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Gamma-scintigraphic study of the gastrointestinal transit and in vivo dissolution of a controlled release diclofenac sodium formulation in xanthan gum matrices

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Abstract

A xanthan gum matrix controlled release tablet formulation containing diclofenac sodium was evaluated in vitro and was found to release the drug at a uniform rate. The gastrointestinal transit behaviour of the formulation as determined by gamma scintigraphy, using healthy male volunteers under fasted and fed conditions, indicated that gastric emptying was delayed with food intake. In contrast, the small intestinal transit remained practically unchanged under both food statuses. Therefore, the delay in caecal arrival observed in the fed state can be attributed to the delay in gastric emptying. Rate of diclofenac sodium absorption was generally higher in the fed state compared to the fasted state, however the total amount absorbed under both food statuses remained practically the same. The rate of in vivo dissolution of the drug in the fed state was faster compared to that in the fasted state. Thus, at the time of caecal arrival, in vivo dissolution was complete in the fed state, unlike in the fasted state, where almost 60% of the drug was delivered to the colon.

Keywords: Controlled release; Diclofenac sodium; Gamma scintigraphy; Gastrointestinal transit; Xanthan gum matrix

1. Introduction

The gastrointestinal transit behaviour of orally administered dosage forms may depend on such physical properties as density and size (Davis et al., 1986) or whether the dosage form is single or multiparticulate in nature (Coupe et al., 1991). Since these properties are fixed once the choice of the dosage form has been made, it is imperative to study the effect of the physiological and morphological features of the different regions of the gastrointestinal tract on the gastrointestinal transit properties of the dosage form, as drug release and the subsequent bioavailability of the drug largely depends on these variables. This is particularly true for controlled release dosage forms,

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which are designed to release the drug over an extended period of time in the gastrointestinal tract.

Gastric emptying of solid dosage forms is highly variable but is generally delayed in the presence of food (Davis et al., 1984). The small intestine, by virtue of its huge surface area, is the principal site for absorption for most drugs (Koch-Weser and Schechter, 1981; Davis et al., 1984). Transit time through the small intestine typically takes 3–5 h, is fairly constant and is unaffected by food (Cammack et al., 1982; Davis et al., 1984). It follows that any delay in gastric emptying would accordingly cause a delay in caecal arrival of the dosage form. Although some drugs, for example theophylline (Staib et al., 1986) and metoprolol tartrate (Godbillon et al., 1985), have been shown to be absorbed in the large intestine, in general, absorption in this part of the intestine is usually incomplete and erratic (Koch-Weser and Schechter, 1981).

Diclofenac sodium is a non-steroidal anti-inflammatory drug, widely used in the treatment of rheumatoid disorders and other chronic inflammatory diseases (Zuckner, 1986). It is characterized by rapid systemic clearance (Kendall et al., 1979; Willis et al., 1979) and thus necessitates repeated daily dosing when a course of treatment with this drug is required. Therefore, therapy with diclofenac sodium warrants the use of a sustained release formulation for prolonged action and to improve patient compliance (Willis et al., 1981).

Controlled release formulations are, by necessity, more complicated than conventional ones and require more rigorous methods for their evaluation. Therefore, reliance on plasma kinetic measurements alone may not suffice, since they indicate solely the bioavailability of the drug. Additional information regarding the gastrointestinal transit behaviour or in vivo drug release characteristics in the different regions of the gastrointestinal tract can be used to improve its dosage form design.

The purpose of this work was therefore to study the gastrointestinal transit properties and in vivo release of a controlled release tablet formulation of diclofenac sodium under fed and fasted conditions.

2. Materials and methods

2.1. Materials

The following materials were used: diclofenac sodium and magnesium stearate (Nutech Drugs, India), xanthan gum (Rhodigel Caisse Rhone–Poulenc Chemie, France), mefenamic acid (NPCB, Malaysia), acetonitrile (HPLC grade, Mallinkrodt Chemicals, USA), ammonium formate (R&M Chemical, UK), concentrated hydrochloric acid (Mallinkrodt Chemicals, USA), microcrystalline cellulose (Avicel PH-101, FMC Corporation, USA) and Amberlite resin (IRA-420C, 100–200 wet mesh, Sigma Chemical Co., USA).

2.2. Preparation and radiolabelling of the tablets

Matrix controlled release tablets of diclofenac sodium were prepared by wet granulation using the formula indicated below:

Diclofenac sodium	100 g
Xanthan gum	30 g
Microcrystalline cellulose	70 g
Water	100 g

Granules of approximately 200 mg weight containing 100 mg diclofenac sodium were compressed after lubrication with 1% magnesium stearate using a rotary tabletting machine (Chung Yung Industrial, Taiwan) equipped with 8 mm flat-faced punches.

The dimension of the tablets prepared were 8.2 mm in diameter and 4.5 mm thick.

2.3. Radiolabelling the tablets with Technetium-99 (^{99m}-Tc)

Prior to labelling the tablets, a hole of 1 mm diameter was drilled through the center of the tablets (from top to bottom) with an electric driller. The thickness of the tablets was approximately 4 mm. About 50 mg of Amberlite resin was soaked in about 3 ml of ^{99m}Tc (Malaysian Institute of Nuclear Technology) and containing about 2 GBq of activity. The mixture was left for

about 30 min, with intermittent shaking. The supernatant was then discarded and the radiolabelled Amberlite resins were washed thrice, each with 10 ml of normal saline. These were then dried with a hair dryer and two drops of Eudragit NE 40D (Rohm GmbH, Darmstadt, Germany) latex added with a Pastuer pipette. After mixing the latex with the resins into a uniform consistency, a portion was packed into the drilled hole with a spatula avoiding spreading on the surface of the tablet. The radiolabelled tablet was then dried with a hair dryer. The above procedure usually produced an activity of about 100 MBq. To ensure that the radiolabelled material remained within the tablet and did not disintegrate during its passage in the gastrointestinal tract, the tablets were kept for about 20 h at 40°C for coalescence of the Eudragit polymer to occur. This works out to slightly more than three half-lives of ^{99m}Tc, ($t_{1/2} = 6$ h). Thus at the commencement of the study, the activity in the tablet was about 10 MBq. The activity of the labelled tablet were determined using an Atomlab 200 gamma detection well (Biodex Medical System).

2.4. Determination of the density of the tablets

The average density of the tablets was determined using a gas multipycnometer (Quantachrome Corporation, USA). The total weight of ten tablets was divided by their corresponding volume as determined from the multipycnometer. Four measurements were carried out and the average density calculated.

2.5. In vitro dissolution studies

In vitro drug release from the tablets before and after radiolabelling was determined using the paddle method of the USP 23 dissolution apparatus (Sotax, Model AT 7 CH 4008, Switzerland). The test was conducted with 900 ml of distilled water maintained at 37.0 ± 0.5°C at a paddle rotation speed of 100 rpm. Samples of 5 ml volume each were collected at predetermined intervals using an automated fractional collector (SDX, Model FR00-084, Malaysia) and then replenished with the same amount of fresh distilled water over a 12-h period. The amount of drug dissolved was determined spectrophotometrically at a wavelength of 277 nm using a Hitachi U2000 UV/VIS spectrophotometer. The studies were conducted in six replicates.

2.6. In vivo study design

Six healthy male volunteers aged between 25 and 39 years and weighing between 57 and 79 kg took part in the study after providing written informed consent. All were briefed about the nature of the study and product studied. The study was approved by an Ethics Committee on Clinical Studies. These volunteers were not taking any medications before and during the study and had no recent history of gastrointestinal disorders. Drug administration was conducted in a crossover fashion as shown below:

Group	Period		
	I	II	III
1	Labelled tablet (fasted)	Labelled tablet (fed)	Drug solution (fasted)
2	Labelled tablet (fed)	Labelled tablet (fasted)	Drug solution (fasted)

In the fasted state, each volunteer was dosed after an overnight fast one radiolabelled tablet with 150 ml of mineral water containing 5 MBq of activity for the purpose of outlining the stomach. The mineral water was radiolabelled by reconstituting 5 mg of diethylenetriamine pentaacetic acid, DTPA (Radpharm Scientific, Austrailia) with 2 ml of ^{99m}Tc containing 5 MBq activity, and allowing to stand for about 10 min. This was then added to enough mineral water to make 150 ml. In the case of fed state, each volunteer was administered one radiolabelled tablet immediately after a standard high fat-breakfast with 150 ml of the mineral water containing the radiolabel as above. The washout

period between the two phases of study was 1 week. On a third occasion, after a washout period of 1 week, each volunteer was administered 100 mg of diclofenac sodium dissolved in 150 ml of phosphate buffer solution (pH 7) USP, after an overnight fast.

2.7. Food intake

Food and drink were withheld for at least 2 h after dosing. Lunch and dinner comprising chicken and rice were served at 4 and 10 h after dosing respectively in all the cases. In the case of the fed state, a standard high-fat breakfast comprising two slices of buttered bread, one fried egg, one slice of cheese, one chicken sausage, one boiled potato, 240 ml of whole milk and 180 ml of orange juice was served after an overnight fast. This recipe was adopted with slight modification from 'In Vivo Bioequivalence Guidelines' USP23-NF18 (1995).

2.8. Blood sampling

Blood samples of about 5 ml volume were taken via an in-dwelling cannula placed in the forearm into heparinized containers at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 18, 24, 30 and 36 h after dosing. For the buffered drug solution, blood samples were collected at 0 (pre-dose) 5, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after dosing. The blood samples were centrifuged at 3500 rpm and the plasma separated into plain containers and then kept frozen at -20°C until analysis.

2.9. Measurement of diclofenac sodium concentration in plasma

Diclofenac sodium concentration in plasma was determined by a high performance liquid chromatographic (HPLC) method. The HPLC system comprised of a Gilson 305 pump, a Gilson 119 UV/VIS detector (Gilson Medical Electronics, France) a YMC-Pack ODS-A column [5 μm, 150×4.6 mm ID], (Japan). The mobile phase comprised 0.01 M ammonium formate and acetonitrile (50:50, v/v) adjusted to pH 3.5 with concentrated HCl. Analysis was run at a flow rate of 1.5 ml/min with the detector operating at 280 nm.

Prior to analysis, diclofenac sodium was extracted from plasma by the following procedure. A 0.5 ml aliquot of plasma was accurately measured into a 2.0 ml Eppendorf microcentrifuge tube followed by the addition of 50 μl of 20 μg/ml mefenamic acid in 50% methanol as internal standard, 50 μl of 4M HCl and 1.5 ml of dichloromethane as extraction solvent. The mixture was vortexed for 1 min and centrifuged at 14 000 rpm for 15 min. The organic layer was transferred into a new Eppendorf tube and evaporated to dryness at 45°C under nitrogen gas. The extraction was repeated with 1 ml of fresh solvent and the supernatant added to the dried residue of the first extraction. After evaporation to dryness, the dried residue was reconstituted with 80 μl of mobile phase and 50 μl injected on to the column.

Standards of diclofenac sodium were prepared by spiking into drug-free plasma, a concentration range of 31–8000 ng/ml. Standard curve evaluations of the precision, accuracy and recovery values of the assay method were performed using these standards. The recovery for diclofenac sodium and the internal standard were all above 90% whilst the coefficient of variation and error rate for both within and between-day assays were smaller than 10% in the concentration range used. In addition, detector response was found to be linear over this range.

2.10. Gastrointestinal transit monitoring

Two reference markers of 1 MBq activity each were firmly attached to the skin of the volunteers at the left lobe of the liver and the lower right coastal margin for the purpose of repositioning when image acquisition was resumed. At the moment of ingestion of the tablet, the volunteer was seated comfortably in front of the anterior head of a gamma camera (ADAC Solus Dual Head Imaging System). Blood samples were taken simultaneously at predetermined intervals described earlier. The data collection and storage was done on-line a computer (Pegasy's Tower, ADAC Lab). Images were viewed on a computer

monitor (ADAC Lab). Acquisition was performed at 60 s per frame until gastric emptying was complete. Thereafter, static images were acquired at 10–15 min intervals. During this time, the volunteer was allowed to move away from the camera. After about 6 h of acquisition, the capture time was increased to 120 s per frame to compensate for the radioactive decay of the ^{99m}Tc (half-life of ^{99m}Tc is about 6 h). Image acquisition was continued until caecal arrival of the tablet.

2.11. Data analysis

The in vivo dissolution of diclofenac sodium under fasted and fed conditions were estimated using a model independent deconvolution technique described by Langenbucher and Moller (1983). This numerical algorithm requires that the output and weighting functions be entered on each occasion for a set of regular time points, which are invariant. Experimentally measured values of concentration time data were interpolated as described by Langenbucher and Moller (1983). An inherent sensitivity of the algorithm however, is a tendency towards instability whenever there is noise in the supplied raw data (Langenbucher and Moller, 1983). This can generally be avoided by initial smoothening of the raw data. Since multiple peaks were observed in the plasma concentration profiles of most of the volunteers in the present study, and can affect the computation, the mean plasma values of the six volunteers, which provided a smoother curve, were used. Thus, the mean plasma concentration under fasted and fed conditions were used as the output functions whilst the mean plasma concentration obtained after administration of the drug solution was used as the weighting function.

Other pharmacokinetic parameters studied were, the area under plasma concentration versus time curve ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}) and the associated time taken to reach the maximum plasma concentration (T_{max}). C_{max} and T_{max} were obtained directly from the raw data (Weiner et al., 1981) whilst the area under the plasma concentration time curve was calculated by adding the area from time zero to the last measurable concentration AUC_{0-t}, to the area obtained from the last measurable concentration to infinity, $AUC_{t-\infty}$. The former was calculated using the trapezoidal formula. Calculation of the elimination rate constant from the plasma concentration time profile of sustained release tablet formulations containing diclofenac sodium has been reported to be unreliable due to multiple peaks in the plasma concentration time profile (Suleiman et al., 1989; Damman et al., 1993) as was found in the present study. Therefore, $AUC_{t-\infty}$ was calculated by extrapolating the last measurable plasma concentration to the time axis (Nace and Wood, 1987). In all the cases, the estimated $AUC_{t-\infty}$ was found to be less than 15% of $AUC_{0-\infty}$.

2.12. Analysis of gamma scintigrams

Both gastric emptying and caecal arrival times were determined from the images obtained from the gamma camera. The gastric emptying time (GET) was taken to be the time when the tablet just left the area outlined by the radiolabelled solution in the stomach. Since the radiolabelled solution emptied faster than the tablet, it was possible to outline the orocaecal junction prior to the ceacal arrival of the tablet. Consequently, the caecal arrival time (CAT) was the time when the tablet just appeared to have entered the caecum. The small intestinal transit time (SITT) was then calculated by subtracting the GET from the CAT.

2.13. Statistical analysis

$AUC_{0-\infty}$ and C_{max} were analyzed statistically using an analysis of variance procedure (ANOVA) that distinguishes effects due to group, subject/group, period and treatment (Wagner, 1975) after logarithmic transformation. T_{max} values were analyzed using the Wilcoxon signed-rank test for paired samples, whilst the GET, SITT and CAT values were compared using the ANOVA procedure described above. A statistical significance was indicated when $P < 0.05$.

3. Results and discussion

3.1. In vitro dissolution

The in vitro dissolution profiles of the diclofenac sodium controlled release tablet preparation before and after radiolabelling are shown in Fig. 1. It is apparent that the two profiles were essentially superimposable, indicating that the labelling technique did not cause any change in the rate of drug release.

Most techniques of radiolabelling tablets using ^{99m}Tc have involved the incorporation of the radioisotope on a suitable material such as DTPA or Amberlite by chelating or ion-exchange mechanisms (Casey et al., 1976; Daly et al., 1982) followed by mixing with the other excipients and then compressing into tablets. Another method of labelling that has been used is the adsorption of a solution of the radioisotope on a preformulated tablet containing Amberlite (Sugito et al., 1990). In both methods the incorporation of the chelating agent may alter the drug release profile of the original tablet formulation and may not be suitable for preformulated marketed products.

In the present study, the amount of material lost due to drilling the hole in the tablets was negligible, and there was not much change in the density of the tablet before and after radiolabelling (1.49 and 1.44 g/cc, respectively). Moreover, it was also observed from the dissolution study that the radiolabel did not get detached throughout the duration of the study as the tablet slowly eroded away. Thus, the method employed in the present study is not only simple to carry out, but also applicable to preformulated products.

3.2. In vivo bioavailability under fasted and fed state

The mean plasma diclofenac sodium concentration profiles of the tablet preparation dosed fasted and fed are shown in Fig. 2, while that of the solution in Fig. 3. Higher plasma levels were achieved under fed condition for up to 10 h post dosing but decline was more rapid thereafter, suggesting a faster rate of drug absorption when the preparation was dosed with food. In addition, multiple peaks were observed, especially in the fasted state, in accord with the findings of Chan et al. (1990). A lag time of absorption was observed in two volunteers dosed fasted and three dosed in the fed state (Table 1) after administration of the tablet preparation, but not for the drug solution. The lag time was estimated by extrapolating the initial ascending portion of the individual plasma concentration versus time curves to the time axis.

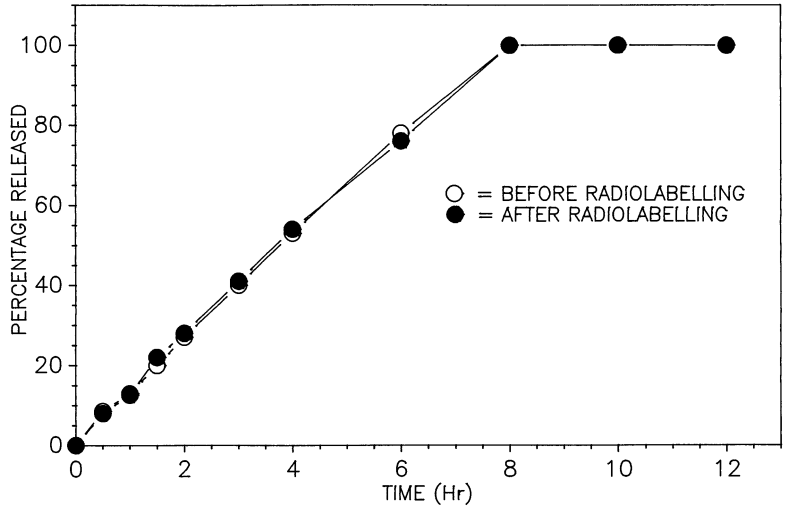

Fig. 1. In vitro diclofenac sodium release before and after radiolabelling.

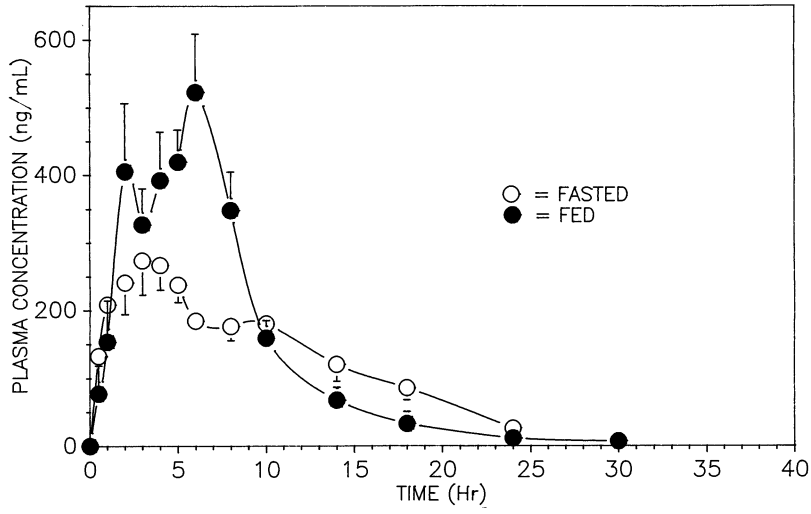

Fig. 2. Mean diclofenac sodium concentration under fasted and fed situations.

However, the lag time observed was relatively brief. In the case of the drug solution, plasma drug levels increased achieving a peak at approximately 0.5 h after dosing but also declined rapidly thereafter. In addition, no multiple peaks were observed in the individual plasma profiles of the volunteers.

The mean lag time, C_{max}, T_{max} and $AUC_{0-\infty}$ obtained under fasted and fed conditions after administration of the tablets are shown in Table 1. It can be seen that the T_{max} values were increased significantly ($P = 0.016$) when the preparation was dosed in the fed state, being consistent with the findings of Willis et al. (1981), Chan et al. (1990) and Thakker et al. (1992). Relating these values to the gastric emptying of the tablets as determined using gamma scintigraphy (Table 2) it can be seen that there was a direct relationship

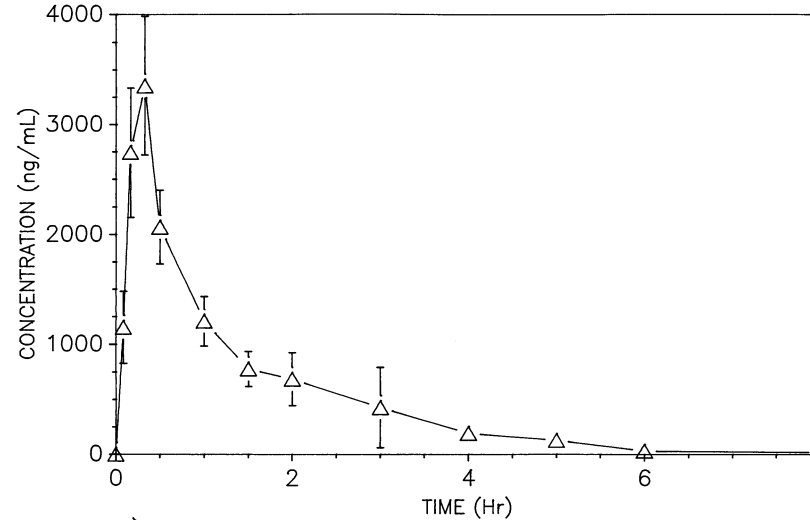

Fig. 3. Mean diclofenac sodium concentration after administration of the buffered drug solution.

Table 1
Numerical values of T_{lag}, C_{max}, T_{max} and $AUC_{0-\infty}$ obtained under fasted and fed states

Volunteer	T_{lag} (h)		C_{max} (ng/ml)		T_{max} (h)		$AUC_{0-\infty}$ (h ng/ml)	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
1	0.3	0	187.3	866.1	4	6	1832.8	4547.9
2	0	0.3	430.4	542.6	1	6	4523.7	5198.2
3	0	0.7	372.8	438.9	1	6	3555.0	2857.5
4	0.2	0.3	306.8	800.6	4	5	2559.7	4204.2
5	0	0	282.5	680.3	3	4	4876.9	3651.3
6	0	0	502.3	640.5	3	6	3707.1	4482.8
Mean	0.08	0.21	347.0	661.5	2.6	5.5	3509.2	4156.9
S.D.	0.13	0.27	112.2	158.5	1.3	0.8	1153.5	811.2

between T_{max} and gastric emptying. When dosed with food, gastric emptying was delayed and the T_{max} values were correspondingly increased. Notwithstanding the longer T_{max} however, the preparation also achieved higher C_{max} values when dosed in the fed state. Thus, it appeared that there might be some interaction between the food and the formulation resulting in a faster release and absorption.

There was an almost two-fold increase ($P = 0.055$) in the mean C_{max} value in the fed state as shown in Table 1, being consistent with the findings of Riad and Sawchuck (1989). Suryakumar et al. (1992) also reported a significant increase in C_{max} with concomitant administration of an enteric-coated diclofenac sodium tablet with famotidine, an H_2 receptor antagonist. However a reduction in C_{max} has also been reported by Willis et al. (1981) with enteric coated tablets when dosed in the fed state, whilst Zmeili et al. (1996) reported no significant change in C_{max} in the fasted and the fed states with their enteric-coated controlled release tablet.

Hydration rates of xanthan gum matrices have been shown to be slower at lower pH values. Under such circumstances, the matrix structure rapidly loses its integrity due to the absence of the outer hydrated barrier, permitting rapid influx of water into the matrix system with attendant faster rate of drug release (Fu Lu et al., 1991). The higher C_{max} values observed in the fed state in present study may be attributable to a relatively longer duration of exposure of the tablets to the lower pH environment of the stomach because of the delayed gastric emptying (Table 1). Therefore, at the time of gastric emptying, diclofenac sodium release from the tablets was more facilitated in the fed state compared to the fasted state.

Table 2
Individual GET, SITT and CAT values obtained under fasted and fed states

Subject	Fasted (min)			Fed (min)		
	GET	SITT	CAT	GET	SITT	CAT
1	83	216	229	325	200	525
2	118	211	329	296	192	488
3	98	198	296	375	205	580
4	102	138	240	95	150	245
5	75	136	211	380	181	561
6	60	223	283	315	210	525
Mean	89.3	187.0	276.3	297.6	189.6	487.3
S.D.	20.8	39.5	43.1	104.2	21.9	122.9

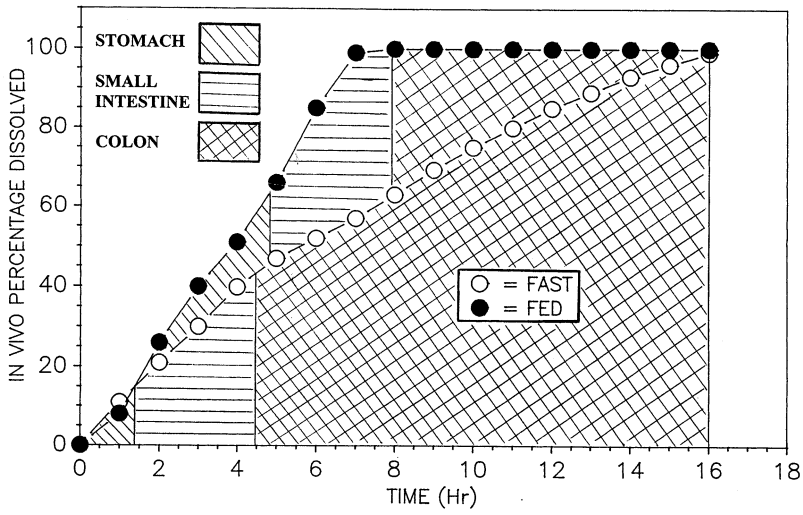

Fig. 4. Mean diclofenac sodium in vivo dissolution under fasted and fed states and transit times.

Although a slightly higher mean $AUC_{0-\infty}$ value was obtained in the fed condition, there was no statistically significant difference in the $AUC_{0-\infty}$ values between the two dietary states ($P = 0.343$). Also there was no statistically significant difference when the $AUC_{0-\infty}$ values of these dietary states were compared to that of the buffered drug solution ($P = 0.369$). These results are in agreement with the findings of Riad and Sawchuck (1989). It may be inferred that food does not affect the extent of drug absorption of the preparation.

3.3. In vivo dissolution

Because of instability of numerical algorithms when there is noise in the supplied raw data, as was observed in the present study due to multiple peaks, (Langenbucher and Moller, 1983) the mean plasma concentration obtained in the fasted and fed conditions were used as the plasma response data because the mean values gave a smoother curve. Whilst the use of individual data sets would be a more appropriate analysis, the use of the mean values nevertheless still provided an insight in comparing the in vivo dissolution between the two dietary states.

The mean percentage input or in vivo dissolution profiles obtained after deconvolution of the plasma response data under fasted and fed conditions are presented in Fig. 4 together with the residence times of the preparation in the various regions of the gastrointestinal tract. It can be seen that an initial delay in dissolution occurred in the presence of food. This was transient however, lasting about 1 h. Thereafter, release was rapid reaching a plateau within 6 h, confirming the fact that gastric emptying of dissolved/released diclofenac sodium was occurring even in the presence of food. On the other hand, drug release was more gradual and somewhat slower under the fasted condition. Thus, comparing the two in vivo release profiles, it can be inferred that under the fed state, there was a transient delay in in vivo drug dissolution followed by a more rapid dissolution. This explains the higher C_{max} achieved under the fed condition compared to the fasted state.

Table 3 shows the mean percentage drug dissolved when the preparation was in the different regions of the gastrointestinal tract. In the fasted state, only approximately 15% was dissolved while the tablet was in the stomach, compared to 65% in the fed state. This suggests that, food might have maintained a sufficiently high pH to allow

some dissolution of diclofenac sodium to occur but low enough to affect the hydration of the xanthan gum resulting in a more rapid release as discussed previously. The results of this scintigraphic study clearly indicate that absorption of the drug need not occur only when the tablet has been emptied into the small intestine. In addition, drug release appeared to be completed during residence of the tablet in the small intestine in the fed state (Table 3). In contrast, in vivo dissolution was still incomplete during transit in the small intestine in the fasted state. Dissolution and absorption appeared to be still occurring in the caecum.

At the time of caecal arrival, a substantial amount of diclofenac sodium (approximately 58%) was maintained in the tablets in the fasted state. This as explained earlier might be due to the short GET and effective hydration of the xanthan gum polymer in the small intestine (alkaline pH). On the other hand, tablets had been depleted of diclofenac sodium due to favourable dissolution in the fed state in the small intestine explained earlier. However, in view of the absence of any significant difference in the $AUC_{0-\infty}$ between the fasted and fed states, it follows that dissolution and absorption of most of the delivered drug (58%) in the fasted state was occurring in the large intestine. Hence the concept of 'reserved length' of absorption (Ho et al., 1977) does not appear to apply to diclofenac sodium and therefore the use of this drug as a controlled release formulation is warranted.

Table 3
Percentage of diclofenac sodium dissolved in various regions of the gastrointestinal tract

Site	% Dissolved	
	Fasted	Fed
Stomach	15	65
Small intestine	27	35
Large intestine	58	0

3.4. Gastrointestinal transit times

The individual values of GET, SITT and CAT under fasted and fed conditions are indicated in Table 2. The GET values under fed condition (mean = 297.3 min) were significantly increased ($P = 0.0064$) when compared to those in the fasted state (mean = 89.3 min). However wide inter subject variations in the GET values were observed under both fasted and fed conditions, the magnitude of which is comparable to that reported by Coupe et al. (1991). This may be because gastric emptying is not only affected by the physical properties of the dosage form such as size and density (Sugito et al., 1990), but also by the dietary condition or amount and composition of the meal (Han et al., 1982). Davis et al. (1984) studied the gastric emptying properties of tablets with similar size and density as those used in the present study and reported a mean GET of 164 min in the fed state. GET of 30 min to 24 h have also been reported by several workers with a similar diameter as that used in the present study (Rosswick et al., 1967; Muller-lissner and Blum, 1981; Sjoren and Bogentoft, 1982). Thus, it appears that GET is highly variable among individuals.

The ability of a polymer to take up water from mucous has been shown to be a primary determinant of muco-adhesive potential. In this regard, xanthan gum has the ability to potentially increase the stomach retention time through bio-adhesion or swelling (Tobyn et al., 1996). This rather variable parameter may further exert some uncertainty in GET.

The average SITT of dosage forms is now generally accepted to be 180 min ($\pm$ 60 min) and is apparently unaffected by physical form (Davis et al., 1986) or dietary condition (Christensen et al., 1985). The average SITT under fasted and fed conditions obtained in the present study were 187 and 189.6 min, respectively, the difference being not statistically different ($P = 0.799$) and is in good agreement with that observed by the above workers (Christensen et al., 1985; Davis et al., 1986). The SITT also appeared to be less variable as indicated by the smaller standard deviation

compared to GET, which further indicates that rate of transit through the small intestine is more consistent and is affected by fewer physiological variables than gastric emptying.

The delay in gastric emptying in the fed state was manifested in an increase in mean CAT with a time of 487.3 min against 276.3 min in the fasted state. Statistical analysis showed a significant difference ($P = 0.0163$) between the CAT values of the two states. Since the SITT between the food status were not significantly different, it is clear therefore that the difference in CAT times was attributable to differences in GET. On the whole however, the GET, SITT and CAT values obtained in the present study are comparable to those reported in the literature (Han et al., 1982; Christensen et al., 1985; Davis et al., 1986).

4. Conclusion

The radiolabelling technique used in the present study appears to be applicable not only to laboratory scale formulations but to preformulated ones as well. Gastric emptying was delayed in the presence of food, which consequently led to a delay in the caecal arrival of the tablet. This was the case because the SITT remained practically the same under both dietary conditions. Rate of absorption was higher in the fed state compared to the fasted state, due to the longer exposure of xanthan gum matrix to the acidic environment of the stomach. Results of the in vivo dissolution confirmed that dissolution of diclofenac sodium was occurring in the fed state, such that, at the time of caecal arrival, the tablets were depleted of diclofenac sodium. On the other hand, a substantial amount of drug was retained in the tablets during the gastrointestinal transit in the stomach and the small intestine in the fasted state. Nevertheless, it appears that the remaining portion of diclofenac sodium was released and absorbed in the caecum, suggesting that absorption of diclofenac sodium is not limited to the small intestine only, but the large intestine as well.

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