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Bimodal release of ibuprofen in a sustained-release formulation: a scintigraphic and pharmacokinetic open study in healthy volunteers under different conditions of food intake

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Summary

The position of a radiolabelled sustained release ibuprofen formulation containing 800 mg drug and labelled by the addition of 10 mg [^{111}In] ion-exchange resin has been followed by gamma scintigraphy in 11 healthy male and female volunteers. The study was conducted first in 5 volunteers who received the tablet with a light breakfast and then as a cross-over study in a separate group of 6 volunteers who had either fasted or ingested a heavy breakfast. Mean times ($\pm$ S.D.) for gastric emptying of the unit were 1.0 $\pm$ 0.4 h (fasted, $n = 6$), 2.0 $\pm$ 0.9 h (light breakfast, $n = 5$) and 8.8 $\pm$ 5.9 h (heavy breakfast, $n = 4$). There were no significant differences in small intestinal transit time (mean $\pm$ S.D.) which averaged 4.5 $\pm$ 2.1 h, 2.4 $\pm$ 0.9 h and 2.9 $\pm$ 1.2 h, respectively. The unit was observed to remain intact until it reached the ascending and transverse colon where it broke into two or three pieces or completely disintegrated. In two subjects, in which the tablet had been administered with a heavy meal, the unit remained in the stomach for more than 15 h. The presence of food markedly altered the pharmacokinetics of the drug which, in fasting subjects, was characterised by a double peak in the plasma concentration time profile. The light breakfast caused a levelling of the two peaks to a plateau lasting from 4 to 13 hours, whereas after the heavy breakfast only the secondary peak was evident. The secondary peak appears to be due to a disintegration of the matrix after 12–14 h coupled with a high absorptive capacity for the drug in the ascending colon. There was no evidence of adhesion of the unit to the gastrointestinal mucosa.

Introduction

Ibuprofen (Brufen) is a non-steroidal anti-inflammatory drug which was the first of the now well established "propionics". It was first available for the treatment of rheumatic and painful conditions in 1969. It has been estimated that around 100 million people have been treated with the drug and its risk/benefit ratio is such that it is now available without doctor's prescription in many countries of the world.

Following ingestion of standard tablets under fasting conditions, maximum plasma concentrations are achieved 1–2 h after administration. The rate of elimination is rapid with a terminal half-life of elimination from the plasma of around 2 h in both elderly and young subjects (Crampton et al.,

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personal communication). The rise in drug concentration in the therapeutically relevant tissue, the synovial fluid, tends to lag behind that in the plasma (Glass and Swanell, 1974). The short half-life of the drug necessitates considerable modification of the absorption characteristics to achieve a once-daily dosage regimen. To this end a new formulation of ibuprofen, Brufen R, has been designed.

In the development of sustained-release dosage forms, it is important to establish the relationship between the position of the formulation in the gastrointestinal tract and the plasma concentration–time profile. This aids the identification of areas of maximum absorption of drug and leads to the optimisation of the drug release profile. Gamma scintigraphic techniques are now well established as a suitable method for the investigation of the behaviour of drug formulations in man, particularly with regard to the gastrointestinal transit and the effect of food (Davis et al., 1984; Wilson et al., 1984, 1987). A suitable marker such as micronised 'Amberlite' resin radiolabelled with indium-111 or technetium-99m is incorporated into the formulation mix prior to final manufacture of the unit. This allows the disintegration and dissolution of the dosage form to be followed in vivo by external scintigraphy.

The objective of the present study was to correlate the behaviour, position and rate of disintegration of a sustained-release ibuprofen tablet within the gastrointestinal tract with the plasma concentration in healthy volunteers under different conditions of food intake. In addition, the images obtained were examined for evidence of adhesion of the formulation to the gastrointestinal mucosa. The tablets were tagged with indium-111 labelled ion-exchange resin incorporated during manufacture and administered with water containing technetium-99m diethylenetriaminepentaacetic acid to outline the stomach and large intestine.

Materials and Methods

Preparation of the dosage form

Ion-exchange resin (Amberlite IRA-120) was milled and sieved to obtain a powder having a mean size of 37 μm. ^{111}InCl (110 MBq in 2 ml 0.04 N HCl) was mixed with 550 mg of the milled Amberlite resin which was oven-dried at 90 °C for 20 min. The dried, labelled resin was mixed with granules and the other excipients prior to compression of the sustained-release tablets. Each tablet contained 800 mg ibuprofen and 10 mg micronised Amberlite resin labelled with indium-111 (1 MBq on the day of investigation). The crushing strength (Schleuniger) of a sample of the tablets was measured, individual tablet weights were checked and acceptable tablet cores film-coated. The dissolution profile was measured using USP XXI apparatus II (paddles 100 rpm, 900 ml phosphate buffer pH 7.2) and USP XXI apparatus II (paddles at 150 rpm, stationary basket, borate buffer pH 8.6).

Technetium-99m labelled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) was prepared by addition of (^{99m}Tc) sodium pertechnetate to a DTPA kit (CIS Products, London, U.K.). Three MBq ^{99m}Tc-DTPA was added to the 30 ml water which was administered with the tablets to the volunteers.

Anatomical radiolabelled markers were prepared by addition of 0.1 MBq $^{111}InCl_3$ to a 2 × 2 cm size filter paper wrapped within a waterproof tape.

Study protocol

Eleven healthy volunteers, 6 males and 5 females age range 19–21 years, took part in the study. Ethical approval for the study was obtained from the University Hospital Ethical Committee and permission to administer the isotopes from the DHSS. The protocol was explained to each subject both verbally and in written form; written consent to participate in the trial was obtained prior to a full medical examination.

The study was conducted in two parts with 5 male volunteers receiving the tablet with a light breakfast in the first part and 6 volunteers receiving the tablet in a crossover between a fasted regime and a heavy breakfast. Subjects were fasted overnight and reported for the trial at 07.30 h. They then remained fasted or were given a breakfast as detailed in Table 1. At 08.00 h, a predose blood sample was taken from each subject, fol-

TABLE 1

Details of breakfast meals

Light breakfast	Heavy breakfast
2 slices lightly buttered toast	2 fried rashers of bacon
5 g marmalade	2 fried eggs
100 ml orange juice	1 fried tomato
	2 slices toast
	10 g butter
	5 g marmalade
	1 mug tea with 30 ml milk
	100 ml orange juice
Total calorific value = 646 kJ	Total calorific value = 3327 kJ

lowed by further samples taken at 1, 2, 4, 6, 8, 10, 12, 14, 16 and 24 h.

The radioactive markers were taped to the abdomen immediately opposite the stomach on anterior and posterior planes. This was to provide a reference position for each scintiscan. Shortly after 08.00 h subjects received the test formulation together with 30 ml water containing 3 MBq ^{99m}Tc DTPA. Anterior and posterior images of 30 s duration were recorded on the gamma camera at 15 min intervals until the tablet left the stomach, followed by half-hourly scans until the formulation reached the ileocaecal junction. After this time subjects were imaged at hourly intervals for the rest of the study.

Morning refreshment for all subjects consisted of 100 ml orange juice and 1 biscuit given at 10.30h (362 kJ) followed by lunch at 12.30 h which consisted of sirloin steak (8 oz), chipped potatoes, peas, salad, 100 ml orange juice and apple crumble and custard (4160 kJ). In the afternoon, subjects consumed 100 ml orange juice (143 kJ).

Analysis

Gamma camera images were analysed by identification of the stomach and the large intestine from the image in the technetium channel for each subject. Templates were then constructed referring the position of the anterior and posterior marker to these organs. This allowed the gastric residence time and colon arrival of the unit to be assessed. Regions of interest were constructed around the tablet and the pixel activity and area were calculated to quantify the erosion of the unit. The data obtained were corrected for background radiation and radioactive decay of the isotope. The technetium counts were corrected for the 30% overlap of indium intensity into this channel. The point at which the matrix disintegrated was noted.

From the data obtained in the second trial, the cumulative in vivo release of radioactivity was plotted as a function of the square root of time (Higuchi, 1963) to examine whether the processes governing release from the matrix were affected by ingestion of food.

Results and Discussion

In vitro release profile

The formulation studied was a film-coated gel-matrix tablet containing 800 mg ibuprofen. The tablet was formulated to form a gel layer on contact with water, which was eroded and regenerated as aqueous media penetrated further into the tablet. The release of ibuprofen was expected to occur by a mixed erosion-diffusion system as described by Higuchi (1963). Plots of the percentage of the label remaining associated with the tablets versus $\sqrt{}$time from the data obtained in the second trial are shown in Fig. 1. At first sight, the data showed reasonable correlation between the two variables with correlation coefficients better than

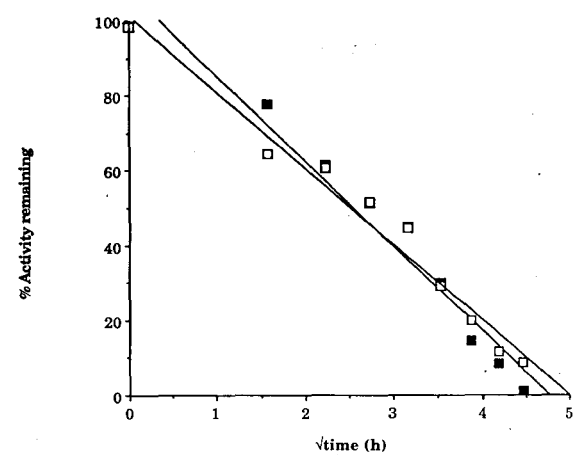


Fig. 1. Higuchi plots of the mean rate of disintegration of the matrix in six volunteers when fasted (□) and after a heavy breakfast (■).

TABLE 2

Gastrointestinal transit times (h) of the iboprofen tablet in fasted and fed volunteers

	Gastric emptying	S.I. transit	Tablet disintegrated	T_{cmax}	C_{max}
Fasted					
JL	0.67	3.10	10.63	4.00	21.50
BJ	1.25	3.15	11.69	12.00	21.60
EW	1.27	4.03	13.40	4.00	18.40
MF	1.70	5.60	11.93	4.00	12.20
SB	0.77	8.30	12.86	4.00	21.30
JK	0.57	3.00	14.85	4.00	15.40
Mean	1.04	4.53	12.56	5.33	18.40
S.D.	0.44	2.09	1.48	3.27	3.89
Light breakfast					
DS	2.10	1.92	6.00	6.00	13.90
SD	2.07	2.43	6.00	4.00	20.80
CR	2.02	1.93	6.00	8.00	15.90
GP	3.05	1.95	3.30	8.00	12.80
PD	0.60	3.90	6.00	12.00	17.60
Mean	1.97	2.43	5.46	7.60	16.20
S.D.	0.88	0.85	1.21	2.97	3.16
Heavy breakfast					
(Excl) BJ	< 15.77			12.00	40.00
JL	5.35	4.00	11.95	10.00	49.70
EW	0.53	1.90	12.76	14.00	13.90
MF	11.18	2.00	12.04	16.00	15.80
SB	11.22	3.70	12.01	12.00	16.00
JK	15.77	–	15.37	14.00	44.10
Mean	8.81	2.90	12.83	13.20	27.90
S.D.	5.92	1.10	1.46	2.28	17.48

0.98. However, a consistent sinusoidal variation suggested that the behaviour is not adequately described by the Higuchi model.

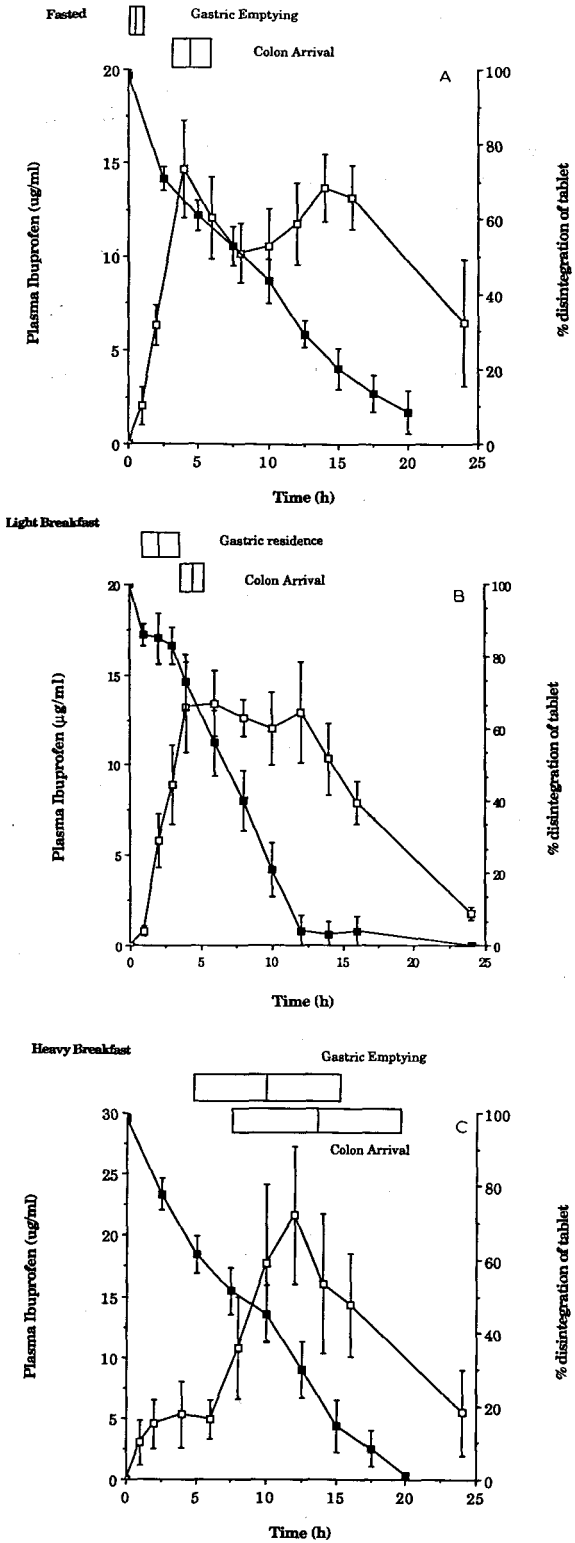
Gastrointestinal transit of the tablets

In fasted subjects the tablet was emptied from the stomach within 2 h of ingestion (Table 2). When the tablet was given with a light breakfast, gastric emptying of the unit was slowed but all subjects had emptied the tablet from the stomach by 3 h.

The heavy breakfast markedly delayed gastric emptying of the unit and in two subjects the tablet remained in the stomach for longer than 15 h. This finding is in accordance with our previously published work, showing that the intake of a meal of calorific value greater than 3000 kJ markedly suppresses the migrating myoelectric complex, responsible for sweeping indigestible material from the stomach. The occurrence of adhesion to the gastrointestinal mucosa in these two subjects was examined by plotting the position of the tablet relative to the abdominal surface markers. Movement of the unit in the stomach was clearly visible and it gradually eroded, albeit at a slower rate than in the small intestine.

Intestinal transit was defined as the time from which the tablet left the stomach and entered the caecum. The values obtained, between 2.5 and 4.5 h, are in agreement with previous scintigraphic studies. After a variable delay at the ileocaecal junction, the tablets were seen to enter the ascending colon where they eroded or broke up into several pieces. Disintegration was complete by the time the tablets had entered the transverse colon.

In the present study, double peaks in the plasma concentration at around 4 and 12 h after dosing were noted in 10 of the 17 profiles and were particularly evident when the tablet was given in the fasting state. Fig. 2 shows the mean plasma



concentration-time profiles, the cumulative rates of disintegration and the position of the tablets in the three treatment regimens. In both the subjects who remained fasted and those given a heavy breakfast with the tablet (Fig. 2a, c) double peaks in the plasma concentration profile were noted to correlate with slight increases in the rate of disintegration.

Parr et al. (1987) have described the scintigraphic assessment of a sustained release ibuprofen tablet (800 mg) which was radiolabelled by incorporation of 2 mg of [^{170}Er] erbium oxide into the tablets. The tablets were then irradiated by a neutron source which converted the [^{170}Er] to [$^{171}Er_2$], a gamma emitter with a half-life of 7.5 h. The radiolabelled tablets were then administered to 8 fasted volunteers and the transit and dissolution of the tablets was followed by gamma scintigraphy. Several of the subjects in the latter study were observed to have two peaks in the ibuprofen serum concentration–time curves and the authors comment that this phenomenon had been observed previously in the fasted state. Since the drug does not undergo enterohepatic recirculation, the double peak was ascribed to loss of integrity of the dosage form in the large bowel.

Shah (1988) has described a bimodal release pattern from drug-polymer matrix tablets. This mode of release, first described by Heller and Baker (1980), is characterised by an initial fast release of drug, followed by a relatively constant release for a period of time and a second mode of fast release. Like the model described by Higuchi (1963), bimodal release involves the simultaneous processes of gelation, swelling, drug dissolution, counter directional diffusion and surface erosion of the matrix. Heller and Baker characterise such a system as an inert matrix whose permeability increases as an exponential function of time, the solution of which leads to an expected bimodal release pattern. Fig. 3 shows the in vivo rates of disintegration of the matrix measured by scintigraphy, plotted for fasted and fed regimes in the

Fig. 2. Relationship between the mean plasma ibuprofen concentrations (□) and the rate of disintegration of the matrix (■) after administration of the tablets with the 3 feeding regimens.

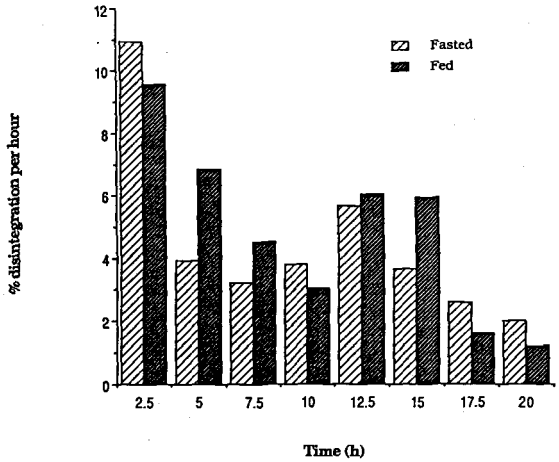


Fig. 3. Mean rate of disintegration of the matrix per vs time in fasted volunteers and in the same subjects after a heavy breakfast.

present study in which a bimodal release pattern was clearly evident. It appeared that once 50% of the matrix had eroded, the gel layer became more friable and disintegration proceeded more rapidly. The mechanism in this case is clearly different to that described by Heller and Baker, but would be expected to yield the bimodal profile seen in this study and reported by Shah (1987) and Parr et al. (1987). In the treatment of rheumatoid arthritis where peak concentrations are required some hours after the patient has retired, bimodal drug release may offer therapeutic advantages since it maintains the plasma level over a 24 h period.

The bioavailability of a drug from a formulation is influenced by a complex interplay of physiological and physiochemical factors; however it is accepted that the primary determinant of absorption is the rate at which drug is released from the formulation into solution (see Wilson and Washington, 1988). This, in turn, is affected by the rate of disintegration of the dosage form, which increases the surface area and hence the amount of drug exposed to the medium. Food influences the rate at which a dosage form travels through the gastrointestinal tract, particularly with regard to gastric emptying and spread of the disintegrated fragments of single unit dosage forms. Food also provides an adsorbing surface for released drug and causes changes in the viscosity of the gastrointestinal fluid in which the drug is presented to the absorbing mucosa. When the dosage form is in the stomach, the presence of food will retard presentation to the absorptive surfaces of the small intestine (Wilson et al., 1987). In both studies the heavy breakfast provided a large volume for non-specific adsorption and the amount of drug presented to the absorptive epithelium in the upper intestinal tract was decreased, since it was released from the stomach dispersed in chyme. The presence of food did not affect the rate of release from the formulation and therefore it can be reasonably concluded that changes in gastrointestinal transit and the adsorbing surface caused by the size and nature of the meal were predominantly responsible for the changes in the absorption profile.

In all subjects the peak plasma concentration was reached at around 13.00 h, when the tablet was in the ascending colon. For the light breakfast, the plasma concentration-time profile showed a plateau between 4 and 12 h and secondary peaks were not so evident. Previous studies of NSAIDs in sustained-release formulations conducted by our group have suggested that the ascending colon represents an important site of absorption for this class of drugs (e.g. salicylates, ketoprofen and ibuprofen) and for β-blockers such as oxprenolol (Wilson and Washington, 1988). It appears that the strategy of sustained release in conventional pharmaceutical formulations will only work if the drug is reasonably well absorbed in the ascending and transverse colon, the residence in these parts of the large bowel providing the opportunity for a prolonged absorption period.

In conclusion, the data show that this sustained release formulation exhibited a bimodal release pattern of ibuprofen. It is interesting that this behaviour was not evident in the in vitro USP test and provides an example of the value of gamma scintigraphy in the assessment of dosage forms.

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