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Gastrointestinal transit of an osmotic tablet drug delivery system

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The gastrointestinal transit of a radiolabelled osmotic tablet drug delivery system has been monitored in groups of young and elderly healthy subjects, using gamma scintigraphy. The gastric emptying and small intestinal transit times were similar for both groups of subjects. The units were observed to move through the gastrointestinal tract at about the same rate as the released contents, arriving at the caecum on average 7 h after dosing. The data suggest that tablet adhesion to the mucosal surface is unlikely to be the mechanism responsible for the side effects reported for the indomethacin formulation Osmosin.

The development of a small osmotically-driven device, consisting of an osmotic core containing drug surrounded by a semi-permeable membrane with a delivery orifice, was first described by Theeuwes (1975). This system found application in drug therapy for several drugs including indomethacin, where the sustained zero-order delivery of the drug was thought to be a therapeutic advantage. However the incidence of reported adverse reactions to the controlled release of indomethacin formulation Osmosin, including bleeding and perforation of the intestinal tract, led to withdrawal of this product in late 1983. One suggestion was that the system was adhering to the mucosa and releasing drug in intimate contact with the gut wall.

Florence et al (1984) have shown that the external polymeric film of the Osmosin tablet binds strongly to glass and to porcine oesophagus when partially hydrated. Oesophageal sticking of other formulations, including capsules and tablets, is well documented (Channer & Virjee 1982; Kikendall et al 1983), and is exacerbated if the patient is supine or takes the formulation without water (Fisher et al 1982). However, there have been few reported incidences of tablets sticking further down the gastrointestinal tract.

The technique of gamma scintigraphy has previously been used to follow the transit of dosage systems in man by ourselves and a number of other workers (Davis et al 1984a; Wilson et al 1984; Kaus et al 1984). The objectives of the present work were to design a method of radiolabelling an intact Oros osmotic pump system for scintigraphic studies and to follow the movement of the unit down the gastrointestinal tract of young and aged healthy volunteers.

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Materials and methods

Preparation of tablets. Two batches of tablets were prepared.

Batch A of placebo Osmosin tablets was radiolabelled with indium-111 adsorbed on to Amberlite CG 120 cation exchange resin powder (200–400 mesh) from a solution of indium chloride in 0·04 M hydrochloric acid. A hole 1·5 mm in diameter was drilled centrally into the edge of the tablet to a depth of 7 mm. This was packed with the radiolabelled resin, which had been air-dried in an oven at 100 °C. After introduction of approximately 9 mg of powder, the hole was sealed with epoxy resin adhesive (Araldite Rapid). Care was taken to restrict the resin seal to less than 4 mm^2 of the surface of the edge of the tablet.

The second batch of Tablets (B) was prepared in the same way as batch A. Additionally, [^{99m}Tc]pertechnetate-labelled Amberlite IRA 400 anion exchange resin powder was incorporated into the Araldite adhesive (Fig. 1). At the time of administration, both batches contained 1 MBq indium-111 and batch B, 1–2 MBq technetium-99m. The method of labelling is illustrated in Fig. 1.

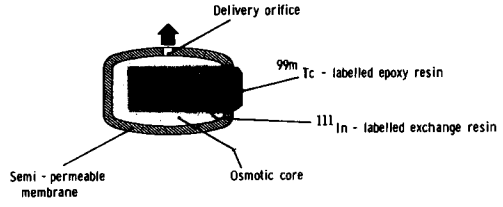

FIG. 1. Schematic diagram of a radiolabelled osmotic tablet. Method of double-isotope labelling of the tablets in Batch B. For Batch A, the tablets were sealed with epoxy resin not labelled with technetium-99m.

In-vitro studies

The mode of release of the indium tracer was investigated in a simple in-vitro experiment. A hole having a diameter slightly less than that of the tablet was made in the base of a small plastic beaker. The beaker was inverted and placed in a 500 ml beaker. The tablet was positioned with its laser drilled delivery orifice aligned with the hole. Water was added until the tablet was completely submerged as shown in Fig. 2. With the system at room temperature (20 °C) and without agita-

tion, tracer release was monitored over 24 h using a gamma camera.

In-vivo studies

Protocol A. Six healthy male volunteers (20–22 years), after giving written informed consent, participated in the study. At 9 am, after an overnight fast, the subjects consumed a breakfast of approximately 50 g cornflakes and 200 ml milk. This was followed by 100 ml orange juice radiolabelled with 3 MBq [^{99m}Tc]-labelled diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) to outline the anatomy of the gastrointestinal tract. A radiolabelled tablet from batch A was then taken with the orange juice; each subject being instructed to swallow the tablet whole and to avoid chewing or biting the unit. An anatomical marker was taped to the abdomen anteriorly overlying the liver to provide a reference point. Immediately after taking the tablet the distributions of the radiolabelled preparations were monitored using a gamma camera as described previously (Davis et al 1984a, b). Images were recorded, with the subject standing, at approximately half-hourly intervals for 8 h and subsequently at about 10 and 24 h after dosing. The subjects were not allowed to eat nor drink during the first hour after taking the tablet and records were kept of all the subsequent eating and drinking.

Protocol B. Six healthy female subjects (62–75 years) participated in the study after giving written informed consent. The subject preparation, dosing and imaging procedures were similar to those adopted in protocol A. The changes in procedure were: (a) each tablet was radiolabelled with both indium-111 and technetium-99m; (b) the orange juice was labelled with only 1 MBq of technetium-99m in order to avoid masking the technetium in the tablet; (c) the duration of monitoring was limited to 9 h for the convenience of the subjects; (d) slightly less frequent monitoring was carried out than with the younger volunteers since lunch, tea and coffee breaks were more protracted.

Results and discussion

In-vitro experiments confirmed that release of the marker occurred through the laser-drilled hole and that none escaped through the wall of the device nor through the epoxy resin plug. This is illustrated in Fig. 2.

For each subject the position of the stomach relative to the reference marker was established from the early images of the [^{99m}Tc]DTPA solution. In both sets of studies the location of the indium-111 tracer, both within the device and following its release were readily identifiable from the images. Release of tracer from the tablets could be visualized by about 3 h after dosing. After approximately 8 h, this released activity was seen to be dispersed throughout the colon. In four of the younger subjects, the unit moved steadily through the small intestine but in the two remaining subjects the tablet remained in the stomach for at least 10 h. By the following day insufficient tracer remained associated with the device to ascertain the exact position of the unit. Intake of food and drink throughout the first day of the study altered the position of the tablet in the stomach in these two subjects, demonstrating that the device had not adhered to the stomach wall. In the USP test (Method II) the devices have been observed to float in the suspending medium (phosphate buffer pH 7·5) after 6 h. This observation supports the in-vivo evidence that, in the presence of food, the device may lose sufficient contents to make it buoyant and thereby retard gastric emptying. Release of indium-111 from the device in the dissolution apparatus, showed that the release of the tracer followed zero-order kinetics for approximately 6 h. Although the effect of food on release of tracer has not been studied in the present experiments, other studies confirm zero-order release from osmotic pumps in the gastrointestinal tract, independent of the size of the meal or nature of food taken with the device (Davis et al 1984a).

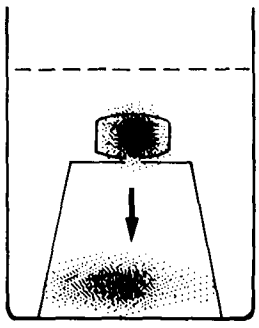

FIG. 2. Diagram illustrating release of indium-111 from delivery orifice of the radiolabelled tablet. The radiotracer was released into the interior of the beaker and no activity was detected in the surrounding medium.

In the second study the incorporation of technetium-99m into the epoxy resin plug facilitated the location of the device. It was therefore easier to identify the positions of the tablets. In five of the elderly subjects transit times through the small intestine were similar to those in the young volunteers. In one subject a point source could not be discriminated from the released indium-111 (Table 1). In general, the device moved through the small intestine at about the same rate as the released contents.

Table 1. Transit times for the placebo Osmosin tablets (n = number of subjects).

	Young subjects (h)	Elderly subjects (h)
Gastric emptying	3·1 + 0·4 (n = 4)	2·8 + 1·6 (n = 6)
Caecum arrival	7·6 + 1·9 (n = 4)	6·9 + 1·8 (n = 5)

The outer layer of the formulation is a regular film coat based on a water soluble cellulose ether. The adhesive properties of the outer film coat have been implicated as a contributory cause of intestinal perforation seen with this formulation (Day 1983). However a higher incidence of delayed oesophageal rather than intestinal transit would be expected. Florence et al (1984) have commented that it was unlikely that the adhesive properties of the semi-wetted surface would persist until the tablet reached the lower intestine. A similar material hydroxypropylmethylcellulose (HPMC) is used as a non-disintegrating, slowly-eroding base in a number of pharmaceutical formulations. Tablets of HPMC have been monitored in man using the technique of gamma scintigraphy (Daly et al 1982) and have been shown to move through the intestines with no evidence of sticking. In all cases studied, the units were observed to move between sequential images confirming onward progression down the gastrointestinal tract. This suggests that adhesion of the device to a mucosal surface is unlikely to be the mechanism responsible for the reported adverse reactions.

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Ring-substituted β-methoxyphenethylamines: a new class of psychotomimetic agents active in man

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Four members of a new class of psychotomimetic agents have been synthesized and evaluated in man. These compounds, which incorporate a β-methoxy group onto a β-phenethylamine sidechain, are the first reported psychotomimetics which are structural analogues of the neurotransmitter noradrenaline. These substances are more potent than the corresponding phenethylamines (lacking a β-methoxy group) but less potent than the correspondingly substituted amphetamine derivatives.

Psychotomimetic drugs are of continuing interest as tools for the study of sensory and mental processes. As their action is eventually expressed within the human central nervous system (CNS), there has been much effort to relate them, functionally or structurally, to neurotransmitters (Shulgin 1981; Nichols 1984). The many psychotomimetic indoles are recognizable analogues of 5-hydroxytryptamine. The acetylcholine family includes Ditran, quinuclidinyl benzilate, and related parasympatholytic agents. The largest group, the phenethylamines and their α-methyl homologues, resemble dopamine. There have been no previous reports of any psychotomimetic drugs related to noradrenaline (norepinephrine).

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We have discovered a new class of psychotomimetic drugs (2), the members of which possess a methoxy group in the β-position of the phenethylamine sidechain. In the examples reported here, these β-oxygenated derivatives have a greater CNS potency than their phenethylamine counterparts.

Materials and methods

All new compounds reported here had microanalyses (C,H) that were within 0·4% of the calculated values, and had spectra (infrared, NMR) consistent with the assigned structures. Melting points are uncorrected.

2-Methoxy-2-(2,5-dimethoxy-4-methylphenyl)-ethylamine (2c). A suspension of 2,5-dimethoxy-4-methyl-β-nitrostyrene (Ho et al 1970) (39 g) in warm methanol (300 ml) was treated with a solution of sodium methoxide (9 g sodium in 150 ml methanol). After a few minutes (when the solution was complete and nearly colourless) acetic acid (75 ml) was added followed by water (2000 ml) and the reaction mixture was extracted with methylene chloride (3 × 200 ml). The extracts were pooled, and the solvent removed under vaccum to yield an oil which was diluted with a small amount of