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The effect of food on the in vivo behaviour of enteric coated starch capsules

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Abstract

Eight healthy volunteers were entered into a randomised, open crossover study to investigate the in vivo behaviour of an enteric coated starch capsule. A radiolabelled preparation was administered to each volunteer on two occasions separated by 7 days, once in the fasted state and once after a medium breakfast. The gastrointestinal transit and disintegration behaviour of the enteric coated capsule was followed using gamma scintigraphy. No loss of integrity was observed in the stomach confirming the gastroresistant properties of the preparation. With one exception, all capsules released their contents in the small bowel. Capsule disintegration was influenced by the gastric residence time; capsules which were retained within the fed stomach disintegrated sooner following gastric emptying, compared with capsules which left the stomach rapidly.

Keywords: Starch capsule; Enteric coating; Gamma scintigraphy; Intestinal delivery

1. Introduction

Hard gelatin capsules have been used for many years in oral drug delivery for the encapsulation of pellets or powders (Ghebre-Sellassi, 1989). Recent advances in injection moulding technology have enabled the manufacture of starch capsules (Capill®) (Stepto and Tomka, 1987). Capsules of uniform weight and dimensions have been produced, which comply with the pharmacopeia requirements on microbial limits (Idrissi et al., 1991). The moisture content of the capsules is approx. 14% with more than 50% being tightly bound to the starch. In addition, the capsules show low moisture adsorption with increasing humidity which provides for a product that has good stability properties and reduced susceptibility to changes in storage conditions. In vitro dissolution studies on acetaminophen starch capsules have demonstrated that the release properties of Capill® are well within the USP specification (Cole and Lentz, 1991). Scintigraphic techniques have been used to confirm that the in vivo behaviour of starch capsules is comparable to that

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of traditional hard gelatin capsules (Cole and Lentz, 1991; Doll et al., 1993).

There is considerable interest in the enteric coating of pharmaceutical preparations for targeted delivery of drugs to the small intestine (Hardy et al., 1987; Wilding et al., 1992). Such coatings have been traditionally reserved for drug substances that cause gastric irritation, produce nausea if released in the stomach or which are destroyed by acid or gastric enzymes. However, there have been considerable technical problems in the manufacture of coated hard gelatin capsules, especially since the advent of aqueous coating dispersions (Plaizier-Vercammen et al., 1992). For example, during coating with aqueous spray formulations, the gelatin shell can soften and become sticky due to solubilization, or the gelatin shell can become brittle due to water evaporation and drying, especially at the onset of coating. In addition there are difficulties associated with coating of the 'lipped' hard gelatin capsule which can compromise the protective characteristics of the coating (Thoma and Bechtold, 1992). Aqueous film coating of starch capsules should be considerably easier due to the smooth seal of the filled unit, coupled with the higher bulk density of the capsule which provides for a more uniform coating bed.

The technique of gamma scintigraphy has been used routinely to follow the transit and release characteristics of dosage forms in the human gastrointestinal tract (Davis et al., 1992). Conventional methods of labelling pharmaceutical dosage forms require that the radioactive marker be incorporated as late as possible in the manufacturing process so as to minimize the handling of radioactive materials. In many cases, manufacturing processes are complex requiring specialised equipment and lengthy production techniques. Therefore, in many cases, the manufacturing process must be scaled down to minimise the amount of radioactivity handled and, in the case of complicated delivery systems, such as enteric coated (EC) preparations, this may significantly alter the physical properties of the dosage form. These problems can be overcome by incorporating a stable isotope, as a non-radioactive tracer in the preparation. Subsequent neutron activation converts the tracer into a gamma-emitting isotope (Digenis and Sandefer, 1991; Watts et al., 1991; Davis et al., 1992).

The objective of this study was to investigate the effect of food on the in vivo behaviour of an aqueous EC (Aquateric®) starch capsule formulation in a group of eight healthy volunteers.

2. Materials and methods

2.1. Preparation of clinical supplies

Starch capsules (Capill®) (22 mm in length) were manufactured by Capsugel AG and filled with 470 mg of a placebo formulation containing 2 mg of isotopically enriched samarium oxide (98% ^{152}Sm) using a Bonapace® Benchtop filling machine. Aquateric® aqueous coating was applied to a theoretical weight gain of 8% using a Manesty 24-in Accelacota® with a batch size of 9 kg. In vitro disintegration tests were carried out on the capsules both prior to and following irradiation to ensure integrity of the enteric coat. On each occasion the BP 1988 disintegration test for EC products was performed.

The EC capsules were irradiated, 24 h prior to administration, for 4 min in a neutron flux of 10^{12} neutrons cm^{-2} s^{-1}. The capsules were assayed for radioactive content on the morning of each study day and, at the time of administration, each capsule contained approx. 1 MBq of ^{153}Sm.

2.2. Subjects

This was an open, balanced randomised crossover study conducted in eight healthy volunteers (seven male and one non-pregnant female) aged between 18 and 33 years. Each volunteer was examined by a physician before the study and was judged to be in good health on the basis of medical history, physical examination, routine laboratory data and standard electrocardiogram. The clinical protocol was approved by the Quorn Research Review Committee. The study was conducted in accordance with the Declaration of Helsinki Guidelines for Ethics in Research, and the Association of British Pharmaceutical Indus-

try (ABPI) guidelines for medical experiments in non-patient healthy volunteers. Approval for the administration of radiolabelled preparations to human subjects was obtained from the Department of Health, London. The nature of the trial was explained both verbally and in writing to the volunteers. Each subject provided written informed consent to participate in the study.

2.3. Procedures

Following an overnight fast the volunteers were admitted to the clinical unit at 7:00 a.m. on each morning of the two study periods. Subjects had previously been instructed to fast overnight (from midnight) on the evening prior to dosing. In line with the study randomisation, four of the subjects received a medium breakfast consisting of cornflakes (25 g), whole milk (150 ml), orange juice (150 ml), two slices of toast, butter and preserve and tea or coffee (2500 kJ) at approx. 7:45 a.m. Breakfast was consumed within a 15 min period.

Anatomical markers containing 0.1 MBq $^{99}Tc^{m}$ were taped to the skin over the right lobe of the liver of each subject. The radiolabelled preparation was administered to the volunteers at approx. 8:00 am with 150 ml of water. Anterior scintigraphic images, each of 60 s duration, were recorded at frequent intervals for up to 24 h, using a gamma camera (General Electric Maxicamera) with a 40 cm field of view and fitted with a low-energy parallel hole collimator. During the first 4 h after dosing, images were recorded at approx. 10 min intervals and then at 30 min intervals until 12 h post-dose. The subjects were then allowed to go home but returned to the clinical unit the next morning for a 24 h post-dose image. Volunteers remained moderately active during the study period and all images were acquired with the subjects standing in front of the gamma camera.

The data were analysed to provide information on gastric emptying time and the time and anatomical position of initial and complete capsule disintegration. Gastric emptying of the coated capsule was taken as the mid-time between recording the two images about the transition. Initial capsule disintegration was defined as the time taken for the enteric coating to dissolve followed by the onset of dispersion of the radioactive marker. Complete capsule disintegration was defined as the time of complete dispersion of the capsule contents.

Each volunteer drank 200 ml water 2 h post-dose. A standard lunch and dinner were provided at 4 and 9 h post-dose, respectively. Fluid was allowed ad libitum after lunch.

3. Results and discussion

3.1. In vitro testing

In vitro studies on the EC capsules demonstrated that neutron activation did not alter the integrity of the enteric coating. Disintegration testing showed that the coated capsules remained intact in 0.1 N hydrochloric acid for over 2 h but disintegrated within 20 min after the acid medium was exchanged for pH 6.8 phosphate buffer (Table 1).

3.2. In vivo studies

Typical scintiscans for one subject participating in the study are shown in Fig. 1. The transit and disintegration behaviour of the EC capsule following administration after an overnight fast is shown in Table 2. Emptying from the stomach occurred between 6 and 120 min post-dose (Fig. 1). These data are in very good agreement with previous reports on the emptying of large single unit dosage forms from the fasted stomach (Park

Table 1
In vitro disintegration properties of Capill® coated with Aquateric®

Medium		Non-irradiated	Irradiated
0.1 N HCl	opening time	> 2 h	> 2 h
	disintegration time	> 2 h	> 2 h
Phosphate buffer (pH 6.8)	opening time	< 10 min	< 10 min
	disintegration time	15 min	14 min

$n = 6$.

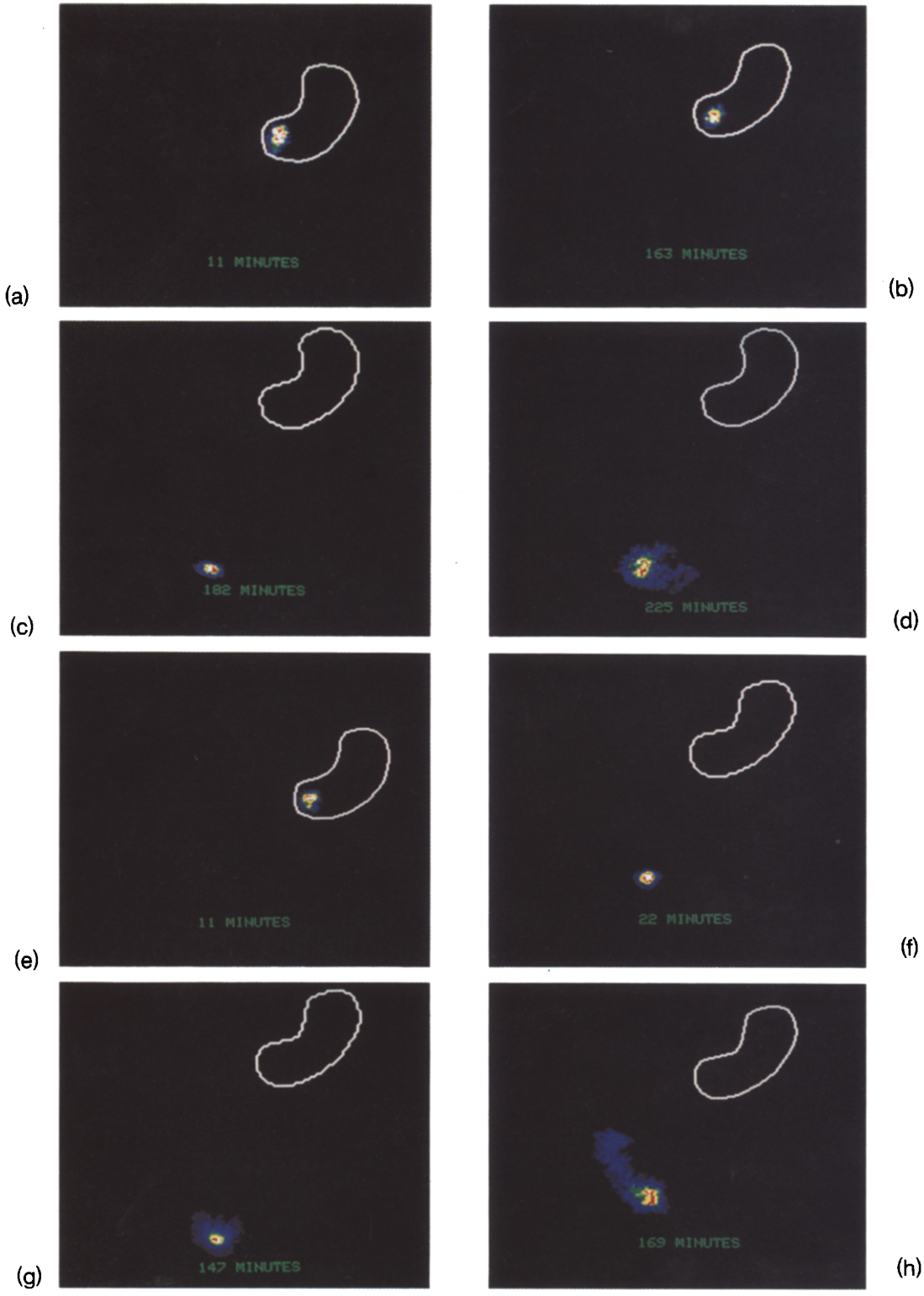
(a)
11 MINUTES
(b)
163 MINUTES
(c)
182 MINUTES
(d)
225 MINUTES
(e)
11 MINUTES
(f)
22 MINUTES
(g)
147 MINUTES
(h)
169 MINUTES

Table 2
Transit and disintegration profile of the enteric coated starch capsules following administration after an overnight fast (min)

Subject No.	Gastric residence	ICD			CCD		
		post dose	post GE	Site	post dose	post ICD	Site
1	47	103	56	SI	138	35	SI
2	120	194	74	SI	215	21	SI
3	29	155	126	SI	174	19	SI
4	18	85	67	SI	120	35	ICJ
5	25	157	132	ICJ	157	0	ICJ
6	6	74	68	SI	74	0	SI
7	17	153	136	SI	164	11	SI
8	38	141	103	SI	164	23	SI
Mean	38	133	95		151	18	
SD	36	41	33		42	14	
Median	27	147	89		161	20	

$n = 8$.
GE, gastric emptying; SI, small intestine; ICJ, ileo-caecal junction; ICD, initial capsule disintegration; CCD, complete capsule disintegration.

Table 3
Transit and disintegration profile of the enteric coated starch capsules following administration after a medium breakfast (min)

Subject No.	Gastric residence	ICD			CCD		
		post dose	post GE	Site	post dose	post ICD	Site
1 [a]	712 < t < 1464	712 < t < 1464	–	–	712 < t < 1464	–	–
2	213	292	79	SI	318	26	SI
3[a]	720 < t < 1476	720 < *t* < 1476	–	–	720 < t < 1476	–	–
4	173	214	41	SI	231	17	SI
5	108	176	68	SI	187	11	SI
6	176	291	115	ICJ	317	26	AC
7	173	214	41	ICJ	214	0	ICJ
8	232	284	52	SI	319	35	SI
Mean	179	245	66		264	19	
SD	43	50	28		60	13	
Median	175	249	60		274	22	

$n = 6$. [a] Not included in descriptive statistics.
GE, gastric emptying; SI, small intestine; ICJ, ileo-caecal junction; AC, ascending colon; ICD, initial capsule disintegration; CCD, complete capsule disintegration.

et al., 1984; Davis et al., 1988; Khosla and Davis, 1990). In the fasted state, the behaviour of the stomach is controlled by a cyclical physiological mechanism known as the migrating myoelectric complex (MMC), which occurs roughly over a 2 h cycle (Code and Martlett, 1975). The phases of the cycle range from a period of quiescence to strong contractions. It is the contractions of the third phase, the so called 'housekeeper wave' that are important for gastric emptying, since they have the effect of sweeping the indigestible material from the stomach, through the open pylorus and into the small intestine. Gastric emptying in the fasted individuals was therefore

Fig. 1. Scintigraphic imaging of subject 7 following administration of an enteric coated Capill® after a medium breakfast (a–d) and an overnight fast (e–h).

largely determined by how close dosing was to the next housekeeper wave. A dosage form administered just before or during a housekeeper wave (e.g., subject 6) will be emptied rapidly, whilst one administered just after phase III activities will need to wait until the next cycle occurs before it can be expelled from the stomach (e.g., subject 2). However, cases of prolonged gastric residence of enteric coated preparations have been observed in fasted subjects (Fremstad et al., 1979). It has been shown that the housekeeper wave is not always efficient at removing large non-disintegrating systems from the stomach (Coupe et al., 1991). Inefficient phase III activity could be caused by the preparation residing deep in the antrum, possibly proximal to the site of propagation for the MMC. In this study, the enteric coated capsules emptied rapidly from the fasted stomach suggesting that the preparation could be emptied from the stomach easily and efficiently by the housekeeper wave.

The transit and disintegration behaviour of capsules following administration after a medium breakfast is shown in Table 3. On this occasion, gastric emptying occurred between 108 and 232 min post-dose in six of the eight subjects. Following feeding, the MMC is interrupted and the lack of phase III activity results in the retention of large particles and indigestible material in the stomach (Davis et al., 1988). However, in two subjects, gastric residence time was extended further. It was likely that, in these subjects, the medium breakfast interrupted MMC activity for the entire pre-lunch period and therefore individuals did not experience a housekeeper wave during this time interval. As a consequence, the capsules remained in the stomach until 4 h post-dose at which point propagation of an MMC was further delayed by the ingestion of lunch and therefore the preparation continued to be retained in the stomach. This pattern of events was probably repeated following dinner with the result that the capsules were retained within the stomach throughout the first 12 h of the study period. Previous scintigraphic studies on large single unit formulations have demonstrated that continuous eating protocols can lead to prolonged gastric residence times (Wilding et al., 1991). Despite prolonged residence in the stomach both capsules remained intact confirming that the gastroresistance of the coated capsules was not compromised by extended exposure to the gastric milieu. The 24 h post-dose scintigraphic image revealed complete disintegration of the capsule in both subjects. It was therefore not possible to determine either the anatomical site, or the times at which disintegration occurred in these two individuals on this particular study day.

On average, the capsules began to disintegrate at 66 ± 28 and 95 ± 33 min after leaving the stomach following fed and fasted administrations, respectively. This suggests that initial capsule disintegration could be influenced by gastric residence time; the longer the residence time in the stomach, the sooner the capsule disintegrated following leaving the stomach. Although the enteric coating does not dissolve at gastric pH, it is permeable to the gastric milieu. If the capsules are present in the stomach for a sufficiently long period of time it is possible that the underlying starch capsule is digested whilst the integrity of the overall system is protected by the enteric coating. Therefore, on leaving the stomach, the only barrier to the release of the capsule contents is the polymer coating and, once this is eroded, the capsule contents are discharged.

Initial signs of capsule disintegration were difficult to determine and, in some volunteers, little distinction could be made between the time at which initial and complete disintegration occurred. This suggests that overall disintegration occurred within a short time following the onset of capsule break-up. Since consecutive images for a single individual were obtained on average every 10 min, it is probable that complete disintegration occurred very quickly for the majority of individuals. With one exception, complete capsule disintegration occurred in the small bowel.

In conclusion, gamma scintigraphy confirmed the gastroresistant properties of the EC placebo starch capsules. Although feeding caused a predictable delay in transit, the capsules remained intact, despite a prolonged residence time in the stomach. This data were in accord with those previously observed for EC tablets (Wilding et al., 1992). The enteric coating of starch capsules may

prove to be a successful approach to targeted intestinal delivery of drugs that cannot be compressed into tablets and, as such, this type of capsule may be a useful alternative to its gelatin counterpart.

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