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*Report*

# Correlation of Ibuprofen Bioavailability with Gastrointestinal Transit by Scintigraphic Monitoring of $^{171}$Er-Labeled Sustained-Release Tablets

**Alan F. Parr,[1,4] Robert M. Beihn,[2] Robert M. Franz,[3,4] Gregory J. Szpunar,[3] and Michael Jay[1,5]**

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External gamma scintigraphy was used to monitor the gastrointestinal (GI) transit of radiolabeled sustained-release tablets containing 800 mg ibuprofen in eight fasted healthy volunteers. Ibuprofen serum concentrations were determined from blood samples drawn sequentially over a 24-hr period. Serum concentrations and related parameters were correlated to the position of the dosage form in the GI tract from the scintiphotos. The sustained-release tablets were radiolabeled intact utilizing a neutron activation procedure, by incorporating 0.18% of $^{170}Er_2O_3$ (enriched to >96% $^{170}$Er) into the bulk formulation. After manufacture of the final dosage forms, the tablets were irradiated in a neutron flux ($4.4 \times 10^{13}$ n/cm$^2$ · sec) for 2 min, converting the stable $^{170}$Er to radioactive $^{171}$Er ($t_{1/2}$ = 7.5 hr). Each tablet contained 50 μCi of $^{171}$Er at the time of administration. The scintigraphy studies suggested that the greatest proportion of ibuprofen was absorbed from this dosage form while the tablet was in the large bowel. The dosage forms eroded slowly in the small bowel and appeared to lose their integrity in the large bowel. *In vitro* studies showed only minimal effects of the neutron irradiation procedure on the dosage form performance.

KEY WORDS: scintigraphy; neutron activation; bioavailability; ibuprofen; sustained release; gastrointestinal transit.

## INTRODUCTION

The bioavailability of drugs from sustained-release dosage forms is dependent on a variety of factors including the drug release rate, gastric emptying, intestinal residence time, and sites of drug absorption. For a large number of compounds, the bioavailability from specific regions of the gastrointestinal (GI) tract is unknown or has been studied under invasive conditions, e.g., endoscopy. The anatomical position of dosage forms in the GI tract can be monitored *in vivo* in a noninvasive manner using radiolabeled dosage forms and an external imaging device such as a gamma scintigraphic camera. The external scintigraphy technique has been used to monitor the gastric emptying and intestinal transit rates of a variety of radiolabeled dosage forms (1,2). We have recently described a technique in which enteric-coated tablets were radiolabeled for scintigraphic studies using a neutron activation approach, i.e., a stable nuclide was incorporated into the formulation during the manufacture of the dosage form, with subsequent irradiation in a neutron flux (3,4). The resulting radioactive dosage form was administered to human volunteers for *in vivo* scintigraphic evaluation.

In the present study, single-unit sustained-release tablets containing ibuprofen and a stable marker, $^{170}Er_2O_3$, were prepared under industrial pilot-scale conditions. Upon neutron irradiation, the stable $^{170}$Er was transformed into radioactive $^{171}$Er, and the gamma radiation emitted by this isotope was used to monitor the transit of the dosage form through the gastrointestinal tract after oral administration. Blood samples were obtained at regular intervals, permitting ibuprofen serum concentrations and related parameters to be correlated to the position of the dosage form in the GI tract.

## MATERIALS AND METHODS

This study evaluated the transit characteristics of a single-unit ibuprofen sustained-release tablet formulated using an erodible polymer matrix system.

Sustained-release dosage forms containing 800 mg ibuprofen and 2 mg erbium oxide (enriched to >96% $^{170}$Er; Oak Ridge National Laboratories, Oak Ridge, Tenn.) were prepared in bulk under industrial pilot-scale conditions, including both the compressing and the film coating operations. The tablets were subsequently irradiated in a neutron flux of $4.4 \times 10^{13}$n/cm$^2$ sec (University of Missouri Research Reactor) for 2 min, producing enough $^{171}$Er ($t_{1/2}$ = 7.5 hr) so

[1] Division of Medicinal Chemistry, College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536.
[2] Division of Nuclear Medicine, College of Medicine, University of Kentucky, Lexington, Kentucky 40536.
[3] The Upjohn Company, Kalamazoo, Michigan 49001.
[4] Present address: Glaxo Inc., Research Triangle Park, North Carolina 27709.
[5] To whom correspondence should be addressed at College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536-0082.

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that 50 μCi remained in each dosage form 18 hr after irradiation. The radiochemical purity of the dosage forms was determined to be >99%, with minimal contamination from $^{24}Na$ and other isotopes. Following approval from the Institutional Review Board, the $^{171}Er$-labeled sustained-release ibuprofen tablets were administered orally to eight fasting volunteers with 6 oz of water. All doses were administered between 8 and 9 AM. The subjects were positioned beneath the head of a gamma scintillation camera and scanned continuously in a dynamic mode for 1–2 hr. After this time, static scintiphotos were obtained at the blood collection times (see below). All scintigraphic data were recorded on magnetic tape and replayed for detailed computer analysis. The position of the dosage forms in the GI tract was determined relative to external markers placed on the subjects.

Five-milliliter blood samples were obtained via a heparin lock at 0, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 24 hr postadministration. Serum was harvested and frozen immediately after blood collection. All samples were assayed for ibuprofen content (5).

The effect of the neutron irradiation procedure on the *in vitro* dissolution of ibuprofen from these tablets was evaluated. The inclusion of $Er_2O_3$ into the formulation did not affect the *in vitro* drug release profile. Also, drug release from the irradiated dosage form, while slightly faster, was observed to fall within the manufacturer's specifications for the unmodified ibuprofen sustained-release product (i.e., <35% dissolution after 2 hr, 55–80% dissolution after 6 hr, >85% dissolution after 12 hr). The effect of neutron irradiation on the stability of the drug molecule was determined by HPLC with UV detection (254 nm) using a Brownlee $C_8$ reverse-phase column with a mobile phase of acetonitrile:water:glacial acetic acid:0.5 *N* NaOH (110:82:9:1). No drug radiolysis was observed under these irradiation conditions.

## RESULTS

The results of the scintigraphic observations are listed in Table I and show the gastric emptying time of the tablets, as well as the transit time of the tablets through the small bowel and large bowel. In calculating mean transit times through the large bowel the data from seven of the eight subjects were utilized. One subject (subject 8) was observed to have significant amounts of radioactivity remaining in the large bowel at 24 hr. Since scintiphotos were not obtained past 24 hr, a definitive estimate of the total residence time could not be made for this subject. The gastric retention time of the tablets ranged from 10 to 60 min, with a mean (±SD) value of 35 (±20) min. These findings are not uncommon for a tablet administered under fasted conditions. The transit times of the tablets through the small intestine were calculated by subtracting the gastric residence time from the time at which the tablet was observed to enter the large bowel. The ileocecal junction was considered part of the small bowel in this calculation. Small bowel transit ranged from about 2 to 8 hr, with a mean transit time of 4.7 ± 2.2 hr, and exhibited the usual behavior of rapid movement through the earlier segments of the small intestine. The residence time of the tablet in the large intestine based on seven of the eight subjects averaged 10.3 ± 2.7 hr.

Table I. Residence Times for Sustained-Release Ibuprofen Tablets in the Stomach, Small Bowel, and Large Bowel of Fasted Healthy Male Volunteers

| Subject No. | Gastric emptying time (min) | Small bowel residence time (hr) | Large bowel residence time (hr) | Total residence time (hr) |
|---|---|---|---|---|
| 1 | 60 | 3.0 | 14.0 | 18.0 |
| 2 | 16 | 1.7 | 6.0 | 8.0 |
| 3 | 10 | 5.8 | 12.0 | 18.0 |
| 4 | 52 | 7.1 | 8.0 | 16.0 |
| 5 | 50 | 3.2 | 12.0 | 16.0 |
| 6 | 49 | 5.2 | 10.0 | 16.0 |
| 7 | 31 | 3.5 | 10.0 | 14.0 |
| 8 | 11 | 7.8 | >16.0 | >24.0 |
| *X* | 34.9 | 4.7 | 10.3[a] | 15.1[a] |
| SD | 20.4 | 2.2 | 2.7 | 3.4 |
| CV (%) | 58.5 | 46.8 | 26.2 | 22.5 |

[a] Mean calculated excluding the data from subject 8.

The mean ibuprofen serum concentration–time curve for the eight subjects used in this study is shown in Fig. 1. Areas under the serum concentration–time curves (AUC) were calculated using the trapezoidal rule. Two AUCs were calculated for each subject. The first of these was a partial AUC which was calculated from time zero to the time at which the tablet was observed to enter the cecum [AUC(0–$T_c$)]. The second AUC was calculated from time 0 to 24 hr [AUC(0–24)]. Extrapolated AUCs ([AUC(0–∞)] were not calculated from these data since it was not possible to obtain accurate estimates of the terminal elimination rate constant in all subjects due to prolonged absorption. Previous studies (unpublished) have documented that this formulation of sustained-release (SR) is fully bioavailable relative to conventional doses of ibuprofen and that AUC(0–24 hr) represents >95% of the AUC(0–∞) when the latter parameter can be accurately estimated. Hence, AUC(0–24 hr) is a reasonable estimator of the extent of ibuprofen absorbed following this ibuprofen SR formulation.

A statistically significant correlation was observed be-

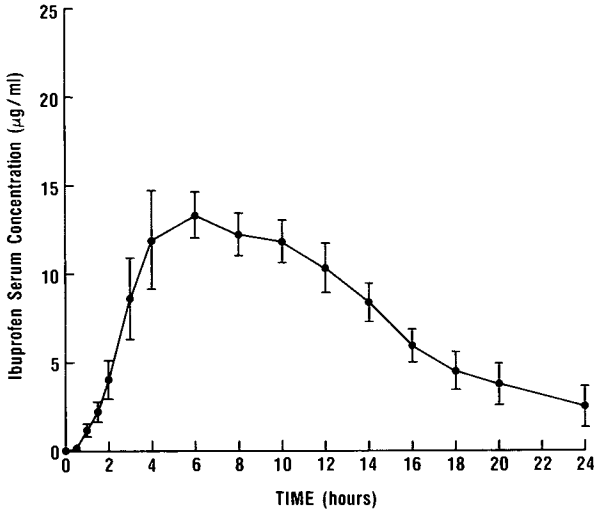


Fig. 1. Average serum ibuprofen serum concentrations versus time for the eight subjects participating in this trial. Error bars represent ±1 standard error of the mean.

Table II. Areas Under the Curve, $C_{max}$, and $T_{max}$ Values in Eight Normal Healthy Volunteers Following SR Ibuprofen Under Fasting Conditions

| Subject No. | Time to cecum (hr) | $T_{max}$ (hr) | $C_{max}$ (μg/ml) | AUC(0–$T_c$) (μg/ml × hr) | AUC(0–24) (μg/ml × hr) | $\frac{AUC(0-T_c)}{AUC(0-24)} \times 100$ |
|---|---|---|---|---|---|---|
| 1 | 4 | 8 | 11.6 | 6.5 | 174.0 | 3.7 |
| 2 | 2 | 6 | 13.9 | 2.1 | 93.8 | 2.2 |
| 3 | 6 | 4 | 24.3 | 77.6 | 223.6 | 34.7 |
| 4 | 8 | 10 | 13.5 | 47.0 | 178.9 | 26.3 |
| 5 | 4 | 4 | 23.5 | 42.7 | 206.3 | 20.7 |
| 6 | 6 | 12 | 18.4 | 42.1 | 200.3 | 21.0 |
| 7 | 4 | 8 | 18.9 | 14.0 | 173.5 | 8.1 |
| 8 | 8 | 8 | 9.98 | 44.6 | 191.5 | 23.3 |
| $X$ | 5.3 | 7.5 | 16.8 | 34.6 | 180.2 | 17.5 |
| SD | 2.1 | 2.8 | 5.4 | 25.3 | 39.0 | 11.6 |
| CV (%) | 39.6 | 37.3 | 32.1 | 73.1 | 21.6 | 66.3 |

tween AUC(0–24) and total GI transit time ($r = 0.892$, $P = 0.0068$, $N = 7$). A marginally significant correlation was also observed between AUC(0–$T_c$) and mouth-to-cecum transit time ($r = 0.68$, $P = 0.063$, $N = 8$). These results indicate that the amount of drug absorbed in a particular segment of the GI tract is a function of the residence time in that segment.

Ratios of AUC(0–$T_c$) to AUC(0–24) were calculated and are shown in Table II. This ratio averaged 17.5%, indicating that the greatest proportion of the area under the curve is generated when the dosage form resides in the large bowel. These data support the premise that ibuprofen is absorbed throughout the entire GI tract.

In one subject (No. 2), an extremely rapid total bowel transit was observed. The dosage form arrived in the cecum within 2 hr and was subsequently defecated after 7 hr. This subject exhibited an extremely low bioavailability relative to the remaining subjects (AUC = 93.8 μg/ml · hr). It is apparent from the data that for ibuprofen, significant drug absorption can occur in the large bowel. For this reason, the total bioavailability is more a function of the total transit time than of the transit in any one anatomical location.

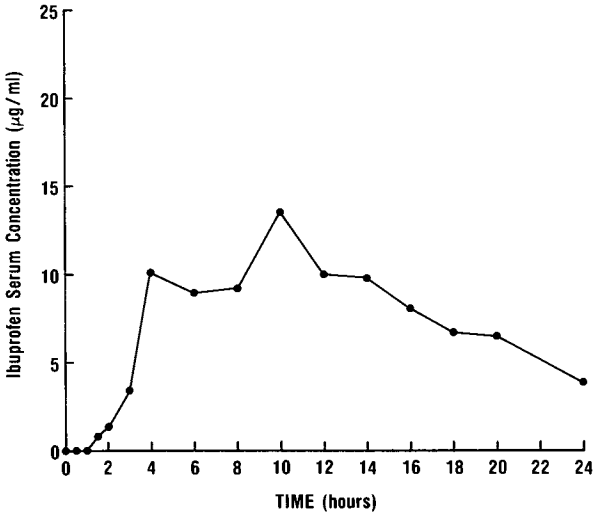


Fig. 2. Plot of ibuprofen serum concentration versus time for a subject exhibiting the double-peak phenomenon (subject 4).

Several of the subjects were observed to have two peaks on the ibuprofen serum concentration–time curves. A representative example (subject 4) appears in Fig. 2. The occurrence of double peaks has been observed previously with this dosage form when administered in the fasted state (unpublished data). It is unlikely that this is due to enterohepatic cycling since double peaks have not been observed following intravenous or conventional oral doses of ibuprofen (6). An absorption peak occurred at 4 hr while the dosage form was still traversing the small bowel. At this point, the absorption of drug was apparently due to slow erosion of the dosage form, as a relatively intact tablet was observed on the scintiphotos up to 8 hr after administration. At 8 hr after administration, the radiolabeled dosage form appeared in the subject's cecum. After 10 hr, the dosage form appeared to lose its integrity, with the radioactivity being spread throughout the ascending colon. A second small absorption peak occurred at 10 hr and was probably due to the loss of integrity of the dosage form in the large bowel. This breakup of the tablet in the cecum and large bowel was observed in every subject. In most subjects (subjects 1, 2, 4, 6, and 7) the peak serum concentration did not occur until the dosage form had passed into the large bowel.

## DISCUSSION

Using the neutron activation approach, we successfully radiolabeled intact dosage forms that were prepared in bulk quantity using industrial pilot manufacturing equipment. Thus, $^{170}$Er-containing dosage forms that were subsequently irradiated with neutrons were prepared under conditions similar to those used for the preparation of commercially available products. This is in contrast to reports in which enteric-coated tablets were radiolabeled by incorporating radioactivity into a small volume formulation, preparing tablet cores, and coating the tablets individually (7). Because the neutron activation procedure involves the incorporation of a stable isotope into the formulation (in the present case, the erbium oxide accounted for less than 0.18%), no radiation hazard was encountered by the formulator and there was no radioactive contamination of the facilities and equipment

during dosage form preparation. The tablets became radioactive only after neutron irradiation and then could be used in the external scintigraphic studies. The $^{171}$Er-labeled sustained-release ibuprofen tablets produced by this procedure had a radionuclidic purity of greater than 99%. The whole-body radiation dose received by the subjects was 0.0065 rem as calculated by the Radiopharmaceutical Internal Dose Information Center (Oak Ridge, Tenn.). In addition, the amount of erbium oxide administered in each dosage form was well below the 1000-mg/kg dose of erbium oxide that was found to have no adverse effects after oral administration to rats (8). Therefore, toxicity from the stable isotope was not a concern.

The correlation of ibuprofen serum concentration with the anatomical position of this sustained-release dosage form indicated that under fasting conditions the tablets eroded during their transit through the entire GI tract. The partial area under the curve which was calculated from time zero to the time when the tablet entered the cecum [AUC(0–$T_c$)] accounted for only 17.5% of the AUC(0–24). This observation suggests that under fasting conditions the large bowel was the major site of drug absorption from this dosage form. After moving into the large bowel, a loss of integrity of the tablets was apparent. This breakup of the dosage forms appeared to have resulted in a second absorption peak in some of the subjects. It is clear from these studies that significant absorption from the large bowel did occur in each subject and that the extent of ibuprofen absorbed was correlated with the total GI transit time. No tablet was observed to be retained in the small bowel for greater than 10 hr in any of the fasted subjects. It appears that for dosage forms of the type tested here, under fasting conditions, large bowel absorption must play a significant role for the success of the product. Drugs that are absorbed only in the small intestine or are poorly absorbed in the large intestine would no doubt be poor candidates for this type of drug delivery system (single unit, erodible matrix).

The present study, as well as previously published reports (3,4), demonstrated that a variety of sustained-release or enteric-coated tablets can be radiolabeled intact using the neutron activation approach and that the bioavailability of a drug can be correlated with the position of the radiolabeled dosage form in the GI tract using external scintigraphy.

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