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The in-vivo evaluation of an osmotic device (Osmet) using gamma scintigraphy

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The release of a radiolabelled marker from an orally administered osmotic pump device (Osmet) has been evaluated in-vivo in a group of 6 subjects, using the technique of gamma scintigraphy. The duration of residence of the pump in the stomach was greatly influenced by food intake. However, the release of the marker from the device was independent of food and position within the gastrointestinal tract. Furthermore, the material released from the osmotic pump was well distributed in the gastrointestinal tract. Good agreement between in-vitro and in-vivo release rates was obtained.

The recent developments of osmotic pump devices have found application both for the investigation of 'steady-state' pharmacology in animals (implanted miniature osmotic pumps), and for the oral delivery of drugs, hormones and vitamins at a near constant rate for a well defined period of time (Theeuwes & Yum 1976; Theeuwes 1981; Eckenhoof & Yum 1981).

The miniature osmotic pump (Alzet, Osmet¶) can provide a continuous uninterrupted administration of a drug at a constant rate for up to 14 days. Systems of this type have now been designed with 8, 12, 24 and 30 h delivery patterns, for oral use in man. These act as simulators of the osmotic pumps that will serve as dosage forms, as well as providing a means of delivering a solution of a new compound within the gastrointestinal tract in a well controlled zero order fashion (Theeuwes 1981). The delivery of the drug is claimed to be substantially independent of the fluctuations in pH, agitation and pressure that can occur in the gastrointestinal tract (Theeuwes & Yum 1976). Additionally, De Leede et al (1981, 1982) have described the use of these systems for the rectal infusion of drugs.

In the present study, the release performance and gastrointestinal transit of Osmet-12h modules have been evaluated in healthy volunteers using the technique of gamma scintigraphy.

MATERIALS AND METHODS

Osmotic pumps and their in-vitro evaluation

Osmet 12 hour systems were obtained from the Alza Corporation, Palo Alto, California (Fig. 1). The devices, made from a styrene-butadiene co-polymer, had a nominal fill volume of 200 μl and a steady state delivery rate of 15 μl h^{-1}. A delay in delivery, defined as the incremental time lag before the modules begin delivery after being submersed in 0·9% NaCl (saline) at 37 °C, was given as 1·25 h. The maximum drug load was quoted as 100 mg of drug suspension or 200 μl of drug solution. The release characteristics of the pumps were tested in-vitro at 37 °C using saline as the release medium. The pumps were filled using a blunt-type 25-gauge filling tube

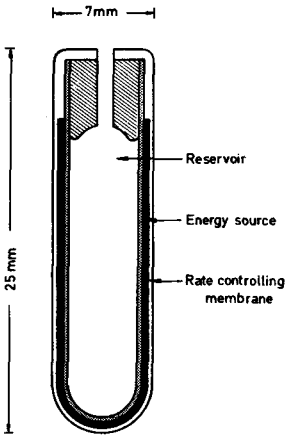

FIG. 1. The osmotic pump device.

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¶ Alzet and Osmet are trademarks.

attached to a syringe either with methylene blue solution or a radiolabelled marker labelled diethylenetriaminepentaacetic acid (DTPA) (CIS (UK) Ltd, London).

The release profiles were determined with and without a plastic tube to moderate the flow and with the orifice in the upwards and downwards positions. The release rates of both markers were similar and conformed well with the release profile provided by the company.

In-vivo studies

The Osmet pumps were filled with DTPA solution (DTPA concentration 0·23 mg ml^{-1}) radiolabelled with 4 MBq ^{111}In-DTPA per unit. The labelled DTPA was prepared using a kit and ^{111}In-indium chloride (supplied by Amersham International, Amersham). A flow moderator tube was not used. Indium-111 labelled DTPA was chosen as a test material since it is water soluble, is not absorbed from the gastrointestinal tract and is suitable for monitoring with a gamma camera. Its use in diagnostic imaging has been discussed by Kelly (1982).

Six healthy male volunteers (age 19–21, height 1·63–1·82 m, weight 70–81 kg) participated on two occasions with informed consent. The osmotic pump device was administered after an overnight fast and either a standard light or heavy breakfast (light breakfast (calorific value—1500 kJ), two toasted slices of white bread lightly buttered and with a scrape of marmalade, 1 glass fresh orange juice; heavy breakfast (calorific value—3600 kJ), 2 sausages, 1 rasher of bacon, 1 fried egg, 1 fried tomato, 1 piece of fried bread, coffee with milk and sugar if desired). The position of the pump in the gastrointestinal tract and the release of the indium labelled marker was followed by standing the subjects in front of a gamma camera (General Electric), having a field of view of 40 cm diameter, fitted with a medium energy (300 keV maximum) parallel hole collimator. Anterior and posterior images of 60 s duration were taken at suitable intervals and the data recorded by computer. A region of interest was defined around the image of the pump and the recorded counts corrected for background and radioactive decay. A geometric mean value was calculated; this was approximately independent of the depth of the source (Tothill et al 1978).

The volunteers were also given a suspension of ion-exchange beads (diameter 0·7–1·2 mm) labelled with technetium-99m. These beads provided anatomical information concerning the size and shape of the stomach and colon, thereby facilitating the interpretation of the images obtained for the osmotic device. A dual radionuclide recording facility was used to record both technetium-99m and indium-111 distributions simultaneously. Technetium-99m emits gamma radiation of lower energy than indium-111 and therefore did not interfere with the analysis of the indium-111 release.

Following dosing, the volunteers were allowed to drink and eat normally during the study. On the second occasion the same subjects repeated the investigation after ingestion of the other breakfast.

RESULTS

The technique of gamma scintigraphy allowed both the position of the pump in the gastrointestinal tract to be ascertained and the quantity of material remaining in the device at a given time to be measured. Fig. 2 shows some typical radionuclide images, with the pump in different regions of the gastrointestinal tract, together with released activity. This released activity can precede or follow the unit depending on whether the unit was emptied rapidly from the stomach or retained for a long time. The importance of food in determining the transit of the device in the gastrointestinal tract is evident from the data in Table 1. This aspect will be discussed in detail elsewhere.

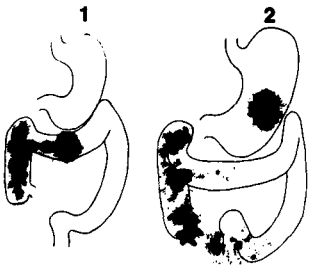

FIG. 2. Radionuclide images showing the osmotic device in different regions of the gastrointestinal tract and the release of the indium-111 labelled marker. 1. Osmotic device administered following light breakfast—9 h post administration. The device is in the transverse colon. The released activity is in the ascending colon. 2. Osmotic device administered following heavy breakfast—9 h post administration. The device is in the stomach. The released activity is in the distal small intestines, ascending and transverse colon.

The release profiles for the ^{111}In-DTPA marker from the pumps, after light and heavy breakfasts had been eaten, are shown in Fig. 3. It can be seen that the release is unaffected by the presence of food or the position of the device in the gastrointestinal tract (stomach, small intestine, large intestine). The

combined data for the release of indium-111 after administration of the Osmet device following the ingestion of light or heavy breakfasts are shown in Fig. 4 together with data for the release of marker materials in-vitro. The correlation between in-vitro and in-vivo data is good.

Table 1. Transit of osmotic pump in gastrointestinal tract–pooled data for 6 volunteers.

Time after admin. (h)	Number of units in region of interest: Light breakfast			Heavy breakfast		
	Stomach	Small intestine	Colon	Stomach	Small intestine	Colon
1	5	1	0	6	0	0
2	4	2	0	6	0	0
3	2	4	0	6	0	0
4	2	3	1	6	0	0
5	2	2	2	6	0	0
6	2	1	3	6	0	0
8	2	0	4	6	0	0
10	1	0	5	4	2	0
24	0	0	6	0	0	6

DISCUSSION

In the operation of the Osmet device, water is osmotically imbibed across the semipermeable membrane, swelling the osmotic compartment and squeezing the drug reservoir uniformly along the axis. Since water is incompressible and the semipermeable membrane is (to a first approximation) rigid, the unit net volume of influx of water causes unit volume displacement of solution from the reservoir (Eckenhoff 1981). This can be expressed mathematically as

$$\frac{dv}{dt} = K\frac{A}{L}(\Pi o - \Pi e)$$

where A is the membrane area, L the thickness, K the membrane permeability to water, Πo the osmotic pressure of the driving agent and Πe the osmotic pressure of the environment (7·7 atmos. for saline at 37 °C) (Theeuwes 1981). Thus the flow rate can be altered by adjusting the membrane permeability and osmotic pressure (and to some extent

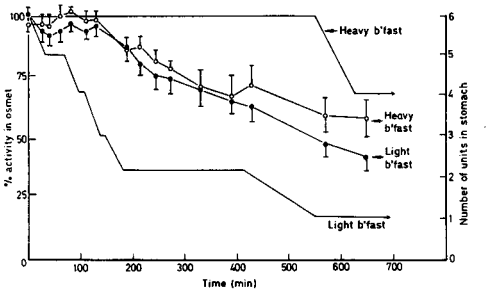

FIG. 3. In-vivo release of ^{111}In-DTPA from osmotic pumps under different intakes of food, mean ± s.e.m., n = 6.

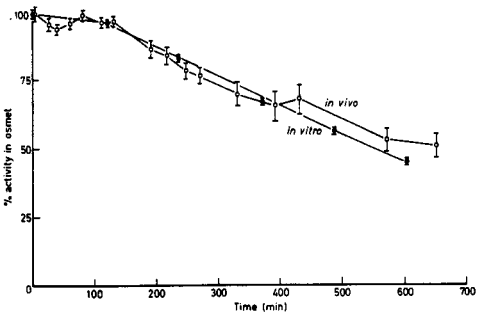

FIG. 4. In-vitro (○) and in-vivo (●) release profiles for the release of marker substance from osmotic pumps. In-vivo, n = 12, in-vitro, n = 10 mean ± s.e.m.

the area and thickness of the membrane). It is to be expected that the release will be independent of pH and agitation conditions.

The data in Figs 3 and 4 demonstrate that the release of the indium-111 labelled marker from the osmotic devices approximates to a zero order relation and that the rate of release of a marker in-vivo is similar to that obtained in-vitro. The presence of food has no effect on the release profile, nor does the position of the device within the gastrointestinal tract. The delay in start up, when the device is imbibing water, is approximately 2 h.

When the heavy breakfast had been taken the osmotic pump was retained in the stomach for at least 9 h. However, the released activity became well distributed in the gastrointestinal tract.

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