmacokinetic parameters.

When the drug is administered as a wax-matrix slow-release (SR) tablet, multiple peak behavior is often observed in the resulting plasma profiles (6). This behavior may reflect changes in the performance of the dosage form with changes in the pH of its environment within the gastrointestinal (GI) tract.

Radiotelemetric technique with a Heidelberg capsule (HC) has been employed to detect gastric emptying and the onset of drug absorption from EC formulations (7–11). This approach could also be used to establish whether the multiple-peak behavior observed with the SR tablet is related to changes of the intraluminal pH in different segments of the GI tract.

This study was designed to evaluate the HC technique in optimizing the blood sampling schedule for bioavailability studies involving an EC tablet and to relate changes in plasma concentrations of the drug with changes in the pH environment of the dosage form in the gut.

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0724-8741/90/1000-1026$06.00/0

METHODOLOGY

Evaluation of Heidelberg Capsule Performance

The accuracy of the HC radiotelemetric device (Electro-Medical Devices, Inc., Norcross, GA) was evaluated by comparing the pH values obtained from the system with those obtained from a calibrated pH meter. The HC was activated in 0.9% normal saline solution and calibrated with pH 1 and pH 7 standard buffer solutions as recommended by the manufacturer. Simultaneous pH readings were made in USP simulated gastric fluid (pH 1.2) for 2 hr, followed by USP intestinal fluid (pH 7.2) for 22 hr, using both the HC and a calibrated pH meter.

Clinical Study Procedures

Eight male subjects were initially enrolled into this randomized, open-label, four-way crossover study. Two additional subjects were enrolled at a later time to refine the observations for EC treatment only. After giving written informed consent, the subjects who met the inclusion criteria were confirmed to be in good health by physical examination, medical history, and clinical laboratory tests. Subjects with clinically significant concurrent illnesses, a history of gastrointestinal surgery or disease, dyspepsia or epigastric pain, or hypersensitivity to NSAIDs were excluded. No alcohol was allowed for 24 hr and no concomitant drug treatment was allowed for 7 days prior to, or during, the study. Fecal guaiac (Hemoccult) tests were performed on entry into the study and at 24 hr after each treatment. The physical examination was repeated at the conclusion of the study.

Each of the original eight subjects were randomly assigned to receive the following treatments, separated by a 1-week washout period.

Treatment A: HC + 75 mg of diclofenac sodium powder dissolved in 100 ml, pH 7.4, 0.05 *M* phosphate-buffered aqueous solution (BAS).

Treatment B: HC + one 75-mg EC tablet.

Treatment C: HC + one 100-mg SR tablet.

Treatment D: HC alone.

Prior to initiating the study, a 0.4-mm hole was drilled through the center of the EC and SR tablets. The weight loss due to drilling was less than 0.4%, and the associated loss of active drug was not significant. Surgical thread was then looped through this hole and secured in place using a small amount of acrylic glue on both faces of the tablet. The reduction in surface area of the tablet available for dissolution was also not significant. No change in the *in vitro* dissolution behavior under USP conditions for these, as compared with untreated EC and SR tablets, was observed, indicating that the threading procedure did not affect the integrity of the coating or the dissolution performance of either tablet.

Subjects fasted for at least 12 hr overnight before each treatment day. A light snack (one slice of toast, one pat of butter, and 50 ml of orange juice) was given 15 min before administering the assigned treatment. The HC was then activated and attached, through a small hole at the top of the device, to either the EC or the SR tablet by means of the surgical thread. The HC and tablet combinations in Treatments B and C, or the HC alone in Treatment D, were administered with 100 ml of water. In the case of Treatment A, the HC was taken concomitantly with the drug solution. Output from the HC was monitored continuously until after the last blood sample was taken on the treatment day.

On each occasion when the drug was administered, 10-ml venous blood samples were drawn into heparinized tubes (Venoject) immediately before dosing (predose), and at the following times for the respective treatments.

Treatment A: 5, 10, 20, 30, 45, and 60 min and 1.5, 2, 3, 4, 5, 6, and 8 hr after administering the solution.

Treatment B: hourly after dosing with the EC tablet and prior to gastric emptying. At the first sign of gastric emptying (a change of at least 3 pH units in the output of the HC) samples were drawn at 5, 10, 20, 30, 45, and 60 min and at 1.5, 2, 3, 4, 5, 6, and 8 hr thereafter. If the subject failed to empty the EC tablet/HC combination within 5 hr, blood collection was terminated and the treatment repeated on a second occasion.

Treatment C: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hr after administering the SR tablet.

Heparinized blood samples were centrifuged, and the plasma was separated and frozen immediately. Samples were kept frozen until they were analyzed.

A small snack consisting of a nonalcoholic drink and a coffee cake was permitted at 1 hr after gastric emptying. A light lunch consisting of small sandwiches, a choice of a nonalcoholic beverage, fruit, or a single portion of ice cream was served at 5 hr after dosing, regardless of whether or not gastric emptying of the dosage form had occurred by this time. Dinner was served 10 hr after dosing. Subjects were either sitting or ambulatory during the main study days and were not permitted to sleep in a supine position for the first 14 hr after dosing.

Analytical Procedure

The concentration of diclofenac sodium in plasma was determined using an established HPLC technique (12). The drug concentrations in the study samples were calculated from daily calibration curves. The variability in the calibration curve values were within the expected range (2.6 to 11.2% CV values over a 10- to 800-ng/ml drug concentration range). Quality-control plasma samples, spiked with known amounts of drug, were prepared at the outset of the analysis and were assayed periodically throughout the study. The mean (SD) concentrations estimated for the 100- and 400-ng/ml samples were 100.3 (5.1) and 397.3 (22.0) ng/ml, respectively. The corresponding CV values were less than 5.5% for both concentrations. Some study samples were also reanalyzed on a later occasion. The differences between the original and repeat estimates were generally less than 10%. These results demonstrated good control and reproducibility of the assay.

Pharmacokinetic Calculations

Standard pharmacokinetic parameters were calculated from the plasma concentration–time data. C_{max} was the high-

est observed concentration and T_{max} was the time at which C_{max} occurred. T_{lag}, the absorption lag time, was the last time point at which a nondetectable plasma concentration was observed before the onset of absorption. Adj T_{max}, the adjusted time to peak, was taken as the difference between T_{max} and T_{lag}. AUC-inf was calculated by the linear trapezoidal rule, plus any residual area (usually small), which was calculated as the concentration at the last measured time point divided by the terminal rate constant. The terminal rate constant was determined by linear regression analysis of the log-linear terminal phase of the plasma concentration–time profile. At least three points were used in the determination, and the correlation coefficient values had to be greater than 0.95 for the estimate to be accepted.

RESULTS

The initial eight subjects were aged 23 to 45 (mean, 25) years. Their weights ranged from 66 to 85 (mean, 79) kg, and their heights ranged from 173 to 186 (mean, 180) cm. The two additional subjects (9 and 10) were aged 30 and 34 years, respectively; their weights were 80 and 90 kg and both had heights of 178 cm.

In Vitro Validation of the Heidelberg Capsule

The pH values measured by the HC agreed well with the calibrated pH meter over 24 hr. The HC tended to slightly underestimate the pH value, but the differences never exceeded 0.5 unit. These results are consistent with the manufacturer's specification (i.e., accuracy within ±0.5 pH units) and indicates that the HC is capable of providing reliable pH values for 24 hr after activation. This finding is also consistent with other published information (8,13).

Clinical Observations

The drug and HC were well tolerated by all subjects. Transient abdominal pain was experienced by two subjects (007 and 008) during Study Period 4 (both Treatment B) which lasted for about 0.5 hr but quickly resolved within 1 hr of receiving food. No other adverse effects were reported by any of the 10 subjects. Fecal guaiac tests performed on entry, and at 24 hr after each treatment, were negative. No clinically significant findings were reported for the terminal physical examinations.

Gastric Residence Times

Gastric residence times (GRT) for each treatment, estimated from the HC data, are presented in Table I.

Mean intrasubject GRT, 15 min after a light snack, ranged from 1.3 to 2.8 hr for the original eight subjects. Intersubject GRT values averaged 2.0, 1.9, 2.0, and 1.7 hr, respectively, after administering the HC with BAS (Treatment A), HC with EC (Treatment B), HC with SR (Treatment C), and HC alone (Treatment D). The lack of any differences between treatments indicates that diclofenac did not affect gastric emptying of the HC. The overall mean (SD) GRT for all eight subjects was 1.9 (0.8) hr. GRT values in this study are consistent with the data observed after a light breakfast in a previous study (9).

Plasma Concentration–Time and pH–Time Data

Representative plasma concentration–time, and pH–time, profiles are shown in Figs. 1–3.

Treatment A. There was no delay in the appearance of drug in the circulation following administration of the BAS. In general, plasma drug levels increased rapidly, achieved an early peak, and then declined rapidly (Fig. 1). Secondary peaks, shoulders, or inflections were observed in all profiles for the BAS treatment. Four of eight subjects (Subjects 002, 005, 006, and 008) exhibited multiple-peak behavior within the first few hours after dosing. This occurred before gastric emptying of the HC in all cases (for example, see Fig. 1, Subject 002, a representative subject).

Table I. Summary of Diclofenac Sodium Pharmacokinetic Parameters After Oral Administration of Various Formulations

	Mean (SD)			
Parameter	Treatment A (BAS)	Treatment B (EC)	Treatment C (SR)	Treatment D (HC)
Gastric residence time (GRT), hr	2.00 (0.45)	1.89 (1.16)	2.00 (0.89)	1.72 (0.74)
Lag time (T_{lag}), hr	0.00 (0.00)	[1.00 (0.00)][a]	1.06 (0.86)	—
Median	0.00	[1.00]	2.00	
Range	—	[—]	0.00–2.00	
Peak time (T_{max}), hr	0.43 (0.65)	[1.83 (0.26)]	2.69 (1.16)	—
Median	0.17	[2.00]	3.00	
Range	0.08–2.00	[1.50–2.00]	0.50–4.00	
Adjusted peak time (Adj T_{max}), hr	0.43 (0.65)	[0.83 (0.26)]	1.63 (1.22)	—
Median	0.17	[1.00]	1.00	
Range	0.08–2.00	[0.50–1.00]	0.50–4.00	
Peak concentration (C_{max}), ng/ml	1175.8 (835.0)	2074.1 (1412.1)	694.2[b] (247.38)	—
AUC-inf, ng·hr/ml	1906.9 (508.1)	2362.9 (867.8)	2163.5[b] (494.9)	—
Half-life ($T_{1/2}$), hr	1.52 (0.37)	1.56 (0.37)	2.53 (1.87)	—

[a] [—] Time scale adjusted to the commencement of GRT as time zero.
[b] Normalized to 75-mg dose.

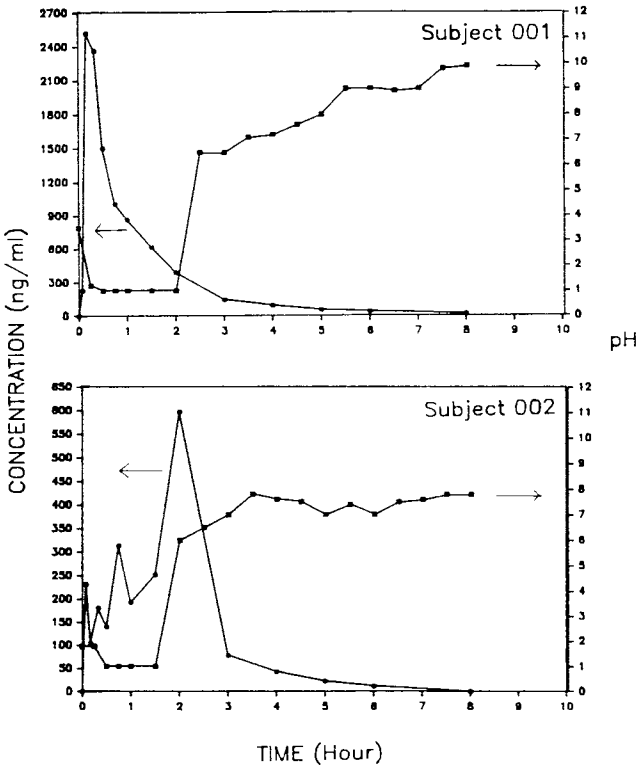

Fig. 1. Representative plasma concentration–time and pH–time profiles after administering the HC with BAS (Treatment A). Upper panel: Subject 001, the only subject who exhibited a uniform smooth plasma profile in this treatment. Lower panel: Subject 002, a representative subject who exhibited a nonuniform, irregular plasma profile.

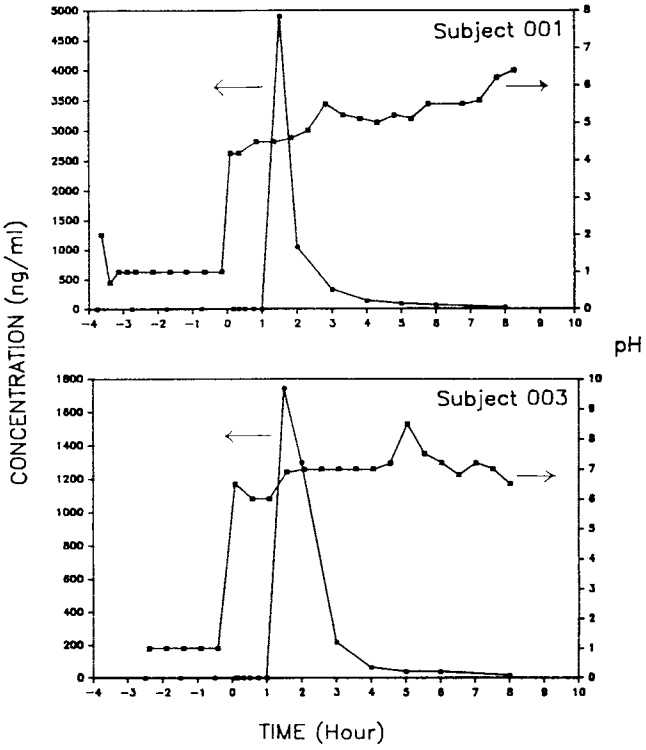

Fig. 2. Representative plasma concentration–time and pH–time profiles after administering the HC with EC (Treatment B). Time scale adjusted to the commencement of GRT as time zero. Upper panel: Subject 001. Lower panel: Subject 003.

Treatment B. As expected, all subjects exhibited single-peak profiles with highly variable lag times after dosing with the EC tablet. However, once absorption was initiated, the increase in plasma levels was extremely rapid and peak levels were quickly achieved. The decline from peak was equally rapid and levels were low or undetectable by 8 hr after the start of absorption.

When the EC tablet profiles were adjusted to coincide with gastric emptying of the HC, the variability disappeared and the onset of absorption was extremely consistent, at 1 hr after emptying of the EC tablet/HC combination (Fig. 2). This result was not anticipated since *in vitro* disintegration and dissolution of the EC tablet occur within 5 to 10 min and 30 min, respectively. Because of the unexpected delay between gastric emptying and the onset of drug absorption, two additional subjects were added to the EC phase of the study. In these individuals, the plasma sampling schedule was adjusted by an additional hour after gastric emptying to characterize better the plasma concentration–time profile. The results obtained were qualitatively and quantitatively similar to those obtained in the initial group. The absorption lag times were again estimated to be the GRT plus 1 hr.

Treatment C. A variable onset of absorption (0–2 hr) was observed for the SR tablet, followed by a rapid increase in levels to achieve a lower peak level than obtained with the other treatments. The decline from the peak was less rapid than for the EC tablet or BAS treatments, and measurable levels were maintained for a longer period after dosing. Only one of eight individuals (Subject 002, Fig. 3) exhibited multiple-peak behavior after administering the SR tablet. Interestingly, this subject had an extremely short GRT (0.5 hr), with the major plasma peak occurring at 0.5 hr and the secondary peak occurring at 8 hr after dosing. These observations are at variance with previous findings where no lag time was detected after administering the SR tablet under fasting conditions, and multiple peaks were frequently observed. Further, there was no delay in the onset of absorption following gastric emptying of the SR tablet in all cases (for example, see Subject 004, Fig. 3).

Attachment of EC and SR to the Heidelberg Capsule

All plasma levels for the EC and SR treatments were nondetectable before gastric emptying of the HC-tablet combinations (Figs. 2 and 3). This result confirms that drilling a hole in the EC and SR tablets, and subsequently sealing the hole with glue, did not cause premature tablet disintegration and drug release in the stomach. It is also consistent with the *in vitro* data which showed that tablet performance was unaffected by the procedure of attaching the dosage forms to the HC.

Bioavailability Assessment

The pharmacokinetic parameters estimated from the data for the original eight subjects are summarized in Table I. The AUC and C_{max} values for the SR were normalized to the 75-mg dose for the purpose of comparison with the other

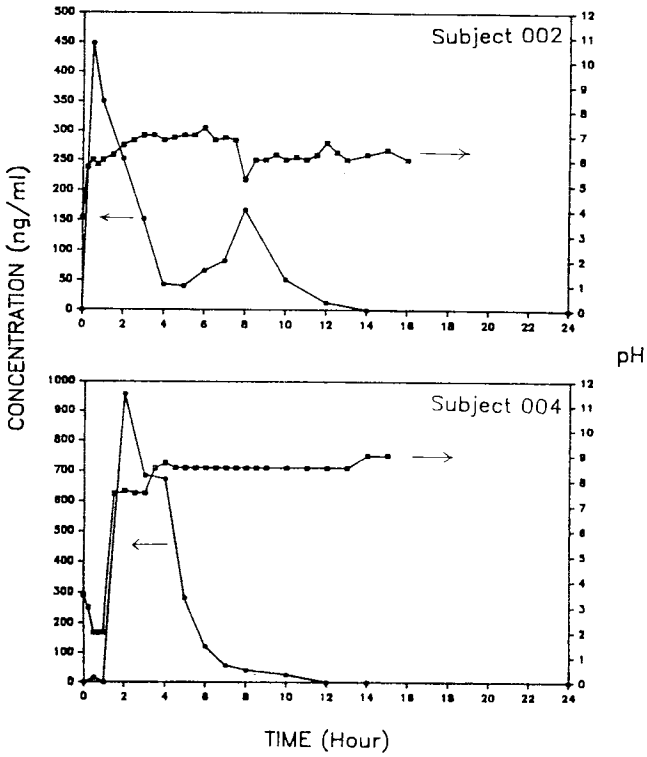

Fig. 3. Representative plasma concentration–time and pH–time profiles after administering the HC with SR (Treatment C). Upper panel: Subject 002, the only subject who exhibited multiple peaks in this treatment. Lower panel: Subject 004, a representative subject who did not exhibit a multiple-peak profile. Notice that the drug release coincided exactly with the GRT.

formulations. The normalization was supported by the fact that linear pharmacokinetics has been demonstrated for the drug up to a 150-mg dose (14).

The AUC-inf values averaged 1906.9 ng·hr/ml for BAS, 2362.9 ng·hr/ml for EC, and 2163.5 ng·hr/ml for SR (after adjustment for the dose difference). The average (SD) relative bioavailabilities, as determined by the ratios of AUC-inf values for the EC and SR tablets to BAS, were 1.14 (0.28) and 1.15 (0.09), respectively. These data demonstrate that the EC and SR dosage forms delivered equivalent amounts of drug to the systemic circulation which were greater than that delivered by the BAS treatment. The lower AUC values after BAS may be a consequence of the multiple-peak behavior observed for this treatment and the associated difficulty in characterizing the whole profile with a fixed and limited plasma sampling schedule.

The C_{max} values for the BAS and EC treatments, and for the SR treatment (after adjusting for the dose difference), averaged 1176, 2074, and 694 ng/ml, respectively. As expected, the C_{max} values for the SR tablet were significantly lower than those for both the BAS and the EC tablet treatments. Interestingly, the C_{max} values for BAS were also lower than those for the EC tablet, despite the fact that the times to peak for the former treatment were shorter.

Median T_{max} values were 0.17 hr for BAS, 2.0 hr (post-GRT) for EC, and 3.0 hr for SR, respectively. The corresponding median T_{lag} values were 1.0 hr post-GRT for EC and 2.0 hr for SR. No lag time was observed for BAS. After adjustment for T_{lag}, the median Adj T_{max} values were 0.17 hr for BAS, 1.0 hr post-GRT for EC, and 1.0 hr for SR, respectively. As expected, the results obtained for C_{max}, T_{max}, T_{lag}, and Adj T_{max} demonstrated that the onset and subsequent rate of absorption were different for the three formulations.

DISCUSSION

Onset of Absorption After EC

The onset of absorption from the EC tablet was extremely consistent at 1 hr after gastric emptying. This result is at variance with the *in vitro* data which showed a disintegrated time of 5–10 min, and complete dissolution within 30 min. Similar disparities between *in vivo* and *in vitro* behavior have been reported for other enteric-coated products in both animals and humans. The onsets of absorption were reported to be 44 min, 3 hr, and 1.2–1.6 hr, respectively, after gastric emptying of enteric-coated aspirin tablets in the dog (11), enteric-coated aspirin granules in humans (15), and enteric-coated naproxen tablets in humans (16). In addition, Heinamaki *et al.* (17), who investigated the fate of multiple-unit enteric-coated formulations in the dog, reported that hydroxypropyl methylcellulose phthalate (HPMCP)-coated granules disintegrated in the proximal part of the small intestine, whereas cellulose acetate phthalate (CAP)-coated granules traveled to the lower part of the small intestine and did not disintegrate until they reached the large intestine. The cumulative evidence from this and other studies indicates that the lag time for enteric-coated formulations is delayed in comparison with the *in vitro* dissolution time for this type of dosage form. The magnitude of the difference may vary with the nature, and probably with the thickness, of the enteric coating of the tablet.

The pH values immediately after gastric emptying and at 1 and 1.5 hr after gastric emptying of the EC/HC tablet combination indicated that, during this time, the pH experienced by the EC tablet in the small intestine ranged from pH 4.5 to pH >9.0, with mean values of 5.6, 6.1, and 6.4, respectively. One possible explanation for the disparity between *in vivo* and *in vitro* behavior could be that the luminal pH was not sufficiently basic and the buffering capacity of the intestinal fluid was inefficient enough to dissolve the coating of the EC tablet. An alternative explanation may be that the volume of intestinal fluid in the proximal small intestine was too small to dissolve completely the coating of the tablet.

Onset of Absorption and Multiple-Peak Behavior

The results obtained from the present study (after a light breakfast) as compared to previous studies (fasting and heavy breakfast) are summarized in Table II.

Since diclofenac is poorly soluble in an acidic medium but is reasonably soluble in a basic medium (0.0003 and 1.3 g/100 ml in USP simulated gastric and intestinal fluid, respectively), drug absorption should depend on the pH of the luminal environment. The pH values in the small intestine are relatively well defined, but basal fasting gastric values are highly variable (18). This variability is considered to reflect the lack of gastric acid secretion in the resting stomach.

Table II. Summary of the Results Obtained from the Present Study (After a Light Breakfast) as Compared to Previous Studies (After Fasting and After a Heavy Breakfast)

Formulation	Fasted	Light breakfast	Heavy breakfast
Nonbuffered aqueous solution	Rapid onset No lag time Multiple peak		
Buffered aqueous solution	Rapid onset No lag time Single peak	Rapid onset No lag time Multiple peak	
Enteric-coated tablet (single tablet)	Rapid onset once absorbed Variable lag time Single peak	Rapid onset once absorbed Highly variable lag time Single peak Absorption occurred 1 hr after gastric emptying	
SR tablet	Rapid onset No lag time Multiple peak	Rapid onset once absorbed 2-hr lag time Single peak Absorption occurred immediately after gastric emptying	Rapid onset once absorbed 4-hr lag time Single peak

Food intake is associated with a short transient increase in gastric pH followed by a sharp fall to consistently low values in response to acid secretion (19). In the present study, pH values only transiently increased to pH 3 or 4 before falling to levels around pH 1, indicating that the administration of food at 15 min before dosing stimulated gastric acid production to a significant extent.

Three factors affect the pH in the stomach: (a) the buffer capacity provided by the buffered drug solution, (b) the basal gastric pH, and (c) the gastric secretion induced by food. The differences in gastric pH between fasting and postprandial conditions may explain the differences in uniformity of the plasma profiles. In the case where the buffered solution was administered under fasting conditions (previous studies), the buffering capacity of the administered solution was probably adequate to prevent precipitation of the drug. The total dose in solution can be rapidly and uniformly delivered to the small intestine, producing a single well-defined peak in the plasma profile.

In the case where the buffered solution was administered 15 min after a meal (present study), the pH of the gastric fluid quickly reverted to a highly acidic state as a result of stimulation of gastric acid secretion. The buffering capacity provided by the drug solution was probably inadequate to prevent the drug from precipitating in the stomach. Variable gastric emptying of this precipitated material could have produced some of the irregularities in the plasma profile shapes for the BAS treatment. In addition, gastric emptying times are known to be longer and more variable after food intake, which may also have contributed to the multiple-peak behavior observed in this study. The initial peak probably represents partial emptying of the drug present in the stomach. Subsequent contractions, or additional water intake, could have induced further gastric emptying of dissolved or precipitated drug, producing a secondary peak in the plasma profile. This more complex emptying pattern for the BAS may also explain the lower C_{max} values observed for this treatment compared with the EC tablet. Interestingly, all multiple-peak behaviors observed for the BAS treatment occurred before the HC left the stomach, supporting the accepted view that the pylorus exerts a sieving effect on gastric content which depends on the size of the object. Gastric emptying of the drug, either in solution or as a precipitate, occurred more quickly than the emptying of the HC.

Multiple-peak behavior was not observed for the SR treatment in this study, whereas it was frequently observed in previous studies. As indicated above, the only difference in study designs was that a light snack was given 15 min before drug administration in the present study, whereas in previous studies, the drug was administered under fasting conditions. A recently completed study (6) has provided supporting evidence for the lack of multiple-peak behavior when the SR tablet is given with food. With a substantial breakfast, a prolonged lag time (4 hr), but a single peak in the plasma profile, was consistently observed for the SR tablet.

Unlike the enteric coating of the EC tablet, the film coating of the SR tablet is not resistant to gastric acid and quickly dissolves in gastric fluid. Therefore, the core of the SR tablet is rapidly exposed to the luminal environment regardless of whether or not the tablet is administered under fasting or fed conditions. Under fasting conditions, the extent to which the drug diffuses out of the core depends on the pH of the gastric fluid. If the gastric pH is high, a significant amount of the drug will be quickly dissolved in gastric fluid and this solution will empty rapidly from the stomach, with an early peak observed in the plasma profile. If the gastric pH is low, only a limited amount of drug will dissolve, and the appearance of significant plasma levels will be delayed. In both cases, emptying of the core into the duodenum will result in the remaining drug being dissolved and rapidly appearing in the circulation. Thus, depending on the gastric pH and on the time of emptying of the SR tablet core, irregular patterns and multiple peaks will be observed in the plasma profiles under fasting conditions.

When the SR formulation is administered after a meal, the environment in the stomach is consistently acidic to prevent significant dissolution or release of the drug. The presence of food will also suppress gastric emptying of the core. Both effects combined can produce a significant lag time in

the appearance of drug in plasma. However, once the core empties into the small intestine, the basic environment facilitates dissolution of the drug, producing significant levels in plasma. Since intraluminal pH in the small intestine shows relatively little fluctuation, drug release and absorption are continuous and the plasma profiles are smooth. Consequently, plasma profiles for the SR tablet administered after food will tend to exhibit longer lag times but more uniform behavior compared with the profiles obtained under fasting conditions.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Mrs. K. Vyas for her technical assistance, Drs. L. Ball and L. Leeson for their dissolution analysis, Mr. S. Shah for his assistance in drilling the tablets, and Ms. Barbara Finn for her assistance in the clinical portion of the study.

REFERENCES

1. H. S. H. Lau, K. Chan, L. Y. Shum, S. Adair, H. Ross, H. Eyring, D. Gause, and V. John. *Pharm. Res.* 6:S-194 (1989).
2. J. V. Willis, M. J. Kendall, R. M. Flinn, D. P. Thornhill, and P. G. Welling. *Eur. J. Clin. Pharmacol.* 16:405–410 (1979).
3. N. Vidon, A. Pfeiffer, J. Godbillon, M. Rongier, S. Gandon, J. Hirtz, J. J. Bernier, and J. P. Dubois. *Br. J. Clin. Pharmacol.* 28:121–124 (1989).
4. H. S. H. Lau, K. Chan, S. Adair, K. Vyas, D. Gause, and V. John. *Pharm. Res.* 6:S-232 (1989).
5. J. W. Willis, M. J. Kendall, and D. B. Jack. *Eur. J. Clin. Pharmacol.* 19:33–37 (1981).
6. L. E. Riad, R. J. Sawchuk, K. Chan, and V. John. *Pharm. Res.* 6:S-229 (1989).
7. P. Mojaverian, M. L. Rocci, D. P. Conner, W. B. Abrams, and P. H. Vlasses. *Clin. Pharmacol. Ther.* 41:11–17 (1987).
8. P. Mojaverian, R. K. Ferguson, P. H. Vlasses, M. L. Rocci, A. Oren, J. A. Fix, L. J. Caldwell, and C. Gardner. *Gastroenterology* 89:392–397 (1985).
9. J. B. Dressman and G. L. Amidon. *J. Pharm. Sci.* 73:935–938 (1984).
10. C. Y. Lui, R. Oberle, D. Fleisher, and G. L. Amidon. *J. Pharm. Sci.* 75:469–474 (1986).
11. P. Mojaverian, K. Chan, A. Desai, and V. John. *Pharm. Res.* 6:719–724 (1989).
12. K. Chan, K. Vyas, and K. Wnuck. *Anal. Let.* 15(B21,22):1649–1663 (1982).
13. V. Vashi and M. C. Meyer. *J. Pharm. Sci.* 77:761–764 (1988).
14. A. Sioufi, H. Stierlin, A. Schweizer, L. Botta, P. H. Degen, W. Theobald, and S. Brechbuler. In E. Koss (ed.), *Voltaren—Recent Findings,* Hans Huber, Berne, Switzerland, 1982, pp. 19–30.
15. M. Alpsten, C. Bogentoft, G. Ekenved, and L. Solvell. *Eur. J. Clin. Pharmacol.* 22:57–61 (1982).
16. J. G. Hardy, D. F. Evans, I. Zaki, A. G. Clark, H. H. Tonnesen, and O. N. Gamst. *Int. J. Pharm.* 37:245–250 (1987).
17. J. Heinamaki, M. Marvola, I. Happonen, and E. Westermarck. *Int. J. Pharm.* 42:105–115 (1988).
18. S. Kuna. *Arch. Int. Pharmacodyn.* 151:79–97 (1964).
19. J. R. Malagelada, G. F. Longstreth, W. H. L. Summerskill, and V. L. W. Go. *Gastroenterology* 70:203–210 (1976).