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Gamma scintigraphic evaluation of film-coated tablets intended for colonic or biphasic release

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Abstract

The gastrointestinal transit and in vivo drug release behaviour of a film-coated tablet formulation was investigated in five healthy human subjects using the technique of gamma scintigraphy. The film coating system consisted of a mixture of pectin, chitosan and HPMC in a ratio of 6:1:0.37 applied to 750 mg cores at a coat weight gain of 9%. The estimated mean values of the gastric emptying time (62±17 min), small intestinal transit time (219±53 min), ileocaecal junction lag time (79±30 min) and the colon arrival time (345 ± 33 min), were similar to published values for the transit of similar sized tablets in humans. The amount of radioactive tracer released from the labelled tablets was minimal when the tablets were in the stomach and the small intestine. There was increased release of radioactivity when the tablets were in the colon due to increased degradation of the film coatings by pectinolytic enzymes resident in the colon. The pectin/chitosan/HPMC film coating system thus acts as a colonic delivery system.

Keywords: Colonic delivery; Biphasic release; Mixed films; Pectin; Chitosan; Gamma scintigraphy

1. Introduction

The use of mixed films comprising pectin/chitosan/hydroxypropyl methylcellulose (HPMC) for the colonic or biphasic delivery of drugs has been described by Ofori-Kwakye and Fell (2001) and Ofori-Kwakye (2002). Manipulation of the proportion of the components and/or the coat weight can lead to films with different permeability characteristics which can give rise to controlled release in the upper gastrointestinal tract followed by accelerated release in the colon (biphasic release) or almost complete delivery to the colon (colonic delivery). The testing of these dosage forms was carried out in vitro using appropriate pH conditions and times to simulate transit through the upper gastrointestinal tract and using pectinolytic enzymes to mimic the degradative conditions in the colon.

The purpose of the current study is to assess the behaviour of tablets, coated with the mixed films, in human volunteers, using gamma scintigraphy. The coating conditions chosen were based on the previous in vitro studies (Ofori-Kwakye and Fell, 2003) and gave approximately 10% release of paracetamol in conditions designed to mimic the upper gastrointestinal tract, and gave accelerated release when exposed to enzymic conditions representing the colon. Radiolabelled diethylenetriaminepentaacetic acid was used as the marker to represent a soluble compound.

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2. Materials and methods

2.1. Materials

Pectin USP was received from Citrus Colloids (Hereford, UK). High molecular weight chitosan was obtained from Sigma-Aldrich (Poole, UK). HPMC was received as Methocel E4M Premium grade from Colorcon (Orpington, UK). Diethylenetriaminepentaacetic acid (DTPA) was received from Amersham International Plc (USA). Technetium-99m (^{99m}Tc) was obtained as the pertechnetate in saline, from Malinkrodt Medical (USA). Ethylcellulose (ethoxy content 48.6%) was received from Sigma Chemical (St. Louis, USA). Potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate 2-hydrate were general purpose reagents from BDH Ltd. (Poole, UK). Pectinex® Ultra SP-L with a standard activity of 26,000 PG/ml (pH 3.5) was obtained from Novo Nordisk Ferment Ltd. (Neumatt, Switzerland) and was used to simulate pectinolytic enzymes in the colon. Hydrochloric acid was supplied by Fisher Scientific (Loughborough, UK). Absolute alcohol (99.7–100%) was obtained from BDH Ltd. (Poole, UK). Distilled water was singly distilled and freshly prepared.

2.2. Tablet manufacture and coating

Tablet cores with a nominal weight of 750 mg were compressed using a rotary tablet machine (Model B3B, Manesty Ltd., Liverpool, UK), fitted with a 1.27 cm diameter normal concave punches, from granules consisting of microcrystalline cellulose (Emcocel LP200, 19.8% w/w; Emcocel LM50, 19.8% w/w), lactose (Pharmatose 450M, 19.8%), paracetamol (39.7% w/w) and magnesium stearate (0.8% w/w), massed with 5% w/v PVP. The tablets, having a breaking load of 9.6 ± 0.7 kp ($n = 20$) and friability of 0.16% w/w were coated with a coating formulation consisting of pectin USP (0.98% w/w), high molecular weight chitosan (0.16% w/w), HPMC E4M (0.06% w/w), glycerol (0.24% w/w) and 0.1 M HCl (98.55% w/w), in a perforated, 61 cm diameter 316L stainless steel coating drum, modified with a base plate to reduce the working capacity (Accelacota 10, Manesty Ltd., Liverpool, UK). The process parameters used to coat the tablets were: inlet temperature (68–70 °C), outlet temperature (50–52 °C), tablet bed temperature (32–35 °C), spray rate (13–15 g/ml), spray gun distance (18 cm), drum speed (8.7 rpm), inlet air flow (7.5–8.2 m^3/h), atomising air pressure (1.5–2.0 bar), and fan air pressure (0.7–1.0 bar). Tablets with a coat weight gain of approximately 9% w/w were produced and stored at room temperature until required. They had a mean diameter of 13.04 ± 0.03 mm and a mean thickness of 6.67 ± 0.06 mm ($n = 10$).

2.3. Radiolabelling

The film-coated tablets were radiolabelled by drilling a small hole through the coating and introducing a radioactive solution. An electric drill (Pillar Drilling Machine, Meddings Ltd., England) was used to drill holes of 1.4 mm diameter to a depth of 3 mm through the centre of the tablets. About 4–7 μl of an aqueous solution of ^{99m}Tc-labelled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) of known radioactivity was instilled into the drilled holes, avoiding contact with the surface of the tablets. The solution was allowed to dry for 15 min in a fume cupboard. A coating formulation consisting of pectin, chitosan and HPMC (6:1:0.37) was used to seal the drilled holes. A secondary seal made up of an ethanolic solution of ethylcellulose (12% w/w) was used to fully seal the drilled holes. The secondary seal extended about 0.5 mm above the surface of the tablets and covered an area slightly greater than that of the hole. The labelled tablets were left to dry overnight before use.

2.4. Stability of radiolabelled tablets

The radioactivity (counts per 20 s) of four ^{99m}Tc-DTPA labelled tablets was determined using a 2 Channel Scintillation Detector Interface (Oakfield Instruments Ltd., Oxford, UK). The tablet with the highest activity was designated as the standard tablet and the remaining three tablets used as test tablets. Dissolution tests for the release of the radioactive material were carried out on the three test tablets in 500 ml of 0.1 M HCl at 37 ± 0.5 °C for 5 h using the BP 2000 dissolution apparatus II (paddle method). The paddle speed was 50 rpm. At 30-min intervals, 5 ml samples were taken and replaced with fresh solution. At the end of the dissolution testing, the test tablets were recovered from the dissolution medium and blotted dry with tissue paper. The activity (counts

per 20 s) of the sample solutions and the standard and test tablets were counted as above. The experiment was repeated with dissolution media of pH 6.0 and pH 7.4 Sorensen's phosphate buffers. The percentage of radioactivity remaining in the tablets after 5 h of dissolution testing was calculated from the initial and final activity of the standard and test tablets with corrections made for background activity and decay.

2.5. Drug release studies

Drug release studies were carried out on the ^{99m}Tc-DTPA labelled and unlabelled film-coated tablets to determine whether the labelling process affected the kinetics of drug release from the tablets. The BP 2000, Apparatus II (paddle method) was used for the drug release studies. The release studies were undertaken at $37 \pm 0.5\,^{\circ}$C in simulated gastrointestinal fluids: pH 1.5 (2 h); followed by pH 7.4 Sorensen's phosphate buffer (3 h); and finally, pH 6.0 Sorensen's phosphate buffer containing 4 ml/l pectinex Ultra SP-L enzymes (7 h). The volume of the dissolution media was 900 ml and the paddle speed was 50 rpm. At regular time intervals, 5 ml samples were taken and replaced with fresh medium. The samples were filtered through 0.45 μm HA membrane filters (Millipore Ltd., UK) and assayed spectrophotometrically at 243 nm for paracetamol.

2.6. Gamma scintigraphy

Five healthy male subjects, having a mean age of 43.2 ± 16.0 years, mean weight of 82.6 ± 15.5 kg, and mean height of 177.0 ± 13.5 cm, were used for the in vivo gamma scintigraphy study. The subjects were all non-smokers and were not on any medication. The study was approved by the University of Manchester Committee on the Ethics of Research on Human Beings. The administration of radionuclides to healthy human subjects was approved by the Department of Health, UK (ARSAC licence).

After an overnight fast (10–12 h) to standardise the conditions of gastrointestinal motility, each subject swallowed a single ^{99m}Tc-DTPA labelled tablet with 150 ml of water. The amount of radioactivity in the tablets at the time of administration to the subjects was in the range of 4.0–6.5 MBq. The location of the labelled tablet in the gastrointestinal tract of each subject was monitored with a Sigma 410 Gamma Camera (Ohio-Nuclear Inc., OH). The single-headed gamma camera had a 40 cm field of view and was fitted with a low energy parallel hole collimator. The camera was set to detect 140 keV gamma radiation emitted by ^{99m}Tc-DTPA. The subjects stood in front of the camera and anterior images were taken for 120 s at 15-min intervals over a period of 8–10 h. The subjects were only allowed to take food and drink about 2 h after tablet administration when the images showed the tablet had emptied from the stomach. The images were recorded on a magnetic disc. The gamma camera was linked to a computer and the images were analysed using MAPS 2000 software (Link Systems Ltd., England). The images gave an indication of the spread of the radiolabel in the various parts of the gastrointestinal tract (GIT).

A determination of the tablet position and the residence time in the various regions of the GIT allowed an estimation of the gastric emptying time (GET), small intestinal transit time (SITT), ileocaecal junction lag time (ICJT), and the colon arrival time (CAT). The MAPS 2000 computer software was used to define regions of interest (ROI) around the images of the tablet in the stomach, small intestine and the colon. The activity of the tablets (counts/region) as they traversed the GIT was determined with corrections made for background activity and radioactive decay. The initial activity of the tablet (time = 0) was designated as 100% activity and the activity of the subsequent images were expressed as a percentage of the initial activity.

3. Results and discussion

3.1. Stability of radiolabelled tablets

The stability of the ^{99m}Tc-DTPA labelled tablets was evaluated in simulated gastrointestinal fluids. The amount of radioactivity released from the tablets after 5 h dissolution testing in 0.1 M HCl (pH 1.5), pH 6.0 and pH 7.4 Sorensen's phosphate buffer solutions was $23.1 \pm 3.3\%$, $18.9 \pm 0.7\%$, and $21.7 \pm 4.6\%$, respectively. Thus, almost 80% of the estimated radioactivity in the tablets at the beginning of the tests remained bound to the tablet cores after 5 h of dissolution testing in each medium. Thus, the labelling procedure is

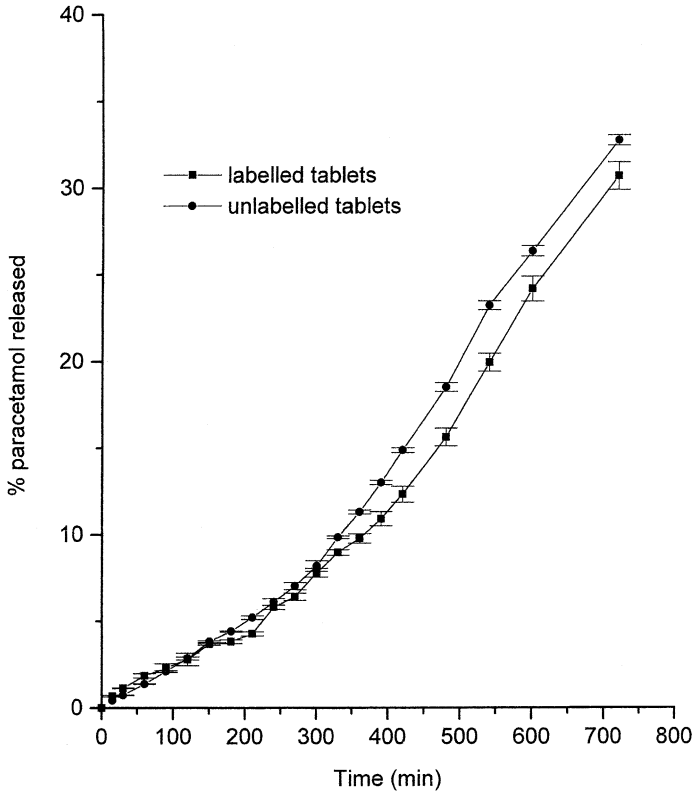

Fig. 1. Percentage paracetamol released with time from radiolabelled and unlabelled tablets.

satisfactory in that there is no sudden release of radioactivity into the dissolution media.

3.2. In vitro drug release

The in vitro release of paracetamol from the ^{99m}Tc-DTPA labelled and the unlabelled film-coated tablets was investigated to determine the possible effect of the labelling process on the kinetics of drug release from the tablets. Fig. 1 shows the drug release profiles of the labelled and the unlabelled film-coated tablets after 12 h dissolution testing in simulated gastrointestinal conditions. The cumulative amount of paracetamol released from the tablets after 12 h dissolution testing were 29.7 ± 0.79% (labelled), and 32.7 ± 0.30% (unlabelled). The similarity in the drug release profiles indicates that the labelling process had no adverse effect on the kinetics of drug release. The labelling procedure involved the drilling of a hole in the centre of the tablets, instillation of ^{99m}Tc-DTPA solution, drying and sealing. There was a negligible change in the weight of the tablets before and after drilling of the holes as tablet drilling caused a minimal loss of material (0.60 ± 0.12% w/w, $n = 10$). The technique of labelling tablets by drilling a hole, adding a radionuclide and sealing has been described previously in the literature (Macleod et al., 1999; Billa et al., 2000; Davis et al., 2001) and is clearly well suited for film-coated tablets intended for gamma scintigraphy studies.

3.3. Gamma scintigraphy

The gastrointestinal transit times of the film-coated tablets for the subjects used in the gamma scintigraphy study are shown in Table 1. The GET in the fasted state was 62 ± 17 min, with a range of 38–83 min ($n = 5$). The gastric emptying times are in agreement with those reported elsewhere for fairly large (>8 mm diameter) tablets (Macleod et al., 1999; Billa et al., 2000).

Table 1
Gastrointestinal transit data of film-coated tablets in human subjects

Subject	GET (min)	SITT (min)	ICJLT (min)	CAT (min)
1	68	195	97	360
2	67	225	106	398
3	53	243	35	331
4	38	162	96	296
5	83	197	61	341
Range	38–83	162–243	35–106	296–398
Mean	61.8	219.6	79.0	345.2
S.D.	17.0	53.9	30.0	33.6

GET: gastric emptying time; SITT: small intestinal transit time; ICJLT: ileocaecal junction lag time; CAT: colon arrival time; S.D.: standard deviation.

The gastric emptying of tablets is influenced by the physical size of the tablets and on whether the tablets are administered in the fed or fasted state (Davis, 1987). The tablets were administered on empty stomach and, being relatively large tablets, will be emptied in an erratic manner depending on their arrival time in the stomach in relation to the contractile activity of the Migrating Motor Complex (Park et al., 1984; Wilding et al., 2001).

The SITT of the coated tablets are determined as the time difference between the exit of the tablet from the stomach and its subsequent arrival in the caecum. The SITT is largely unaffected by physiological conditions and has been found to have an average value of 180–240 ± 60 min (Davis et al., 1986). The mean SITT value of 219 ± 54 min obtained in the current study is in agreement with results reported by other workers (Christensen et al., 1985; Macleod et al., 1999; Billa et al., 2000). The ICJLT ranged between 61 and 106 min with a mean value of 79 ± 30 min, confirming the valve-like action of the ileocaecal junction (Philips et al., 1988) in retaining the large film-coated tablets for significant periods. The CAT in the five subjects ranged between 296 and 398 min. Similar values have been reported in the literature for large non-disintegrating tablets (Abrahamson et al., 1996; Billa et al., 2000). The entry of the tablet in the colon was estimated by reference to the change in the stationary mode of the tablet at the ileocaecal junction to that of continuous upward movement. The GET, SITT, ICJTT and CAT are estimated values and are subject to variations in the imaging time and the time between images.

Table 2
The percentage activity remaining in the tablet in relation to estimated tablet position in the gastrointestinal tract (Subject 1)

Time (min)	Percentage activity remaining in tablet	Tablet position in GIT
1	100.0	Stomach
15	101.2	Stomach
30	99.8	Stomach
60	103.6	Stomach
90	99.6	Small intestine
120	97.7	Small intestine
180	95.3	Small intestine
240	94.8	Small intestine
300	95.2	Ileocaecal junction
360	93.1	Ileocaecal junction
420	72.1	Ascending colon
480	66.3	Ascending colon
510	58.9	Ascending colon
540	53.5	Transverse colon
600	51.7	Transverse colon

Fig. 2 shows the relationship between percentage activity remaining in the tablets and the time after tablet administration for the five subjects. Tables 2 and 3 show the data for the percentage activity remaining in the labelled tablets (relative to the initial activity on administration) for Subjects 1 and 5, respectively and the estimated position of the tablets in the gastrointestinal tract. The data for the radioactivity remaining in the tablets are estimated values as absorption of radioactivity (counts) from the tablets can occur through the overlying tissues as the tablets move along the

Table 3
The percentage activity remaining in the tablet in relation to estimated tablet position in the gastrointestinal tract (Subject 5)

Time (min)	Percentage activity remaining in tablet	Tablet position In GIT
1	100.0	Stomach
15	98.4	Stomach
30	100.4	Stomach
60	97.3	Stomach
90	95.6	Small intestine
120	91.9	Small intestine
150	92.3	Small intestine
180	88.9	Small intestine
240	83.6	Small intestine
270	84.5	Ileocaecal junction
300	81.5	Ileocaecal junction
360	66.7	Ascending colon
420	58.9	Ascending colon
480	56.8	Transverse colon

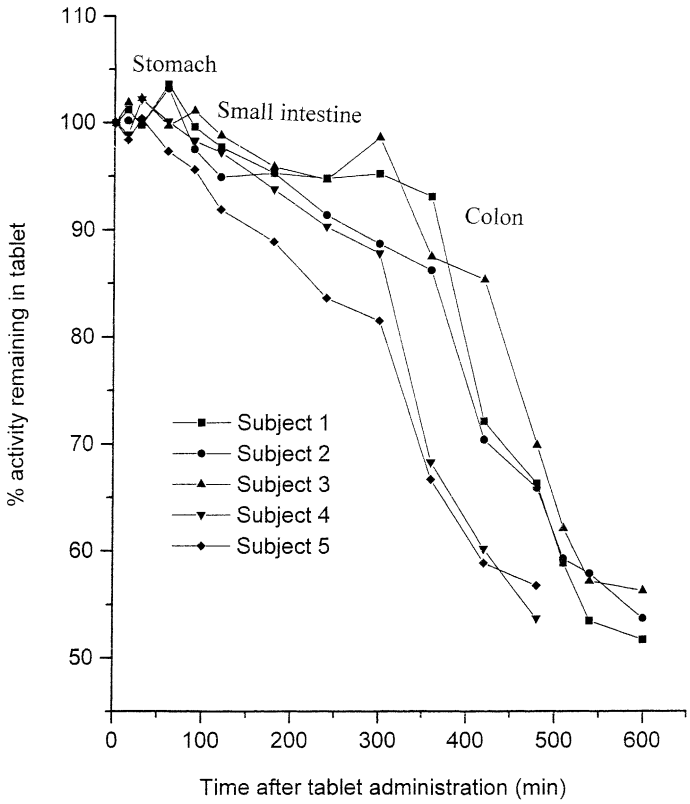

Fig. 2. Radioactivity remaining within the tablet on passage through the gastrointestinal tract.

stomach and the small intestine. A tissue of 1 cm thickness can cause a reduction in counts of about 17%. The radioactivity data reported are therefore subject to the discrepancies caused by the absorption of radioactivity by overlying tissues resulting from the movements of the tablets in the GIT.

In all the subjects, the percentage activity remaining in the tablets showed a general decline with time. The decline in the percentage activity in the tablets is an indication of the release of radioactive tracer as the tablet traverses the GIT. An estimation of the percentage activity remaining in the tablets in the GIT as a function of time after tablet administration shows a limited decline in activity when the tablets were located in the stomach and the small intestine. The decline in the percentage activity was, however, more pronounced when the tablets entered the colon. The increased release of radioactivity upon entry of the tablets in the colon is due to an increase in pectin leaching from the film coating together with an increase in the permeability and/or degradation of the films caused by the pectinolytic enzymes resident in the colon (Ofori-Kwakye, 2002).

The radioactivity remained concentrated in a small area when the tablets were in the stomach. At this point, the tablets were intact and little release of radioactivity occurred, hence the percentage activity in the tablets was high. The spread of radioactivity increased marginally when the tablets were in the small intestine due to increased diffusive release of the radioactive tracer through the hydrated film coatings. The radioactive tracer spread to cover a larger area when the tablets were in the colon and the percentage activity remaining in the tablets was considerably less.

4. Conclusions

This study has demonstrated that tablet coating using mixed films of pectin/chitosan/HPMC is capable

of delivering drugs to the colon and allowing release due to enzymatic breakdown of the coat. Additionally, some limited release was detected in the small intestine which could be enhanced by formulation changes to obtain a biphasic profile.

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