International Journal of Pharmaceutics, 83 (1992) 155–161

IJP 02781

The effect of food on the in vivo behaviour of a novel sustained release formulation of tiaprofenic acid

I.R. Wilding [a], S.S. Davis [a,b], R.A. Sparrow [c], J.R. Bloor [d], G. Hayes [d] and G.T. Ward [d]

[a] *Pharmaceutical Profiles Ltd, 2 Faraday Building, Highfields Science Park, Nottingham NG7 2QP (UK),*
[b] *Department of Pharmaceutical Sciences, University of Nottingham, University Park, Nottingham NG7 2RD (UK),*
[c] *Department of Human Morphology, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH (UK)*
and [d] *Roussel Laboratories Ltd, Kingfisher Drive, Covingham, Swindon SN3 5BZ (UK)*

(Received 9 October 1991)
(Accepted 30 December 1991)

Key words: Tiaprofenic acid; Sustained release; Oral administration; Gastrointestinal transit; Pharmacoscintigraphy

Summary

A novel sustained release tablet formulation of tiaprofenic acid, that has been designed to disintegrate into discrete pellets in the gastrointestinal tract, has been evaluated using a combination of gamma scintigraphy and pharmacokinetics. The performance of the product in vivo was very satisfactory, in that the disintegration of the tableted pellet formulation was rapid. The gastrointestinal transit behaviour of pellets was affected by food, but food did not affect the subsequent absorption of the released drug.

Introduction

Tiaprofenic acid is a non-steroidal anti-inflammatory agent effective in rheumatoid arthritis, osteoarthritis, musculoskeletal disorder, soft tissue injuries and a variety of inflammatory conditions. The drug has a relatively short serum half-life of only 2 h (Singh et al., 1986) and is therefore an ideal candidate for formulation as a sustained release (SR) delivery system. We have previously reported on the gastrointestinal (GI) transit characteristics of an SR pellet formulation of tiaprofenic acid (Davis et al., 1987). However, in order to allow once daily administration, the latter needs to be given as two capsules, each containing 300 mg of drug. A new tablet formulation has now been developed so as to allow once daily dosing with a single entity. On administration, the tablet disintegrates to form discrete pellets which act as individual SR systems, thereby combining the convenience of a single tablet with the desirable properties of a multiparticulate device. The addition of pharmaceutical cushioning excipients enables the tablets to be manufactured under normal production conditions without damaging the SR properties of the pellets.

Correspondence: I.R. Wilding, Pharmaceutical Profiles Ltd, 2 Faraday Building, Highfields Science Park, Nottingham NG7 2QP, U.K.

The non-invasive technique of gamma scintigraphy has been routinely used to evaluate the in vivo performance of novel delivery systems (Davis et al., 1988; Digenis et al., 1990; Hardy et al., 1991; Wilding et al., 1991a,b). Such studies not only provide an insight into the fate of the delivery system but also allow the relationship between in vivo behaviour and drug absorption to be examined (pharmacoscintigraphy).

Conventional methods for the labelling of pharmaceutical dosage forms require the marker to be incorporated as late as possible to minimise the risk of radioactive contamination in production environments. In many cases, the manufacturing process must be scaled down to lower the amount of radioactivity handled, which can, in some cases, significantly alter the behaviour of the dosage form. These problems can be overcome by the use of stable isotopes and neutron activation methods (Digenis and Sandefer, 1991; Hardy et al., 1991). A stable isotope (^{152}Sm, as the isotopically enriched oxide) was incorporated directly into the SR pellets at a low level and tablets were manufactured from the resulting cores. The ^{152}Sm was then converted into a gamma emitting isotope (^{153}Sm), just prior to clinical evaluation by irradiation in a neutron source. By using the neutron activation method, radiation levels were minimised, quality assurance maintained and a complicated delivery system was labelled easily and efficiently.

The behaviour of SR delivery systems is known to be affected by food (David, 1991). In this work, we report on the pharmacoscintigraphic evaluation of the new tablet formulation when given after an overnight fast, or with food in the form of a light or heavy breakfast.

Materials and Methods

Manufacture of labelled dosage forms

Tiaprofenic acid sustained release tablets containing 600 mg of drug were manufactured by Roussel Laboratories Ltd, Swindon. Each tablet contained 2 mg of isotopically enriched samarium oxide (^{152}Sm) which was incorporated during the manufacture of the pelletised portion of the formulation. The tablets released the following quantities of drug as measured using the USP Apparatus 2 dissolution assembly at a paddle speed of 100 rpm and a pH 5 citrate buffer as dissolution medium: 2 h, 29%; 8 h, 59%; 12 h, 70%; 20 h, 83%.

On the day prior to dosing, the tablets were subjected to a neutron flux of 10^{12} n cm^{-2} s^{-1} for 4 min. Each tablet contained approx. 1 MBq of the gamma emitting isotope ^{153}Sm ($t = 47$ h) at the time of administration. Preliminary investigations had demonstrated that neither the presence of the small quantity of samarium oxide nor the neutron activation procedure prejudiced the release behaviour of the formulation or the stability of the drug.

Study design

The study was an open randomized three-way cross-over using seven healthy volunteers; five male, two female (age 19–25 years). Each volunteer received one of the three treatments on three separate occasions with a minimum washout of 1 week between administrations. Approval for the administration of the radiolabelled formulations was obtained from the Department of Health, London. The study was approved by the University of Nottingham Ethics Committee and was conducted in accordance with the Guidelines for Ethics in Research of the Declaration of Helsinki and its subsequent amendments. The estimated effective radiation dose equivalent to each subject for the complete study was 2 mSv.

After an overnight fast from 12.00 p.m., the subjects reported to the clinical unit at 7.00 a.m. On arrival, a blood sample (6 ml) was taken from each subject for a baseline reference of the plasma concentration of tiaprofenic acid. One of the following treatment regimes was administered with 100 ml of water; 600 mg sustained release tablet, after (i) an overnight fast, (ii) a light breakfast (two slices of toast, butter and preserve, orange juice, tea or coffee) or (iii) a heavy breakfast (fried egg, two slices of bacon, sausage, fried bread, two slices of toast, butter and preserve, orange juice, tea or coffee). Lunch was provided 4 h post-dose (two medium filled rolls (not cheese), one packet of crisps, tea or coffee) and

dinner at 10 h post-dose (orange juice, prawn cocktail, steak, chips and vegetables, cheese cake, tea or coffee).

Blood samples were taken either via an indwelling cannula irrigated with heparin or by direct venepuncture at the following intervals (h): 0 (pre-dose), 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0 and 24.0 h. The samples were collected into heparinized tubes and centrifuged to provide plasma which was subsequently frozen at −80°C. Scintigraphic images were obtained at suitable selected time intervals so that profiles for gastric emptying, tablet disintegration and colon arrival could be constructed.

Scintigraphic details

Anatomical markers, containing 0.1 MBq $^{99}Tc^{m}$, were taped to the skin, anteriorly and posteriorly, over the liver and to the right of the stomach. Anterior and posterior scintigraphic images, each of 60 s duration, were taken at frequent intervals throughout the study period, using a gamma camera (General Electric Maxicamera II) having a 40 cm field of view. The camera was fitted with a low-energy (140 keV) parallel-hole collimator. Images were recorded on a computer and stored on magnetic tape for analysis at a later stage.

Regions of interest (ROI) were drawn around the position of the stomach and tablet, using an electric cursor. Stomach and tablet positions for each successive view were identified by reference to both the external marker and the preceding images. To assess the background counts, a third ROI was drawn on each image away from the main area of activity. At later time points, an additional ROI was drawn to identify arrival of the pellets at the caecum. The data were corrected for background activity and radioactive decay. The error due to variation in depth of the formulation within the body was minimized by the calculation of the geometric mean of the corresponding anterior and posterior views (Tothill et al., 1978).

Tiaprofenic acid analysis

The plasma samples were analysed by HPLC (Ward et al., 1982) with a detection limit of 0.1 μg/ml and a linear range up to 20 μg/ml. Samples were analyzed in duplicate.

TABLE 1

Tablet disintegration times ($T_{50\%}$) (min)

Subject	Fasted	Light	Heavy
1	6	16	17
2	6	7	6
3	6	6	16
4	6	17	6
5	19	20	6
6	6	6	6
7	14	11	6
Mean	9	12	9
SE	2	2	2
Median	6	11	6

Student's *t*-test (paired data)

	t	sig
Fasted vs light	−1.40	0.211 (ns)
Fasted vs heavy	0.00	1.000 (ns)
Light vs heavy	0.94	0.383 (ns)

ns, not significant; sig, significant at the 5% level.

Pharmacokinetic analysis

The area under the plasma-time profile to 24 h ($AUC_{0-24\,h}$) was calculated by the trapezoidal rule. The peak plasma concentration (C_{max}) and the time to peak plasma concentration (T_{max}) were derived directly from the plasma concentration profiles of tiaprofenic acid.

Results and Discussion

In vivo disintegration

The time for the in vivo disintegration of the tableted pellet formulation was rapid, typically being in the region of 10 min. In all cases, dispersion of the pellets from the administered tablets occurred within 30 min of ingestion, irrespective of the size of the meal administered (Table 1).

Gastrointestinal transit

The mean profiles for gastric emptying are shown in Fig. 1 and the data derived from the scintigraphic measurements are provided in Table

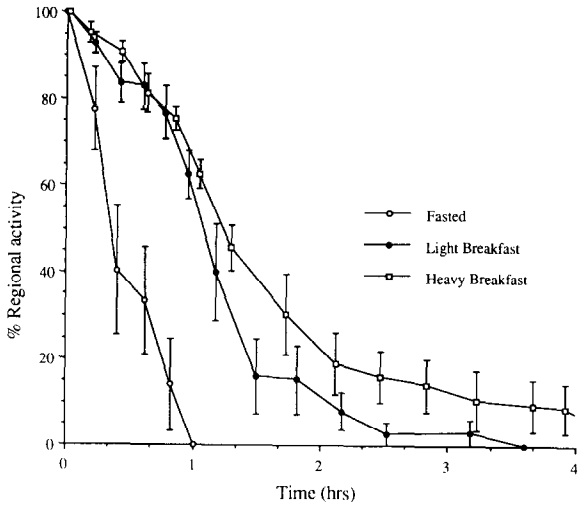

Fig. 1. Mean gastric emptying profiles (±SE) for a novel sustained release formulation of tiaprofenic acid.

2. Under fasting conditions, the gastric emptying of the pellets (released from the original tablets) was rapid and was largely determined by a physiological process known as the migrating myoelectric complex (MMC) (Szurszewski, 1969). This occurs over a 2 h period and has phases of the cycle that range from a period of quiescence to strong contractions. It is the contractions of the third phase of the MMC that are important in gastric emptying, since they have the effect of 'sweeping' indigestible material from the stomach through the open pylorus and into the small intestine. This has sometimes been called the 'housekeeper wave'. In fed subjects a lag phase was observed before emptying commenced (Fig. 2). This is a common occurrence and reflects the redistribution of food from the quiet fundus to the active antrum and the preparation of chyme from solid food (Meyer, 1987). Pellets initially remained in the upper half of the stomach dispersed in the food and then were dispersed throughout the stomach, presumably as the food was redistributed.

In some subjects, the gastric emptying of the pellets was characterised by an almost linear pattern. This type of linear emptying profile has been described previously for the gastric emptying of solid food particles and suggests that the pellets were at least mixed with a certain proportion of the food prior to the start of emptying

TABLE 2

Gastrointestinal transit times (min) of a novel sustained release formulation of tiaprofenic acid

Subject	Gastric emptying ($T_{50\%}$)			Colon arrival ($T_{50\%}$)			SI transit ($T_{50\%}$)		
	Fasted	Light	Heavy	Fasted	Light	Heavy	Fasted	Light	Heavy
1	17	74	60	221	271	288	204	197	228
2	8	111	98	266	250	266	258	139	167
3	20	76	83	231	247	391	211	171	308
4	41	60	73	356	334	433	315	274	360
5	26	46	69	237	193	314	211	147	245
6	53	67	136	266	293	429	213	226	293
7	35	68	71	201	233	301	166	165	230
Mean	29	72	84	254	260	346	225	188	262
SE	6	8	10	19	17	26	18	18	24
Median	26	68	73	237	250	314	211	171	245

Student's *t*-test (paired data)

	t	sig	*t*	sig	*t*	sig
Fasted vs light	−3.61	0.011 (sig)	−0.48	0.649 (ns)	2.17	0.073 (ns)
Fasted vs heavy	−6.34	0.001 (sig)	−4.30	0.005 (sig)	−1.55	0.172 (ns)
Light vs heavy	−1.18	0.283 (ns)	−4.24	0.005 (sig)	−5.06	0.002 (sig)

ns, not significant; sig, significant at the 5% level.

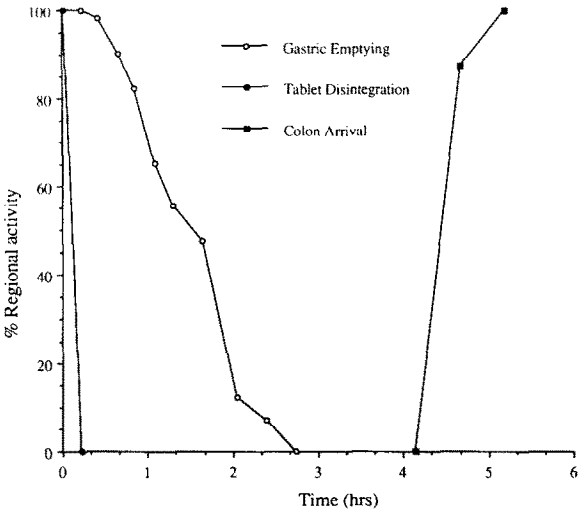

Fig. 2. Transit and disintegration profile for subject 2 after a heavy breakfast.

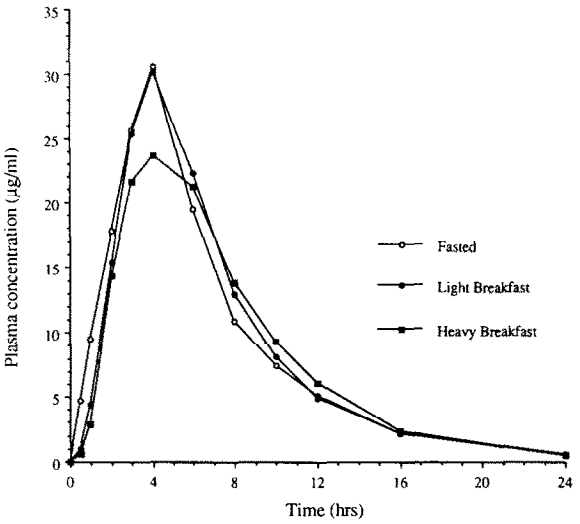

Fig. 3. Mean plasma concentration following administration of a novel sustained release formulation of tiaprofenic acid after an overnight fast, light breakfast or heavy breakfast.

(Fisher et al., 1987). This gradual process of pellet emptying with food should result in the phased presentation of the released drug to the small intestine and could thereby reduce possible irritant effects.

The emptying of the pellets after the light and heavy breakfast was not significantly different. This is rather surprising since, in previous studies, we have demonstrated that an increase in meal size can alter the rate of gastric emptying of multiparticulate dosage forms (Davis et al., 1984, 1987). Certainly, the gastric emptying of food is known to be dependent on the energy content of the meal (Kelly, 1981). Indeed, some have suggested that the rate of emptying of food is such that the number of calories delivered to the duodenum remains constant (Meyer, 1987). Thus, we conclude that in some cases the pellets may not necessarily have been that well mixed with the administered food.

Small intestinal transit and colon arrival

The colon arrival times, expressed as the time for 50% arrival, are listed in Table 2. Small intestinal transit can be determined from the difference in the colon arrival and gastric emptying data. The average time for small intestinal transit was in the range 3–4 h, in line with the suggestions of Davis et al. (1986). There was no statistical difference in transit for the fasted and light breakfast treatment regimes of the study. Interestingly, the heavy breakfast gave rise to a significant increase in small intestinal transit time. In many of the subjects, pellets that had been

TABLE 3

Area under the curve ($AUC_{0-24\,h}$) (in h μg ml^{-1})

Subject	Fasted	Light	Heavy
1	229.2	205.4	239.9
2	254.1	257.4	250.0
3	135.5	147.9	118.7
4	94.4	114.1	111.8
5	154.4	148.8	176.6
6	344.3	346.8	292.4
7	228.0	224.4	200.4
Mean	206	206	199
SE	32	30	26
Median	228	205	200

Student's *t*-test (paired data)

	t	sig
Fasted vs light	−0.13	0.899 (ns)
Fasted vs heavy	0.71	0.506 (ns)
Light vs heavy	0.66	0.535 (ns)

ns, not significant; sig, significant at the 5% level.

distributed through the small intestine because of a process of gradual gastric emptying were observed to regroup at the ileocaecal sphincter before subsequently moving into the caecum. Substantial spreading of the activity associated with the pellets, in the proximal and transverse colon, was noted at later time points.

Pharmacokinetics

The formulation was well tolerated by all subjects and no adverse experiences were reported during any of the study periods. The pharmacokinetic data are plotted in Fig. 3 and are summarized in Tables 3–5.

There were no significant contributions to the variations observed that could be associated with different treatments for both $AUC_{0-24\,h}$ and C_{max}. Furthermore, there were no significant effects due to the week and treatment interaction or carryover. Therefore, it was concluded that there was no difference between the three treatments as expressed in the means of $AUC_{0-24\,h}$ and C_{max}. The data for time to peak plasma concentration (T_{max}) also showed no significant differences among the three treatments. The times to peak plasma level, which ranged from 3 to 6 h with median values of 4 h for each treatment, correlate well with small intestinal transit times. Thus, in terms of rate and extent of absorption of tiaprofenic acid, the three treatments can be considered to be equivalent and the presence of food has no effect on the absorption of the drug from the new formulation. The principal absorption site would appear to be the small intestine.

TABLE 4

Peak plasma concentration (C_{max}) (in μg/ml)

Subject	Fasted	Light	Heavy
1	33.9	30.7	46.7
2	35.9	33.5	31.8
3	27.0	28.0	14.1
4	15.9	25.0	17.8
5	27.7	19.7	33.7
6	54.0	40.6	26.5
7	35.0	37.3	30.1
Mean	33	31	29
SE	4	3	4
Median	34	31	30

Student's *t*-test (paired data)

	t	sig
Fasted vs light	0.76	0.477 (ns)
Fasted vs heavy	0.82	0.443 (ns)
Light vs heavy	0.43	0.682 (ns)

ns, not significant; sig, significant at the 5% level.

TABLE 5

Time to peak plasma concentration (T_{max}) (in h)

Subject	Fasted	Light	Heavy
1	3	4	3
2	4	4	4
3	3	3	4
4	4	4	6
5	3	4	3
6	4	6	6
7	4	4	4
Median	4	4	4

Student's *t*-test (paired data)

	t	sig
Fasted vs light	−1.92	0.103 (ns)
Fasted vs heavy	−1.99	0.094 (ns)
Light vs heavy	−0.35	0.736 (ns)

ns, not significant; sig, significant at the 5% level.

Conclusions

A combined scintigraphic and pharmacokinetic study (pharmacoscintigraphy) has demonstrated that the rate and extent of absorption of tiaprofenic acid from a new tablet formulation, that is designed to disintegrate in vivo to a multiparticulate pellet system, is unaffected by food.

References

Davis, S.S., Physiological factors in drug absorption. *Ann. N.Y. Acad. Sci.*, 618 (1991) 140–149.

Davis, S.S., Hardy, J.G. and Fara, J.W., Transit of pharmaceutical dosage forms through the small intestine. *Gut*, 27 (1986) 886–892.

Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R. and Wilson, C.G., A comparative study of the gastrointestinal transit of a pellet and a tablet formulation. *Int. J. Pharm.*, 21 (1984) 167–177.

Davis, S.S., Khosla, R., Wilson, C.G. and Washington, N., Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. *Int. J. Pharm.*, 35 (1987) 253–258.

Davis, S.S., Washington, N., Parr, G.D., Short, A.H., John, V.A., Lloyd, P. and Walker, S.M., Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal transit as determined by scintigraphy. *Br. J. Clin. Pharmacol.*, 26 (1988) 435–443.

Digenis, G.A., Sandefer, E.P., Parr, A.F., Beihn, R.M., McClain, C., Scheinthal, B.M., Ghebre-Sellassie, I., Iyer, U., Nesbitt, R.U. and Randinitis, E., Gastrointestinal behaviour of orally administered radiolabelled erythromycin pellets in man as determined by gamma scintigraphy. *J. Clin. Pharmacol.*, 30 (1990) 621–631.

Digenis, G.A. and Sandefer, E., Gamma scintigraphy and neutron activation techniques in the in vivo assessment of orally administered dosage forms. *Crit. Rev. Ther. Drug Carrier Systems*, 7 (1991) 309–345.

Fischer, W., Boertz, A., Davis, S.S., Khosla, R., Cawello, W., Sandrock, K. and Cordes, G., Investigation of the gastrointestinal transit and in vivo drug release of isosorbide-5-nitrate pellets, *Pharm. Res.*, 4 (1987) 480–485.

Hardy, J.G., Lamont, G.L., Evans, D.F., Haga, A.K. and Gamst, O.N., Evaluation of an enteric coated naproxen pellet formulation. *Aliment. Pharmacol. Ther.*, 5 (1991) 69–75.

Kelly, K.A., Motility of the stomach and gastroduodenal junction. In Johnson, L.R. (Ed.), *Physiology of the Gastrointestinal Tract*, Vol. 1, Raven, New York, 1981, pp. 393–410.

Meyer, J.H., Motility of the stomach and gastroduodenal junction. In Johnson, L.R. (Ed.), *Physiology of the Gastrointestinal Tract*, 2nd Edn, Raven, New York, 1987, pp. 613–629.

Singh, N.N., Jamali, F., Pasutto, F.M., Russell, A.S., Coutts, R.T. and Drader, K.S., Pharmacokinetics of the enantiomers of tiaprofenic acid in humans. *J. Pharm. Sci.*, 75 (1986) 439–442.

Szurszewski, J.H., A migrating electric complex of the canine small intestine. *Am. J. Physiol.*, 217 (1969) 1757–1763.

Tothill, P., McLoughlin, G.P. and Heading, R.C. Techniques and errors in scintigraphic measurements of gastric emptying. *J. Nucl. Med.*, 19 (1978) 256–261.

Ward, G.T., Stead, J.A. and Freeman, M., A rapid and specific method for the determination of tiaprofenic acid in human plasma by high performance liquid chromatography. *J. Liq. Chromatogr.*, 5 (1982) 165–174.

Wilding, I.R., Davis, S.S., Melia, C.D., Hardy, J.G., Evans, D.F., Short, A.H., Sparrow, R.A. and Yeh, K.C., Characterisation of the in vivo behaviour of a controlled release formulation of levodopa (Sinemet CR). *Clin. Neuropharm.*, 14 (1991a) 305–321.

Wilding, I.R., Hardy, J.G., Maccari, M., Ravelli, V. and Davis, S.S. Scintigraphic and pharmacokinetic assessment of a multiparticulate sustained release formulation of diltiazem. *Int. J. Pharm.*, 76 (1991b) 133–143.