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Research Papers

Pharmacokinetics and in vivo scintigraphic monitoring of a sustained release acetylsalicylic acid formulation

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Summary

The in vivo dissolution and pharmacokinetics of a sustained release aspirin formulation labelled with [^{99m}Tc]diethylenetriaminepentaacetic acid has been monitored in 5 subjects by the use of gamma scintigraphy and drug analysis undertaken of blood and urine samples. The data obtained enabled the position of the tablet in vivo to be related to the plasma and urinary salicylate levels. The study confirms the sustained release properties of the cellulose acetate phthalate formulation.

Introduction

Tablets intended for oral administration can be broadly categorized into 3 forms. These are rapidly-dissolving formulations, gastro-resistant (e.g. enteric-coated) preparations and sustained release dosage forms.

The ingestion of conventional acetylsalicylic acid (aspirin) tablets is associated with an increased incidence of gastric mucosal bleeding (Croft and Wood, 1967; Leonards and Levy, 1972). The gastric irritation is pH-dependent since the drug is

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largely ionized above pH 4. To attenuate the gastric side-effects, buffered preparations of acetylsalicylic acid have been introduced, of varying neutralizing capacity. However, to buffer the gastric contents above this critical pH may require considerable amounts of buffers, markedly increasing the size of the tablet. An alternative approach is to formulate the drug in a polymer which is insoluble at an acidic pH thus retarding the dissolution in the stomach. A further consideration is the required plasma concentration–time profile. Long-term therapy with non-steroidal anti-inflammatory agents can be improved by avoidance of the plasma concentration peaks and troughs seen in multiple dose therapy. Sustained release dosage forms offer a method of minimizing fluctuations in the plasma concentrations with a simple treatment schedule.

A sustained release acetylsalicylic acid formulation (Zorprin, Boots Pharmaceuticals) containing cellulose acetate phthalate has been designed so that the drug dissolves slowly in the acid medium of the stomach, to minimize gastric side-effects, and releases the drug more rapidly as it moves down the intestine. Although in vitro tests and bioavailability trials show that the preparation has sustained release properties, no direct evidence of the behaviour of the tablet in the gastrointestinal tract has been obtained. In particular, it is relevant to determine the site of disintegration of the tablet in the gut.

The monitoring of the in vivo dissolution rates of tablets and capsules using gamma scintigraphy has become established over recent years (Daly et al., 1982; Davis et al., 1982). In the study described in this paper a small amount of a non-absorbable radionuclide-labelled compound has been incorporated into the tablet. This has facilitated the study of the relationship between the blood levels of salicylate and the position of the preparation in the gastrointestinal tract.

Materials and Methods

Preparation of the tablets

Technetium-99m pertechnetate in 2 ml saline obtained by elution from a generator was used to prepare [^{99m}Tc]-labelled diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) solution containing 10 mg DTPA labelled with 75 MBq ^{99m}Tc (C.I.S. (U.K.), London). This was dried at an oven temperature of 80°C for 10 min and the resulting powder mixed with aspirin B.P. (800 mg), maize starch B.P. (40 mg) and cellulose acetate phthalate (10 mg). Tablets, of nominal weight 860 mg were compressed on an instrumented Manesty F3 machine using a 12.5 mm diameter flat-faced punch and die at an upper punch compaction pressure of 172 MN · m^{-2}. Tablets outside of the weight range 840–880 mg were rejected. At the time of administration the tablets contained approximately 4 MBq ^{99m}Tc.

In vitro dissolution tests

The in vitro dissolution rates of aspirin and [^{99m}Tc]DTPA from the laboratory-prepared tablets were compared with aspirin release from the commercial product (Zorprin) using the USP Method II apparatus (Erweka DT-D6), with a rotation

speed of 100 rpm. The salicylate released was continuously monitored by pumping the dissolution media (citric acid–phosphate buffer, pH = 7.4) through a spectrophotometer (Kontron, Uvikon 810) fitted with an automatic 6-cell changer. The absorbance values for each cell, were measured at the isosbestic point of salicylic acid and the parent drug (266 nm). The release of [^{99m}Tc]DTPA was measured by periodically withdrawing samples from the dissolution vessels and determining the radioactivity present using an automatic gamma counter.

In vivo studies

Five healthy male volunteers (age range 21–24 years) each swallowed a radiolabelled tablet together with 200 ml water. The subjects had fasted overnight and had been allowed a light breakfast. The water contained a small amount of [^{113m}In]DTPA (2 MBq) to image the stomach. Small exterior markers containing ^{99m}Tc were taped to the anterior and posterior surfaces of the subject, over the liver to facilitate repositioning of the subject during imaging and to aid identification of the position of the tablet.

Imaging was undertaken with each subject standing, using a gamma camera having a 40 cm diameter field of view, fitted with a medium energy (400 keV maximum) parallel hole collimator. Anterior and posterior images, each of 60 s duration were taken at approximately half-hour intervals for a period of 8 h and the data recorded on computer for analysis. Subsequently regions of interest were defined around the images of the tablet and the activity remaining in the tablet quantified. Corrections were applied for background activity, counts arising from [^{113m}In]DTPA solution and for radioactive decay. Geometric means of the corrected anterior and posterior count rates were used to derive activity–time plots as described by Daly et al. (1982).

Pharmacokinetic studies

Blood samples were taken from an indwelling cannula before the administration of the tablets and then at 0.5, 1, 2 and 4 h post-drug administration. Further venepunctures were performed at 8, 10, 12, 24, 32 and 48 h to complete the plasma concentration time profile. The blood was taken into heparinized tubes on each occasion, centrifuged and 5 ml plasma frozen at −20°C and stored before analysis. Total urine collections were obtained at regular intervals up to 48 h after the dose. Salicylate determinations were carried out using the method of Trinder (1954).

Results and Discussion

The application of gamma scintigraphy to study the gastric emptying of model dosage forms using solutions of [^{99m}Tc]DTPA or [^{99m}Tc]-labelled anion exchange resins is well established (Casey et al., 1976; Curl et al., 1980). The technique has also been used to study the oesophageal transit of tablets and capsules (Fisher et al., 1982) and to monitor the spread of rectally administered foams (Hay, 1982). However, the determination of the exact position of a tablet in the intestines is more

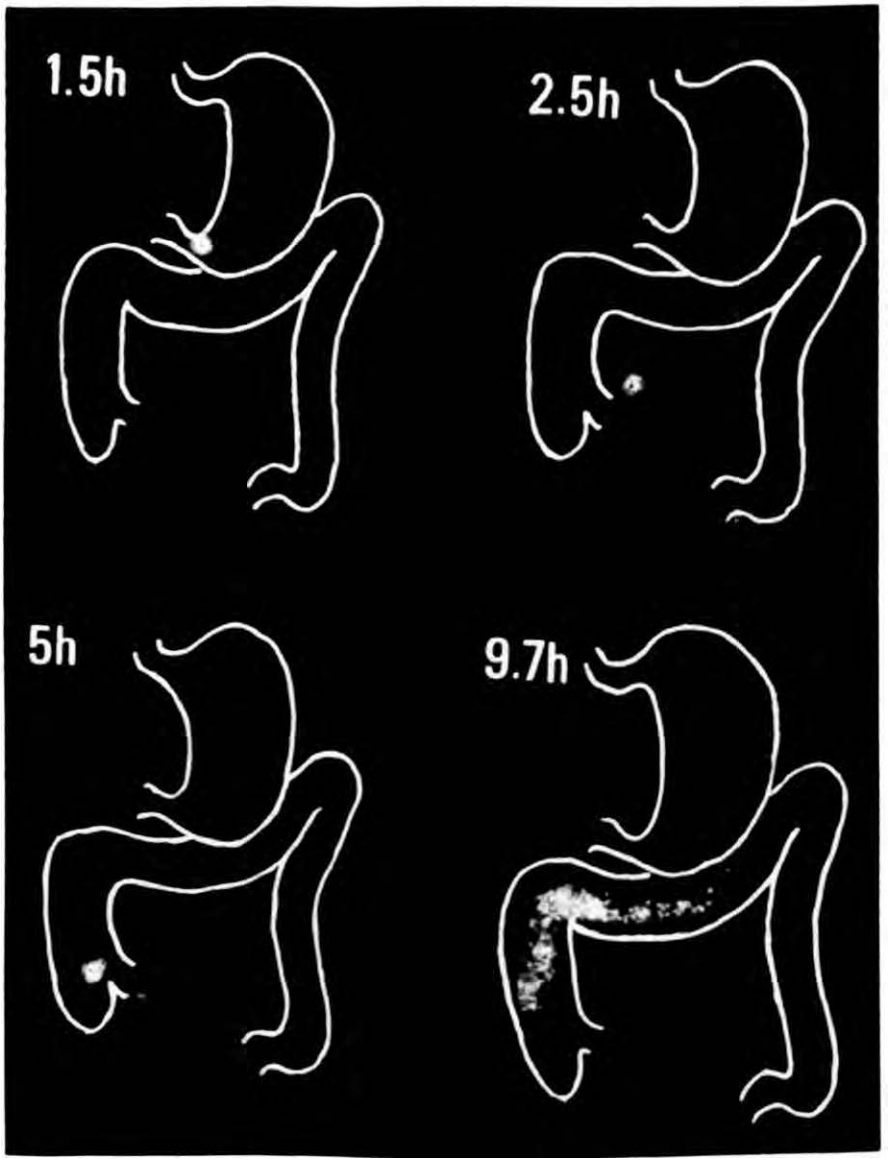

Fig. 1. Scintigraphic images of the tablet in the gastrointestinal tract at 1.5, 2.5, 5 and 9.7 h after dosing.

TABLE 1

GASTROINTESTINAL TRANSIT TIMES OF SINGLE TABLETS DERIVED FROM SCINTIGRAPHIC DATA

Subject	Gastric emptying	Arrival at caecum
1	0.5 h	3.9 h
2	0.3 h	5.0 h
3	5.0 h	7.0 h
4	2.3 h	7.3 h
5	1.8 h	c.8 h *

* Clear image of tablet not seen.

difficult to establish by this technique. The morphology of the large bowel is characteristic and less complex in shape than the small intestine and it was therefore possible to monitor the appearance of the preparation in the colon and thereby

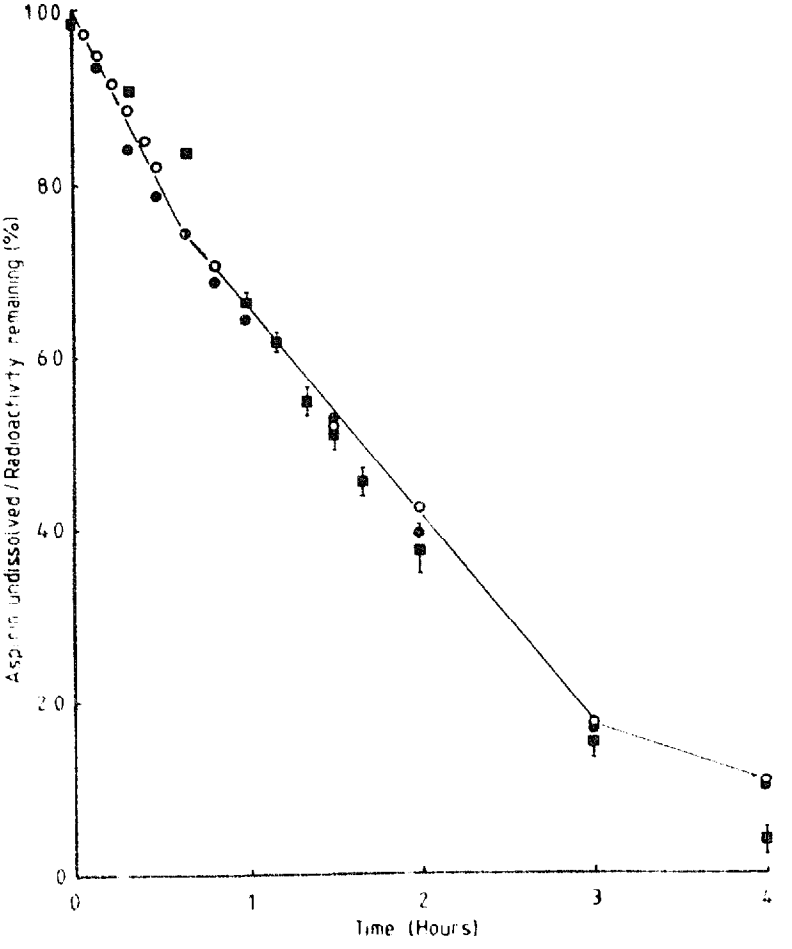

Fig. 2. A comparison of the in vitro dissolution rate using USP Method 2 of acetylsalicylic acid + salicylic acid and [^{99m}Tc]DTPA from sustained release (Zorprin) tablets. Key: ○, salicylates remaining in commercial 'Zorprin' tablets; ●, salicylates remaining in radiolabelled tablets; ■, [^{99m}Tc]DTPA activity in tablets. Data points cover the standard deviation of the mean of 4 determinations.

deduce the transit time through the small intestine.

Fig. 1 shows the computer-printouts of images for one subject of the [^{99m}Tc]-labelled tablets at various times after administration. The preparations were observed to remain intact in the stomach with residence times of up to 2.3 h in 4 subjects (Table 1). The tablet could be seen in the ileum at 2.5 h, whilst at approximately 8 h most activity was observed in the colon. Fig. 1 shows the disintegrated tablet clearly outlining the ascending and transverse sections of the colon by 9.7 h.

In subject 3, the tablet remained in the pyloric antrum for 4 h. This region of the stomach is devoid of parietal cells, and since it is nearest to the duodenum, may be exposed to the neutralizing effect of bile. Thus the local pH may be relatively high. In this subject, a lag in the release of [^{99m}Tc]DTPA was not apparent. Similarly, the plasma salicylate concentration–time profile was indistinguishable from that of the other 4 subjects.

In vitro dissolution tests carried out at pH 7.4 showed that the dissolution of both compounds (acetylsalicylic acid and [^{99m}Tc]DTPA) was rapid (Fig. 2). It was observed that the dissolution of the tablets prepared in the laboratory and containing the radionuclide marker, proceeded at the same rate as the commercial Zorprin samples. With decrease in pH, the rate of release of the drug and the radionuclide marker from the matrix was slower and at pH 4.6, the rate of release of the acetylsalicylic acid was markedly retarded compared with DTPA.

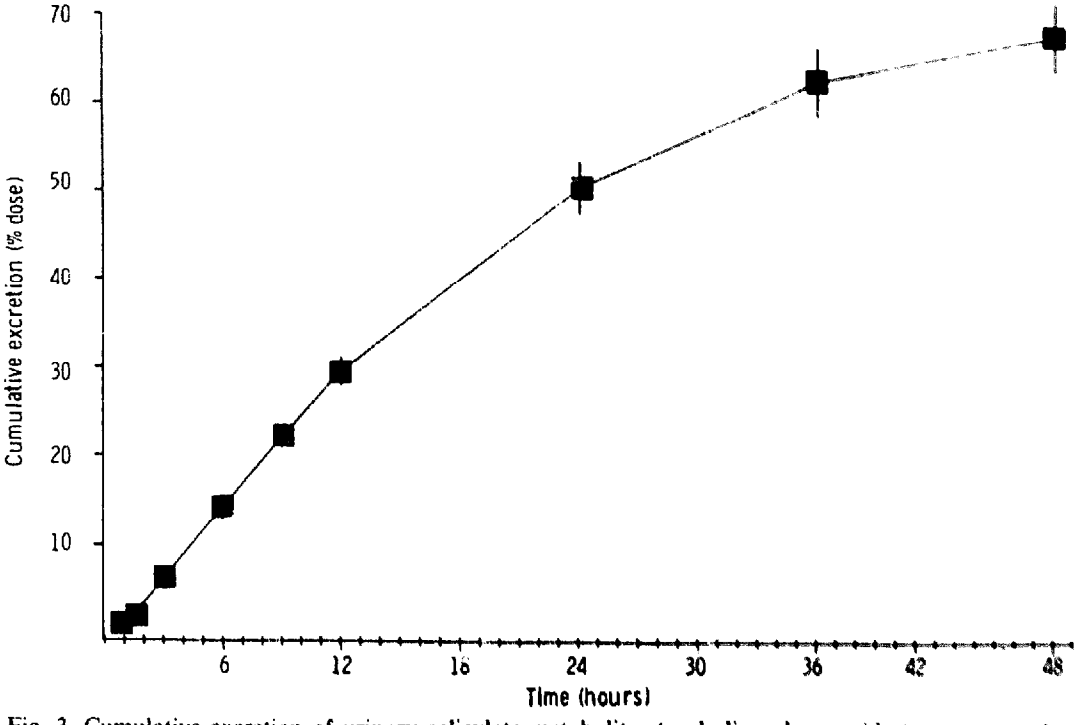

Fig. 3. Cumulative excretion of urinary salicylate metabolites (excluding glucuronides) as percent dose administered following oral administration of 800 mg aspirin as a modified Zorprin formulation. (Mean ± 1 S.D., n = 5 subjects.)

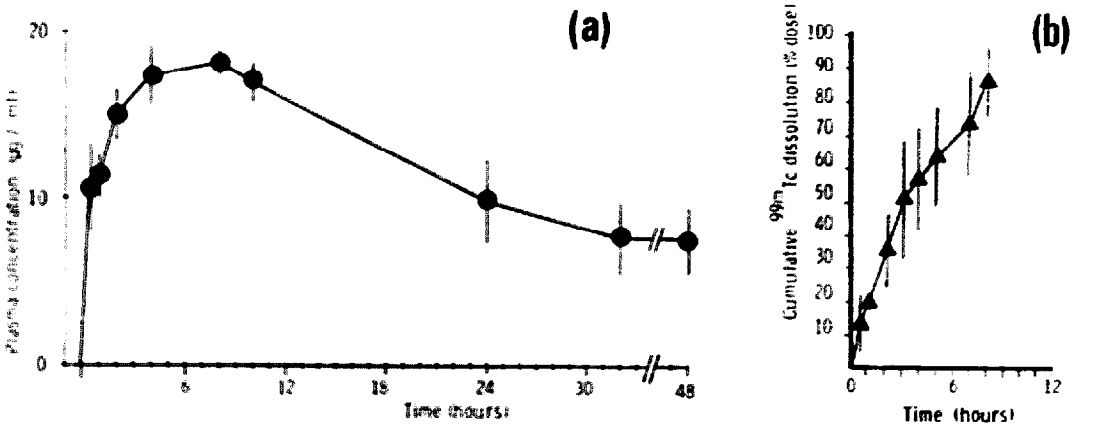

Fig. 4. Comparison of the mean plasma salicylate concentration–time profile (a) with the in vivo release of [^{99m}Tc]DTPA (b) from modified Zorprin tablets. (Mean ± 1 S.D., n = 5 subjects.)

The cumulative urinary excretion of acetylsalicylic acid and metabolites was monitored for the 48 h following drug administration, and the results shown in Fig. 3. The total excreted salicylate metabolites, as measured by reaction with Trinder's

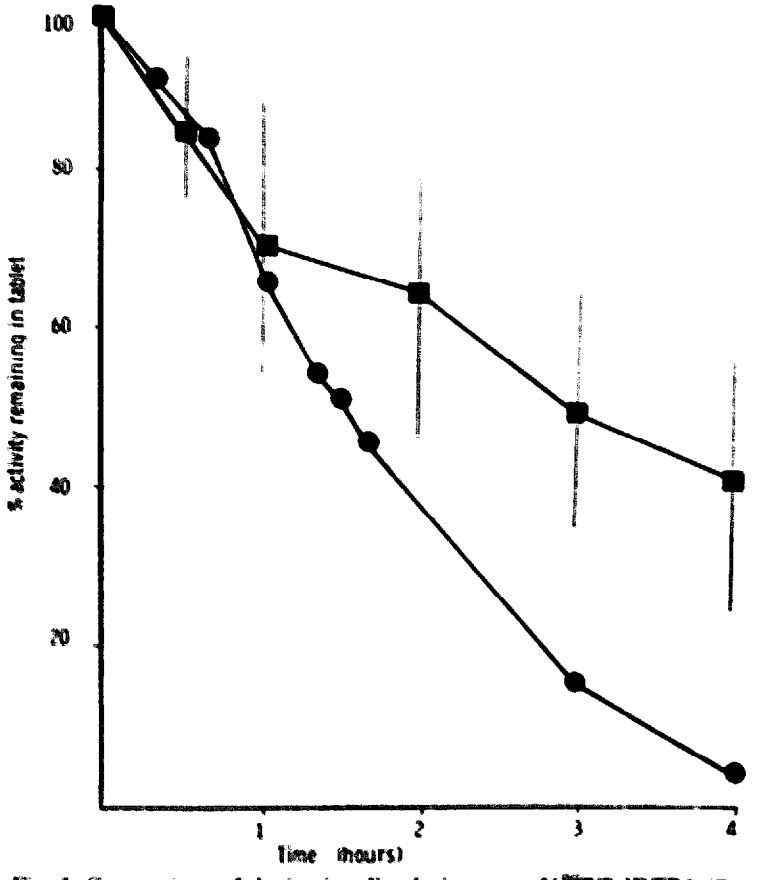

Fig. 5. Comparison of the in vivo dissolution rate of [^{99m}Tc]DTPA (■) with the in vitro dissolution rate of acetylsalicylic acid + salicylic acid (●) using U.S.P. Method 2. Mean ± 1 S.D.; n = 5 subjects for in vivo determinations; data points cover the standard deviation of the mean for the in vitro measurements.

reagent was 70%. This figure excludes the glucuronides which do not react with the reagent unless hydrolyzed prior to estimation. The glucuronides normally comprise 20–30% of the metabolites (Levy, 1961) so it can be assumed that the bioavailability of the product was high. Fig. 4a shows the mean plasma salicylate concentration–time profile in 5 volunteers. A mean plasma peak concentration of 18 $\mu g \cdot ml^{-1}$ (S.D. $\pm$ 2 $\mu g \cdot ml^{-1}$) was achieved at 8 h. The cumulative in vivo dissolution of the [^{99m}Tc]DTPA is shown in Fig. 4b. As may be noted, the dissolution–time profile approximates to zero-order release and correlated well with the absorption phase of the drug. Fig. 5 shows the comparison between the in vivo and the in vitro dissolution of [^{99m}Tc]DTPA from the Zorprin formulation. Dissolution rates estimated from in vivo measurements were approximately half of those measured using the in vitro dissolution test. The slower dissolution times measured in vivo probably reflect both the smaller volume of aqueous phase for dissolution of the tablet (and hence the absence of 'sink' conditions in the gut) and less agitation, causing stagnant diffusion layers around the tablet, which decrease the rate of release of drug.

Conclusions

The present study has confirmed the sustained release properties in vivo of this formulation using pharmacokinetic and scintigraphic techniques. Release of [^{99m}Tc]DTPA from the tablet approximated to a zero-order release profile over a period of 8 h and correlated well with the absorption phase of the drug.

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