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Gastrointestinal transit of a matrix tablet formulation: comparison of canine and human data

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Summary

Controlled release devices, based on high molecular weight hydrophilic polymers, have been shown in studies in dogs to have extended gastric retentive properties. However, the transit characteristics of the formulation in man were very similar to those reported previously for other single unit matrix systems. The results highlight the dramatic differences that can occur between animal models and human subjects and consequently data on gastrointestinal transit obtained in animal models should be interpreted with considerable caution.

The gastrointestinal transit of pharmaceutical dosage forms is of current interest with respect to the design of controlled release dosage forms and the targeting of drugs to specific sites, for example the colon for local and systemic effects (Hardy et al., 1987; Wilding et al., 1992). There is now an increasing tendency to conduct studies in man, so far as possible, using the non-invasive method of gamma scintigraphy (Digenis et al., 1990; Wilding et al., 1991a,b). However, in some situations an animal model may be required, when for example testing out a new strategy with formulation materials that are not generally regarded as safe (GRAS) or with new chemical entities. The dog (Marvola et al., 1986), and more recently the pig (Hildebrand et al., 1991; Larsen and Jensen, 1991) have been used but each has its limitations and drawbacks when attempting to translate animal data to the situation in man. Table 1 compares and contrasts the salient features of the gastrointestinal tract of the dog and of man.

To their cost, pharmaceutical scientists have sometimes used data from the dog as being directly applicable to the human. For example, the cut-off size for the emptying of multiparticulates from the fed stomach is a case in point where (not surprisingly) the limiting size in the dog is very much lower than that in man (Coupe et al.,

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TABLE 1

Comparison of canine and human gastrointestinal physiology (Davis et al., 1986; Dressman, 1986; Khosla et al., 1989; Khosla and Davis, 1990; Coupe et al., 1991)

Parameter	Human	Canine
Gastric acid secretion (mEq./h)	2.2 (female) 3.7 (male)	0.1
Intestinal pH (2 h after gastric emptying)	6.0	7.2
Periodicity of Phase III MMC activity (min) (mean ± SE)	113 ± 11	106 ± 8
Cut-off size for emptying of multiple units (mm)	11–13	2–7
Small intestinal transit time (min) (mean ± SD)	180 ± 60	111 ± 17

1991). In man the minimum size for prolonged retention following post-prandial administration appears to be 12 mm or larger (Khosla and Davis, 1990). We have suggested that the difference in canine and human data could be related to the size of the pyloral aperture in the resting state (Khosla et al., 1989).

Certain putative bioadhesives that seem to perform well in animal models (to include the dog) do not work when tested in human volunteers (Park and Robinson, 1984; Russell and Bass, 1985; Khosla and Davis, 1987; Shalaby et al., 1991). In the present paper, we describe dramatic differences to the gastric retentive behaviour of a matrix system administered to dogs and to man.

While investigating controlled release technology based on high molecular weight hydrophilic polymers, Edgren and colleagues observed a unique phenomenon (Edgren, D., Alza Corporation, 1988; personal communication). Following oral dosing in dogs they found that, at necroscopy (8 or 10 h post-dose), the controlled release systems were often recovered from the stomach. At the start of each study the animals were given a small meal in the form of a 150 g of moist dog food, after which the dosage form was administered. No further food was given. At the end of an 8 h study, 11 out of 16 systems were recovered from the stomach whilst at the end of a 10 h study, 12 out of 15 systems were retained.

The purpose of the present study was to determine whether these systems showed such extended gastro-retention behaviour in man. Gastrointestinal transit, in particular gastric emptying, was measured in healthy subjects using the non-invasive technique of gamma scintigraphy.

Hydrogel type gel core tablets were prepared from hydroxypropylmethylcellulose 2208 (USP) in the form of K100M and K3 grades. The molecular mass of the polymer was 154.6 kDa and was used at a ratio of 25 : 15 K100M/K3. The hydrogel concentration was 40%. Tablets of 700 mg weight, oval in shape, of longest dimension 19 mm were prepared by a direct compression procedure and produced using suitable tooling on a Manesty F3 press. In the animal studies, the systems contained either paracetamol or ibuprofen, however, the tablets used in the human studies were placebos containing lactose as an innocuous excipient together with a small quantity of amberlite resin (IR-120(H)) (10 mg per tablet) labelled with the gamma emitter ^{111}In. There is no evidence in the pharmaceutical literature that either paracetamol or ibuprofen can alter the retention response of the stomach.

The study was approved by the Ethics Committee of the University of Nottingham and was conducted according to the Guidelines of the Declaration of Helsinki and subsequent amendments. The labelled tablets, containing about 1 MBq of radioactivity at the time of administration, were dosed to a group of six subjects (age range 19–24 years) after an overnight fast. The position and integrity of the dosage form in the gastrointestinal tract was followed by placing the subjects in front of a gamma camera fitted with a medium energy collimator as described previously (Coupe et al., 1991). In order to provide an outline of the different regions of the gastrointestinal tract the tablets were taken with a drink of water labelled with 4 MBq of ^{99m}Tc in the form of the non-absorbable chelate diethylenetriaminepentaacetic acid. A light snack consisting of orange juice and a biscuit was permitted 1.5 h after dosing. Lunch and dinner were provided 3.5 h and 9 h post-dose, respectively.

Gastric emptying of the tablet was taken as the mid-time between recording the two images about the transition. The time for the arrival of the tablets in the colonic region were estimated in a

TABLE 2

Gastrointestinal transit parameters for putative bioadhesive matrix tablet system

Subject	Gastric emptying (min)	Small intestinal transit (min)	Colon arrival (min)
1	8	187	195
2	8	135	143
3	102	131	233
4	38	160	198
5	8	222	230
6	23	210	233
Mean	33	173	205
SE	16	16	14

similar manner. The difference between these two times was taken as an estimate of the small intestinal transit time. The individual parameters used to define gastrointestinal transit are provided in Table 2

Gastric emptying times varied between 8 and 102 min. Such times are similar to those reported previously by our group and others for the emptying of single unit systems (Park et al., 1984; Marvola et al., 1987; Davis et al., 1988). They reflect the emptying behaviour of the fasted stomach. Indigestible objects, such as large matrix tablets, will be cleared by a mechanism known as the migrating myoelectric complex (MMC). This has three phases and phase three, which consists of strong contractions, will move material through the open pylorus into the intestines. The MMC has a periodicity of about 2 h and therefore it is to be expected that gastric emptying will occur at any time from almost immediately after dosing to about 120 min. There was no suggestion that the tablets had been retained in the stomach for an unusually prolonged period.

Small intestinal transit was less variable than gastric emptying and an average time of 173 min was obtained. This value is very close to that reported previously by Davis et al. (1986) in an analysis of a range of studies with different dosage forms and under different feeding conditions. Once again there was no suggestion that the transit behaviour of the tablet was different to that observed before for other single unit systems. The recorded times for the arrival of the tablets in the colon are entirely as expected for the transit of a non-disintegrating single unit dosage form.

Dressman (1986) has concluded that the gross physiology of the stomach in humans and dogs is very similar in the fasted state, with similar motility patterns and the gastric emptying of indigestible solids and liquids. However, the prolonged gastric residence time found in the dog for a matrix tablet system did not occur in man. The dogs were given a small meal 0.5 h before dosing but it is unlikely that this had any significant effect on the results obtained since no further food was allowed until the end of the study period.

Recent radiological studies have suggested that the dog is a better model for bioavailability studies under fasted conditions than pigs or stomach emptying controlled rabbits (Aoyabi et al., 1992). However, the results from the present study demonstrate the dramatic differences that can occur between animal models and human subjects and consequently animal data on gastrointestinal transit must be interpreted with considerable caution. Whenever, possible transit studies should be conducted in man. The non-invasive technique of gamma scintigraphy is ideal in this respect.

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