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Research paper

Correlation between *in vitro* and *in vivo* erosion behaviour of erodible tablets using gamma scintigraphy

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ABSTRACT

In vitro and *in vivo* erosion behaviour of erodible tablets consisting of glyceryl behenate and low-substituted hydroxypropylcellulose manufactured using three different methods: direct compression (DC), melt granulation (MG) and direct solidification (DS) was investigated. *In vitro* erosion behaviour was studied using gravimetric and scintigraphic methods. For scintigraphic investigations, the radiolabel was adsorbed onto activated charcoal and incorporated into tablets at a concentration that did not affect the erosion profile. A clinical study was carried out in six healthy volunteers using gamma scintigraphy. Tablet erosion was affected by the preparation method and was found to decrease in the order of preparation method, DC > MG > DS tablets. The mean *in vivo* onset time for all tablets (DC: 6.7 ± 3.8 min, MG: 18.3 ± 8.1 min, DS: 67 ± 18.9 min) did not differ significantly from *in vitro* onset time (DC: 5.3 ± 1 min, MG: 16.8 ± 3.9 min, DS: 61.8 ± 4.7 min). The mean *in vivo* completion times were found to be 36.6 ± 9.7 (DC tablets), 70 ± 18.3 min (MG tablets) and 192.5 ± 39.9 min (DS tablets). Among the three different erodible tablets, MG tablets showed the highest correlation between *in vitro* and *in vivo* mean erosion profile and suggested a potential platform to deliver controlled release of water-insoluble compounds.

1. Introduction

Pulsatile drug delivery systems (PDDS) are designed to release drug after a predetermined lag time either to coordinate drug release with the circadian rhythm of the disease [1] or to deliver drug to a particular site within the gastrointestinal (GI) tract [2]. PDDS have been formulated as pellets [3,4], tablets [5–11] and capsules [2,12,13]. Tablets designed as PDDS often consist of an active core encased within a barrier layer. The lag time before drug release from these tablet formulations is generally dependent on two factors: the rate of barrier layer removal by swelling, dissolution or erosion and subsequent fluid ingress into the core. The barrier layer composition plays an important role in determining the magnitude of the lag time and the mechanism by which it is produced. In a study by Ishino and Sunada [9], the lag time of drug release from a formulation with a barrier layer consisting of a mixture of soluble excipients and wax was dependent on the rate at which porous channels were created following dissolution of the water-soluble components. When ethylcellulose (EC) was used as a barrier layer component [11], the lag time was dependent upon water penetration through the inert EC matrix. Colon-targeted formulations incorporating plant gums khaya and albizia in a tablet barrier layer showed swelling of the tablet followed by slow diffusion of drug from the inner core tablet *in vitro* when exposed to media simulating the pH environment in the upper GI tract [14]. In simulated colonic conditions, rapid drug release was observed, as breakdown of khaya and albizia gum coats occurred in the presence of caecal matter. This illustrates that the lag time built into PDDS tablets generally depends both upon the composition of the barrier layer and also upon the environment to which the tablets are subjected. Most of the aforementioned formulations have, however, not yet been tested in the *in vivo* environment. In contrast to many other PDDS reported in the literature, a press-coated tablet (PCT) with a barrier layer based on an active erosion mechanism has shown robust performance, both *in vitro* and *in vivo* [6]

The novel barrier layer formulation investigated by our group in the current study consists of a low-substituted hydroxypropylcellulose (L-HPC) and glyceryl behenate (GB). L-HPC is a disintegrant and has been used to achieve rapid disintegration of tablets [15,16], while GB is a hydrophobic wax and has been previously reported to display sustained release matrix characteristics [17–20]. By varying the ratio of L-HPC:GB, it should therefore be possible to control the erosion rate of the barrier layer prior to drug release [21]. Our group has previously evaluated this system as a potential

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platform for pulsatile drug delivery [6,10] and demonstrated that both *in vitro* and *in vivo* lag time prior to drug release from the PCTs was dependent upon the relative concentrations of GB and L-HPC. The *in vivo* lag time was independent of fed status and location within the GI tract, and furthermore, a good correlation was observed between *in vitro* and *in vivo* performance. To gain in-depth understanding of the *in vitro/in vivo* correlation of this system, it is necessary to quantify the erosion behaviour of the barrier layer in both situations. In this study, *in vitro* erosion was quantified by gravimetric and scintigraphic methods, while *in vivo* erosion was quantified using gamma scintigraphy.

Gamma scintigraphy has been used for the quantitative determination of *in vivo* dissolution or erosion of a matrix tablets [22–26]. In a quantitative *in vivo* gamma scintigraphic erosion study, solubility of the radioisotope will play an important role in determining its mechanism of release from erodible tablet which is being quantified. Water-soluble compounds such as technetium-99 m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) are released from both hydrophilic and hydrophobic matrix tablets by diffusion [22,24,27–29]. Previous studies have either used water-insoluble chromium-51 [23,30] or a water-soluble radioisotope (indium chloride) complexed with Amberlite resin [25,26] as a marker for the erosion process. However, Amberlite resins used for gamma scintigraphic studies lack FDA status. The current study used ^{99m}Tc-DTPA dried onto activated charcoal which allowed incorporation of the isotope throughout the solid phase, thus meaning that activity would only be released as a result of an erosion process. Activated charcoal has previously been documented as a potential ^{99m}Tc-DTPA carrier for scintigraphic studies [31]; however, it has not yet been reported as a marker to quantify *in vitro* or *in vivo* erosion profiles.

To explore different barrier layer formulation manufacturing methods and investigate the effect on the erosion behaviour of the GB/L-HPC barrier layer, the current study investigated the *in vitro*/*in vivo* erosion performance of tablets prepared from only the barrier layer components. The tablets were prepared either by direct compression, melt granulation or direct solidification. The ratio of GB to L-HPC was fixed at 65:35, as this formulation previously displayed the lowest variability in the *in vivo* lag time [6].

2. Materials and methods

2.1. Materials

All materials used in the current study were of pharmacopoeial grade: low-substituted hydroxypropylcellulose (grade LH-21) (Shin-Etsu Chemical Company, Tokyo, Japan); glyceryl behenate (Compritol 888 ATO) (Gattefossé, Saint Priest Cadex, France); activated charcoal (Merck, Leicestershire, UK). ^{99m}Tc-DTPA was supplied by Radiopharmacy, Western Infirmary, Glasgow, UK.

2.2. Tablet formulation development

2.2.1. Charcoal preparation

Radiolabelled charcoal was prepared by the addition of ^{99m}Tc-DTPA to charcoal (30–200 mg) along with 0.5 mL of water, then evaporating to dryness using a hot air drier. Studies showed no leaching of activity from charcoal in various media (distilled water, pH 1.2 HCl buffer, pH 6.8 phosphate buffer) after incubation for 24 h.

2.2.2. Manufacture of radiolabelled charcoal containing tablets

Tablets were manufactured according to three different methods: direct compression, melt granulation and direct solidification. The tablets were designated DC, MG and DS, respectively. The ratio of GB to L-HPC was 65:35, and approximately 3 mg of radiolabelled charcoal per tablet was used in all formulations. For DC and MG tablets, charcoal was used in a coated form to ensure inert behaviour within matrix, which was prepared as follows: radiolabelled charcoal was mixed with molten GB in a 1:2 weight ratio and allowed to cool until solidified. The resultant dry mass was milled using a mortar and pestle and passed through a 0.3 mm sieve to obtain coated radiolabelled charcoal.

2.2.2.1. Direct compression (DC) tablets. GB (32.5 g) and L-HPC (17.5 g) powders were mixed in a Turbula® mixer for 20 min. The radiolabelled coated charcoal (3 mg) was added to 500 mg of the GB/L-HPC powder mixture. The resultant blend was transferred into a standard 13 mm punch and die set and compressed to 5 tons with a bench press to form a DC tablet.

2.2.2.2. Melt granulation (MG) tablets. L-HPC (7 g) was added to molten GB (13 g) and stirred. Stirring was continued upon removal from heat until formation of granules was observed. The granules were passed through a 1 mm sieve, and radiolabelled coated charcoal (3 mg) was added to 500 mg of the GB/L-HPC granules. The resultant mixture was transferred into a standard 13 mm punch and die set, and compressed to 5 tons with a bench press to form MG tablet.

2.2.2.3. Direct solidification (DS) tablets. It was not necessary to precoat the radiolabelled charcoal with GB for the manufacture of DS as the manufacturing process enabled adequate coating of the charcoal with GB. Radiolabelled charcoal (120 mg) was added to molten GB (13 g), followed by the addition of L-HPC (7 g) and stirred well. The molten mixture was poured into tablet-shaped (13 mm diameter) moulds and allowed to solidify to form DS tablets. The mean weight for the tablets was 518 ± 19 mg (n = 20).

2.2.3. Manufacture of 'cold' charcoal containing tablets

For non-radioactive studies, the ^{99m}Tc-DTPA solution was replaced with water to produce 'cold' labelled charcoal. The 'cold' charcoal containing tablets (DC, MG and DS) were prepared in a similar manner as described in Section 2.2.2.

2.2.4. Manufacture of the tablets without charcoal

Tablets (DC, MG and DS) containing no charcoal were prepared according to the method described in Section 2.2.2 without incorporation of charcoal.

2.2.5. In vitro gravimetric erosion studies

In vitro gravimetric erosion studies were carried out for tablets containing no charcoal and 'cold' labelled charcoal in order to ensure that incorporation of charcoal did not change the erosion profile. Erosion studies were carried out in a dissolution apparatus (USP Apparatus II, 50 rpm, 37 °C, 1L of distilled water). At set time intervals, tablets were removed from the dissolution medium and dried at 50 °C for at least 36 h. The eroded material was quantified by subtracting the weight of the dried tablet cores from the initial tablet weight. Gravimetric erosion studies cannot generate erosion profiles for a single tablet because the tablet core has to be removed from the dissolution apparatus to dry the tablet core, prior to quantifying the amount eroded from that tablet. Six data points at each time interval were determined using one tablet per data point. The mean erosion profile was obtained by plotting the mean of six individual determinations against the corresponding time point.

Dimensional studies were also carried out to determine change of thickness and diameter of DC and MG tablets during repeat *in vitro* erosion studies. At 5-min intervals for DC and 20-min intervals for MG, tablets were removed from the dissolution media, and

dimensions (thickness and diameter) were measured using digital calipers.

2.2.6. In vitro scintigraphic erosion studies

Tablets radiolabelled with approximately 1 MBq of ^{99m}Tc-DTPA-charcoal were tested in a dissolution apparatus (USP Apparatus II, 50 rpm, 37 °C, 1 L distilled water) placed in front of a gamma camera (Siemens E-Cam, Germany) fitted with a low-energy, high-resolution collimator. Dynamic acquisitions were acquired until complete erosion of tablet core was visually observed in all of the dissolution vessels. Regions of interest (ROIs) were constructed around the tablet core, and the counts were background- and decay-corrected to determine activity remaining in the tablet. The % radioactivity released from the tablet at any particular time was determined by subtracting % radioactivity remaining in the tablet at that time from % radioactivity in the tablet prior to the onset of erosion (100%). Time of onset of tablet erosion was recorded in all studies.

2.3. Clinical study

2.3.1. Study design

This was a single-centre, open label, three-way cross-over study in six healthy male volunteers aged 22–46 years (weight 66–90 kg). The summary of subject demographics is shown in Table 1. Subjects were required to have no history of GI tract disorders and be taking no regular medication. The study followed the tenets of the Declaration of Helsinki and was approved by the Glasgow Royal Infirmary Research Ethics Committee and the Administration of Radioactive Substance Advisory Committee. The study was conducted according to good clinical practice.

Subjects fasted for ten hours before each study day. At the beginning of the study day, external radioactive markers were attached to the chest and back. Subjects were dosed with one tablet per study day, 30 min after a light snack consisting of a slice of crispbread with jam and 200 mL of apple juice (500 kJ) to align the migrating motor complex cycles in subjects. Each tablet was given with 240 mL of water and contained 4 MBq ^{99m}Tc-DTPA at the time of dosing.

Scintigraphic imaging was performed with the subject in a standing position. The imaging schedules on each study day differed in order to maximise assessment of the anticipated variation in initial erosion rates. The imaging schedule was at 5- and 15-min intervals for DC and DS tablets, respectively. For MG tablets, the imaging schedule was every 10 min for 120 min, followed by every 15 min thereafter. At each set interval, anterior and posterior static acquisitions of 25 s were collected. Imaging was continued until no evidence of a tablet core remained up to a maximum of 8-h post-dose. A washout period of at least 2 days was allowed between two consecutive studies. A medical assessment was repeated within 10 days after completion of the dosing visits. The total duration of the study was approximately 6 weeks from screening to follow-up.

2.3.2. Scintigraphic data analysis

The scintigraphic images were analysed using the WebLink® image analysis program to quantitatively describe tablet erosion, determine the time and site of onset and completion of tablet erosion, and to establish gastric emptying (GE) time and colonic arrival (CA) time of the tablet core if applicable. Tablet erosion profiles were determined by drawing ROIs around the tablet core. Anterior and posterior images were analysed in this manner, and the geometric mean of the background- and decay-corrected counts was calculated for each pair of images. The % radioactivity released from the tablet at particular time was determined by subtracting % radioactivity remaining in the tablet at that time from % radioactivity remaining prior to the onset of erosion. Precise times for transit events and onset and completion of erosion could not be determined due to the intervals between image acquisitions. The times presented represent the mid-point between the images at which the event was first observed and the previous image. Small intestine transit (SIT) time was calculated as the difference between CA time and GE time.

Table 1
Summary of demographics of subjects.

No. of subjects enrolled	6
No. of subjects completed	6
Age of subjects (mean ± SD, range)	36.5 ± 8.4, range 22–46 years
Race of subjects	5 Caucasian, 1 Asian
Height (mean ± SD)	1.79 ± 0.07 m
Weight at screening (mean ± SD)	73.8 ± 8.8 kg

2.4. Calculation of erosion rate constant

To calculate the erosion rate constant (K_{ER}), a graph was plotted between radioactivity released (from onset of erosion to 80% release) against the time for each tablet, for both *in vitro* and *in vivo* studies. Only activity released up to 80% was used in the calculation of K_{ER} because the release of radioactive isotope followed an asymptotic (constant) value after 80% release. K_{ER} was calculated from the slope of the linear equation using linear regression analysis. The correlation coefficient (r^2) was also determined and only those data with a value higher than 0.90 were included in the comparison.

2.5. Erosion profile comparison and statistical analysis

In vitro erosion profiles were compared using the similarity factor test (f_2-test), which is commonly used in comparison with dissolution profiles [32]. Statistical tests performed on *in vitro* and *in vivo* scintigraphic data (onset, completion and erosion rate constant) were compared as appropriate using either one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons or *t*-test at a significance level of 95% using Minitab™ Release 14.1 (Minitab Inc., Pennsylvania, US).

3. Results and discussion

3.1. In vitro gravimetric erosion studies

Fig. 1 shows the *in vitro* erosion profiles of tablets with and without charcoal. The erosion rate was found to decrease in the order of DC > MG > DS tablets. The concentration of L-HPC was the same in all tablets; however, due to the different manufacturing methods employed, the opportunity for fluid contact with the disintegrant differed. L-HPC particles within the 'dry mix' DC tablets were uncoated by GB allowing dissolution fluid easy access to the disintegrant. L-HPC particles were completely coated by GB in DS tablets due to the melt pour manufacturing process, hindering access of dissolution fluid to the disintegrant, and significantly slowing the erosion process. For MG tablets, the L-HPC particles were distributed within the granules as well as on the surface of the granules prior to compression, leading to a higher level of partially coated L-HPC particles in MG tablets than in DS tablets and an intermediate release profile. Swelling and disintegration properties of L-HPC particles have previously been found to be responsible for the erosion characteristics of tablets [33] and it has also been shown that drug release from matrix tablets consisting of a physical mixture of drug and GB was faster than from tablets prepared by compression of melt granules consisting of the same

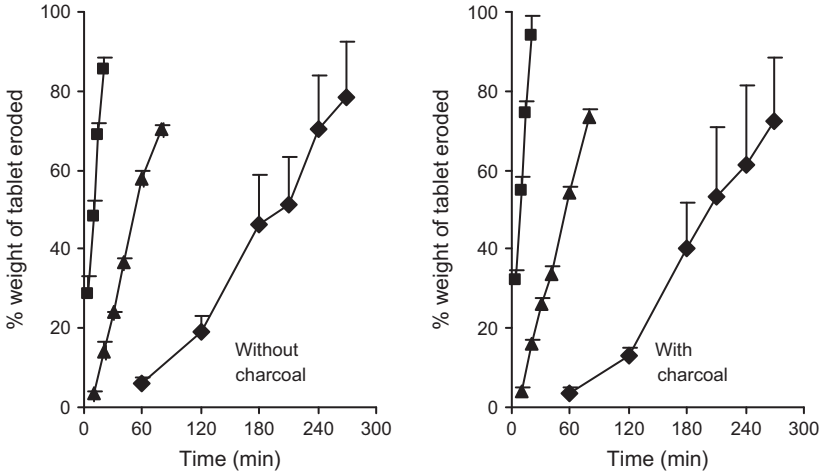

Fig. 1. Effect of manufacturing process on erosion of tablets manufactured by direct compression (■), melt granulation (▲) and direct solidification (♦) processes. Erosion studies were carried out using gravimetric method in 1 L of distilled water at 50 rpm (37 °C). Each data point is mean ± SD of $n = 6$ individual determinations.

components [17–19]. This trend was confirmed in the current study. Zhang and colleagues [18,19] showed that application of a thermal treatment step to tablets prepared by direct compression and melt granulation resulted in a decrease in drug release rate. It was suggested that heating the tablet melted the GB present, which in turn filled the void space within the tablet and formed a fine network of wax [19]. This was similar to the manufacturing method of DS whereby L-HPC was added to molten GB, resulting in the slowest erosion rate among the three tablets studied. The rate of decrease in thickness and diameter of the tablets was 0.033 and 0.034 mm min^{-1}, respectively, for MG tablets, and 0.159 and 0.178 mm min^{-1}, respectively, for DC tablets. The diameter (13 mm) of the tablet investigated in the current study was greater than the thickness of the tablet (3.4 mm), and so with both thickness and diameter decreasing at similar rate, the thickness of tablet determined the time of complete disintegration for DC and MG tablets. It was not possible to determine rate of decrease in thickness and diameter for DS tablets, because in most instances, GB and L-HPC particles eroded from the centre of the flat face of the tablet, leaving behind a toroid-shaped tablet. It was postulated that a combination of irregularity in the surface of the DS tablet and non-uniform distribution of L-HPC particles may have contributed to this effect. During solidification of the DS formulation poured into the mould, a concave dip formed on the upper planar surface, which was observed to act as the point of onset of erosion. This did not occur for the DC and MG formulations, which were manufactured using flat-faced tooling. Further to this, L-HPC is insoluble in molten wax and pouring this suspension in the mould may have resulted in the sedimentation of insoluble L-HPC particles. A future investigation into the localisation of L-HPC particles using a technique such as FT-IR mapping could confirm this second postulation [34].

Mean erosion profiles of tablets containing charcoal were similar to that without charcoal for DC ($f_2 = 60$), MG ($f_2 = 78$) and DS ($f_2 = 59$) tablets, which confirmed that the addition of charcoal did not change erosion profile.

3.2. In vitro scintigraphic erosion studies

Scintigraphic images of the erosion studies in dissolution media indicated that the radioactivity gradually accumulated at the surface of the dissolution media as the tablet eroded and released charcoal. Therefore, performing *in vitro* scintigraphy studies enabled a clear lag time prior to onset of erosion to be observed. Significant differences in the *in vitro* onset of erosion were observed for DC (5 ± 1 min), MG (17 ± 4 min) and DS (62 ± 5 min) tablets ($p \leqslant 0.005$, ANOVA). Prior to complete erosion during *in vitro* gamma scintigraphic studies, floating and rotation of the thin tablet core (at <10% of radioactive counts remaining) prevented accurate localisation of the tablet within the dissolution vessel. Therefore, it was not possible to determine the complete erosion time accurately from gamma scintigraphic images. For future experiments, sinkers are recommended for these kinds of studies to obtain a complete erosion profile. The erosion profiles of the tablets obtained by gamma scintigraphy are shown in Fig. 2. The scintigraphic erosion profiles for DC, MG and DS tablets were comparable to the data points obtained from gravimetric studies. The *in vitro* erosion rate constant for DC (4.65 ± 0.75% min^{-1}, range 3.83–5.52% min^{-1}, $r^2 = 0.96–0.99$; $n = 6$), MG (0.79 ± 0.07% min^{-1}, range 0.69–0.87% min^{-1}, $r^2 = 0.96–0.98$, $n = 6$) and DS (K_{ER} = 0.48 ± 0.07% min^{-1}, $n = 6$, 0.41–0.59% min^{-1}, $r^2 = 0.96–0.97$) was evaluated.

3.3. Clinical study

Table 2 shows *in vivo* transit and erosion parameters. Fig. 3 shows representative scintigraphic images obtained from the

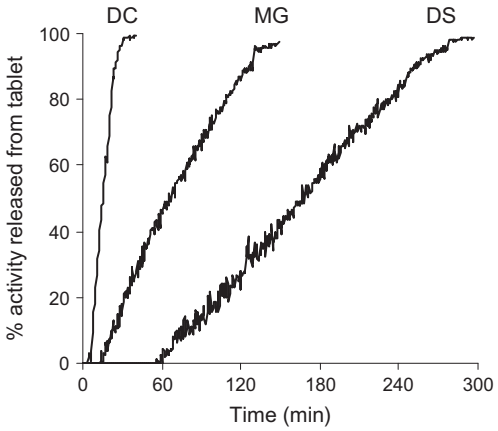

Fig. 2. Representation of mean *in vitro* erosion profile obtained using gamma scintigraphy for tablets manufactured by direct compression (DC), melt granulation (MG) and direct solidification (DS) containing radioactive isotope. Erosion studies were carried out in 1 L of distilled water at 50 rpm (37 °C). Each data point is mean of $n = 6$ individual determinations. SD is not reported for clarity purpose.

in vivo study. The *in vivo* erosion profiles of DC, MG and DS with location within GI tract are shown in Figs. 4–6 respectively.

3.3.1. Direct compression tablets

For DC tablets, the erosion process completed in the stomach for five subjects. For the remaining tablet, onset of erosion was in the stomach and completion was in the small intestine. The gastric emptying time for this tablet core was found to be 32.5 min. The mean onset and completion times for erosion were 6.7 ± 3.8 min ($n = 6$) and 36.6 ± 9.7 min ($n = 6$), respectively. These *in vivo* onset and completion times of erosion were similar to those obtained from *in vitro* gamma scintigraphic studies. No significant difference ($p > 0.05$, *t*-test) was obtained between *in vitro* (5 ± 1 min) and *in vivo* onset of erosion (6.7 ± 3.8 min). Based on visual observation of erosion profiles, the shapes of the profiles of the five DC tablets that eroded in stomach were similar; however, the tablet administered to subject 4 behaved differently (Fig. 4). In this case, the rate

Table 2
Summary of *in vivo* erosion parameters and transit data of tablets ($n = 6$).

Formulation	Subject	Onset of erosion		Complete erosion		GE time (min)
		Time (min)	Site	Time (min)	Site	
DC tablets	1	7.5	S	32.5	S	–
	2	7.5	S	42.5	S	–
	3	2.5	S	27.5	S	–
	4	12.5	S	52.5	S	–
	5	2.5	S	27.5	S	–
	6	7.5	S	37.0	SI	32.5
	Mean (SD)	6.7 (3.8)	–	36.6 (9.7)	–	–
MG tablets	1	15.0	S	142.5	SI	95.0
	2	25.0	S	105.5	SI	65.0
	3	5.0	S	105.5	SI	85.0
	4	25.0	S	115.5	SI	45.0
	5	15.0	S	95.5	SI	55.0
	6	25.0	S	125.0	SI	75.0
	Mean (SD)	18.3 (8.1)	–	114.9 (16.8)	–	70.0 (18.3)
DS tablets	1	52.5	SI	232.5	SI	52.5
	2	97.5	SI	217.5	SI	82.5
	3	52.5	S	232.5	SI	67.5
	4	82.5	SI	157.5	SI	67.5
	5	67.5	SI	142.5	SI	22.5
	6	53.0	S	172.5	AC	53.0
	Mean (SD)	67.0 (18.9)	–	192.5 (39.9)	–	57.6 (20.5)

DC: direct compression; MG: melt granulation; DS: direct solidification; GE: gastric emptying; S: Stomach; SI: Small intestine; AC: Ascending colon.

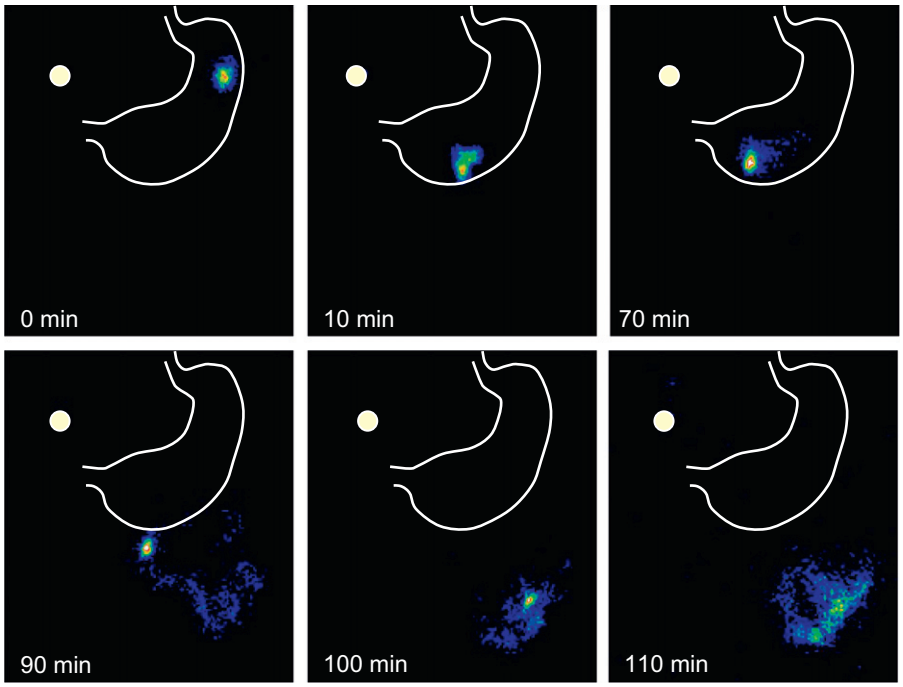

Fig. 3. Representative anterior images of melt granulation tablet in subject 3. A white circle represents the marker used for the alignment of sequential images. A stomach outline is provided for visualisation of the tablet location. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

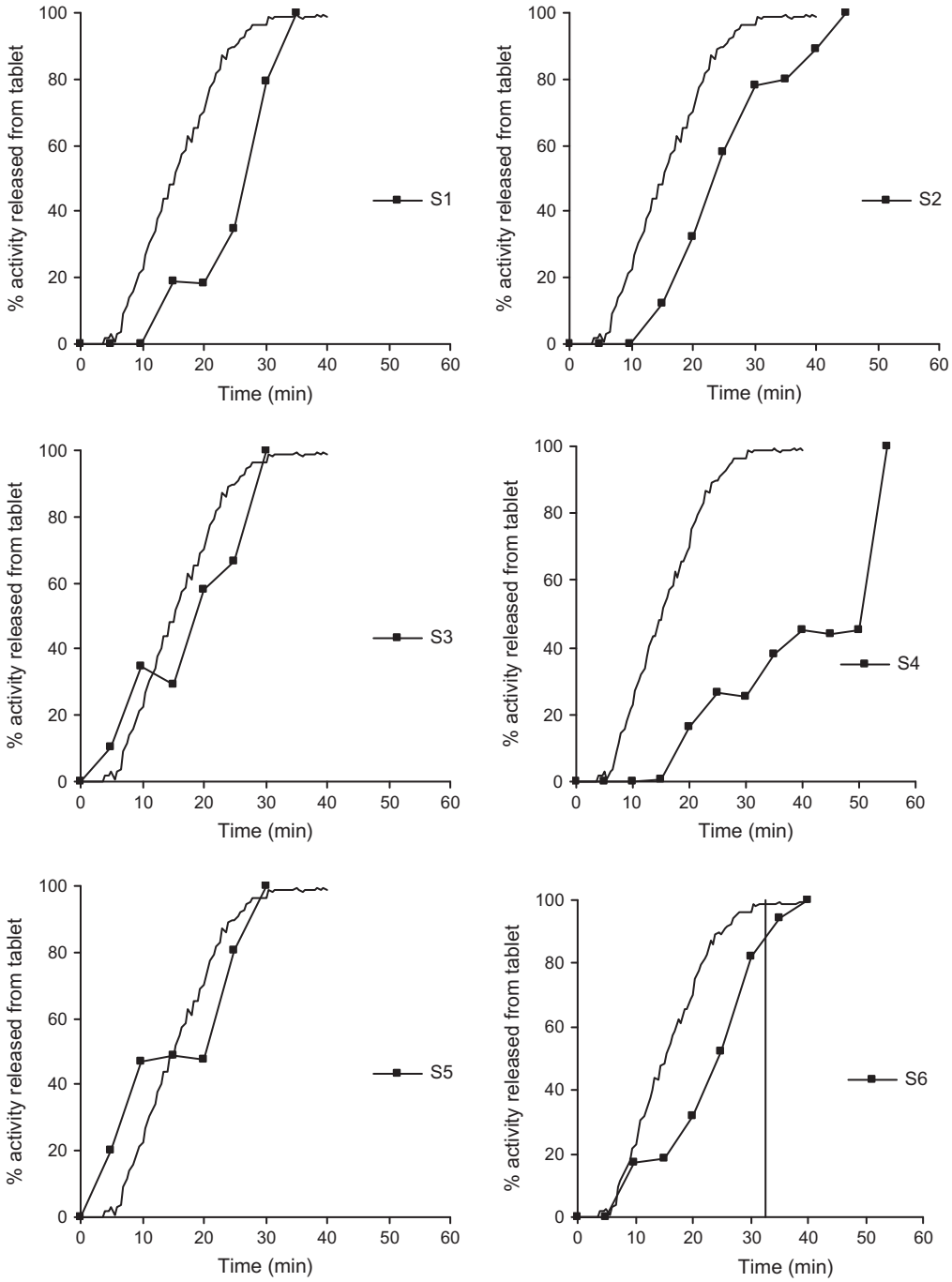

Fig. 4. Individual *in vivo* scintigraphic erosion profiles of DC tablets (■) in subject (S) 1–6 and comparison to mean *in vitro* scintigraphic erosion profile (continuous line, $n = 6$). Vertical line (|) represents virtual boundary between stomach and small intestine.

of erosion for the tablet up to 50 min was slower than for the other tablets. The image for this tablet at 50 min showed more than 50% activity remaining, while the subsequent image at 60 min showed complete erosion. The mean K_{ER} calculated in five subjects (excluding subject 4) with $r^2 \geqslant 0.90$ (range 0.91–0.96) was 3.20 ± 0.45% min^{-1} ($n = 5$, range 2.83–3.99% min^{-1}). This was slightly lower than the K_{ER} obtained from *in vitro* gamma scintigraphic studies (4.65 ± 0.75% min^{-1}, $n = 6$) for the DC tablet, and significant difference was found at $p \leqslant 0.004$ (*t*-test).

3.3.2. Melt granulation tablets

For all MG tablets, the erosion started in the stomach and completed in the small intestine. The times of onset and completion were found to be 18.3 ± 8.1 min ($n = 6$) and 70.0 ± 18.3 ($n = 6$) min, respectively. These values were similar to those obtained from the *in vitro* scintigraphic studies. No significant difference was found between *in vitro* (17 ± 4 min) and *in vivo* (18.3 ± 8.1 min) onset of erosion ($p > 0.05$, *t*-test). Gastric emptying time varied from 45 to 95 min with a mean of 70.0 ± 18.3 min ($n = 6$). Dosage forms are subjected to variable pH during GI transit [35]. Furthermore, major differences in the destructive forces between stomach and small intestine have been reported [36,37]. Irrespective of the duration of exposure in the stomach and small intestine, erosion profiles obtained from all subjects were similar for MG tablets (Fig. 6). The mean K_{ER} calculated in five subjects (excluding subject 2) with $r^2 \geqslant 0.90$ (range 0.92–0.96) was 0.94 ± 0.18% min^{-1}

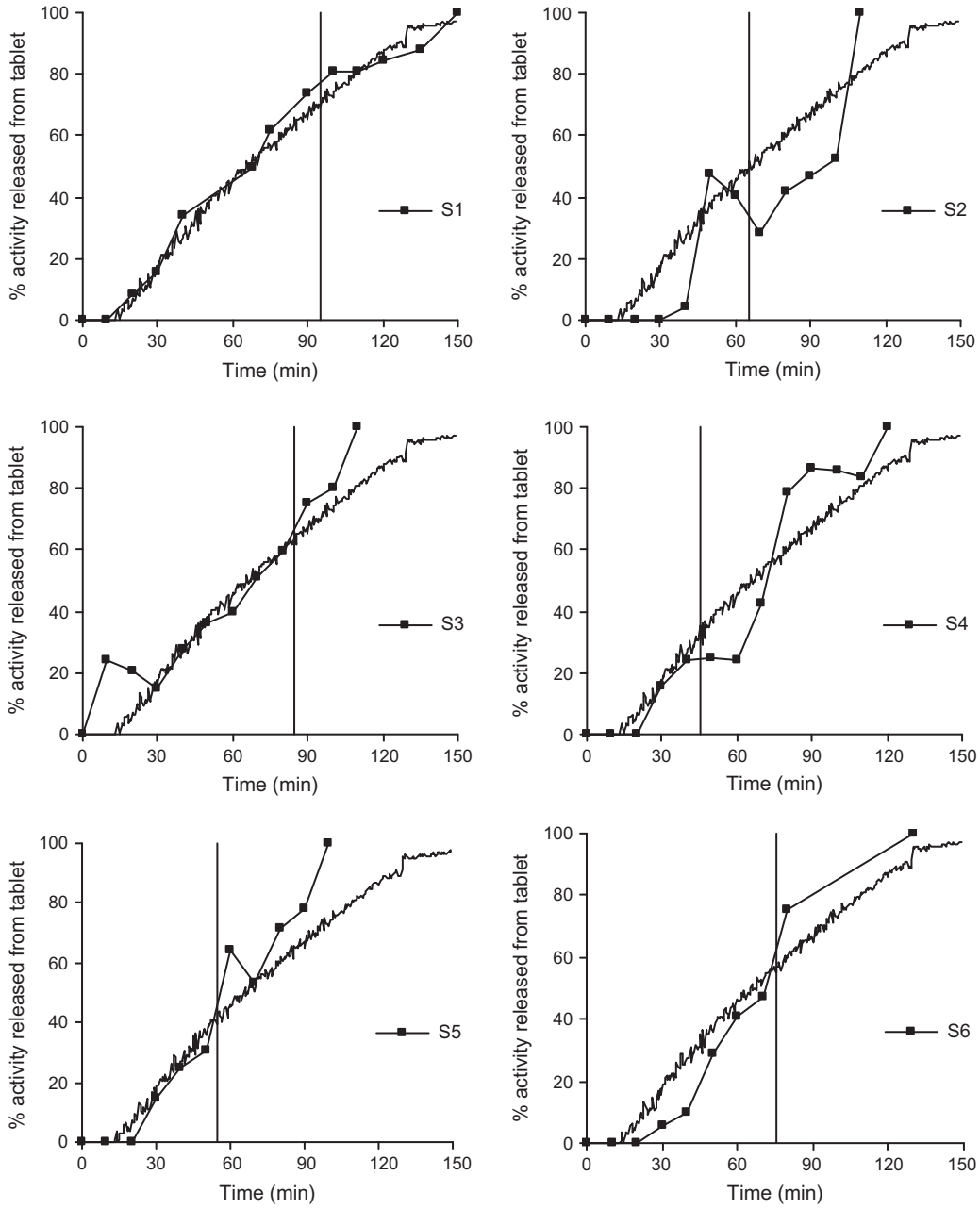

Fig. 5. Individual *in vivo* scintigraphic erosion profiles of MG tablets (■) in subject (S) 1–6 and comparison to mean *in vitro* gravimetric erosion profile (continuous line, $n = 6$). Vertical line (|) represents virtual boundary between stomach and small intestine.

($n = 5$, range 0.72–1.17% min^{-1}). These values were similar to the K_{ER} obtained in the *in vitro* gamma scintigraphic studies ($0.79 \pm 0.07\%$ min^{-1}, $n = 6$), and no significant differences were found between *in vitro* and *in vivo* erosion rates for MG ($p > 0.05$, *t*-test). This may be because the erosion rate of the MG barrier layer of PCT was shown to be unaffected by changes to the pH of dissolution media (pH 2–7) and paddle speed of the dissolution apparatus (0–50 rpm) in a previous study [38]. Furthermore, *in vivo* lag time of MG barrier layer PCTs was also found to be largely independent of location within GI tract in dogs [6].

3.3.3. Direct solidification tablets

Onset of erosion was in the stomach for DS tablets in four subjects, while for the remaining two, onset of erosion was in the small intestine. The mean onset time was found to be 67.0 ± 18.9 min ($n = 6$). Mean gastric emptying time for DS tablets was 57.6 ± 20.5 min ($n = 6$). Five of the DS tablets showed the complete erosion in the small intestine, whereas one disintegrated in the ascending colon with a small intestinal transit time of 85 min. Mean complete erosion time was 192.5 ± 39.9 min ($n = 6$). No significant difference was found between *in vitro* (62 ± 5 min) and *in vivo* (67.0 ± 18.9 min) onset of erosion ($p > 0.05$, *t*-test). The erosion profiles of the DS tablets are shown in Fig. 6 where fragmentation of the tablet core was found in four subjects. The % activity eroded from these tablets in the preceding image prior to fragmentation ranged from 19% to 49%. It has been discussed in Section 3.1 that the *in vitro* erosion of DS tablets was not uniform, leaving behind a toroid-shaped partially eroded core. It is hypothesised that the erosion might have proceeded to a stage where a toroid-shaped tablet core was unable to withstand the

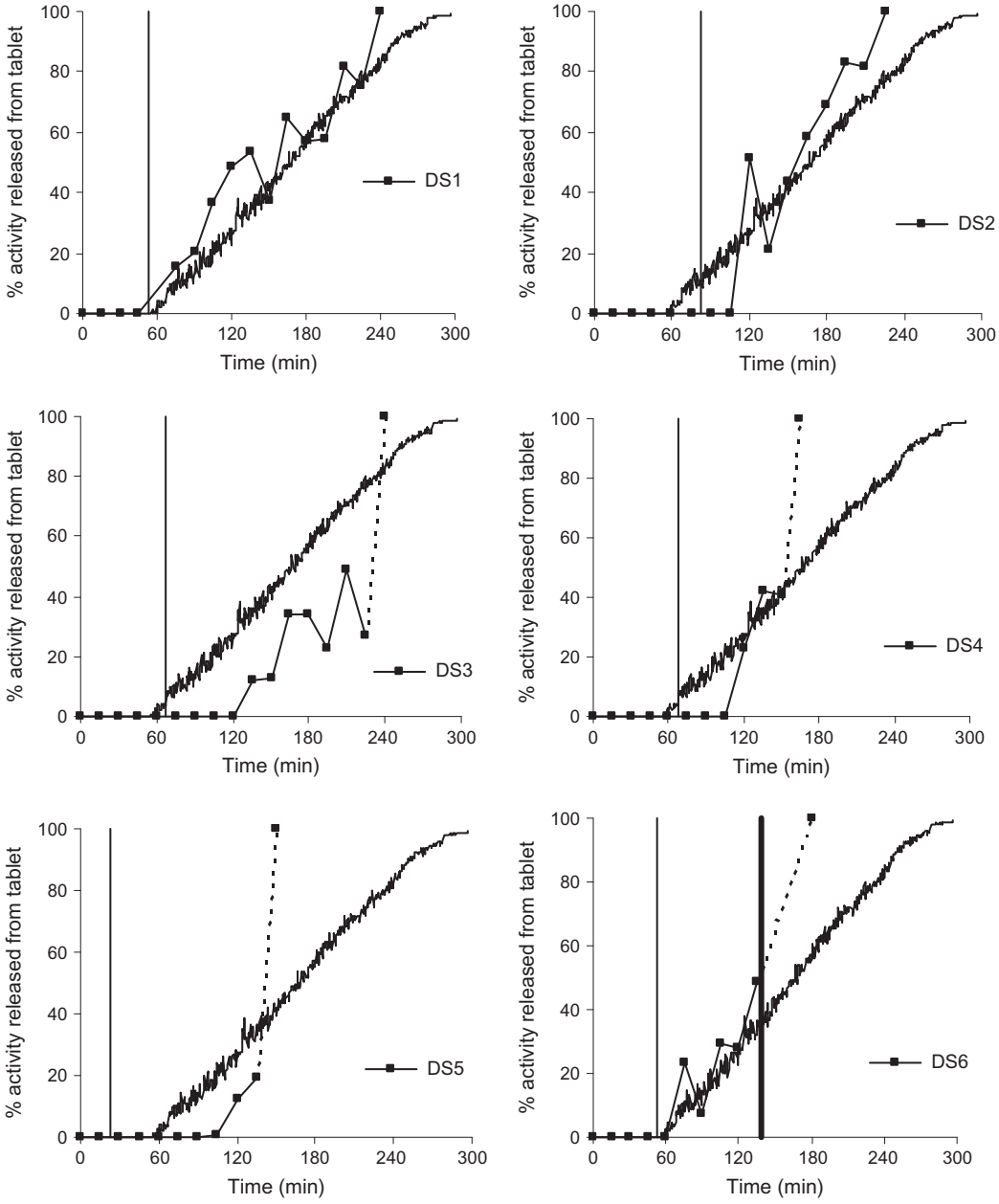

Fig. 6. Individual *in vivo* scintigraphic erosion profiles of DS tablets (■) in subject (S) 1–6 and comparison to mean *in vitro* scintigraphic erosion profile (continuous line, $n = 6$). A broken line (- - - -) represents fragmentation of the tablet *in vivo*. Vertical lines (|) and (⁞) represent virtual boundary between stomach and small intestine, and small intestine and colon, respectively.

destructive forces in the GI tract and complete erosion or fragmentation occurred within a short period. This led to poor correlation between *in vitro* and *in vivo* erosion profile. Only one of the non-fragmented tablets (subject 1) showed $r^2 \geqslant 0.90$ with K_{ER} of 0.44, when fitted into a linear equation. Therefore, no statistical analysis was performed between the *in vitro* ($K_{ER} = 0.48 \pm 0.07\%$ min^{-1}, $n = 6$) and *in vivo* erosion rate constant.

3.3.4. Comparison between in vivo performance of DC, MG and DS tablets

The *in vivo* erosion parameters were found to be dependent on the method of manufacture of the tablet. The mean onset time of erosion and mean time of completion were found to increase in the order DC < MG < DS tablets. Statistical analysis using ANOVA followed by Tukey's multiple comparison showed significant differences ($p \leqslant 0.005$) between the onset time of erosion for DC and DS, and MG and DS tablets; however, no significant difference was found between onset time of erosion for DC and MG tablets. There was a significant difference ($p \leqslant 0.005$, ANOVA) between the mean *in vivo* completion times of DC (36.6 ± 9.7 min), MG (70.0 ± 18.3 min) and DS (192.5 ± 39.9 min) tablets (Table 2). The *in vivo* rate of erosion was found to decrease in the order of DC > MG > DS. This is in agreement with the trend obtained in the *in vitro* studies and those documented in the literature [17–19].

The DC tablets showed good correlation between *in vitro* and *in vivo* erosion rates; however, >80% of the original content of the tablets was eroded within 1 h. This suggested that the lag time will be quite short if these DC formulations are used as a barrier layer component of a pulsatile release tablet. Similarly, due to the lack of robust performance of the DS formulation in both

in vitro and *in vivo* environments, this formulation cannot be used as barrier layer component of a pulsatile release system. The failure of the DS tablets to provide robust performance was postulated to be a result of non-uniform erosion and formation of toroid-shaped tablets during *in vitro* erosion studies as discussed in Section 3.1. Among the three different manufacturing methods employed, tablets manufactured by melt granulation showed the most robust *in vitro* and *in vivo* erosion profile. This MG formulation can therefore be used as a barrier layer component to obtain a lag time prior to pulsatile drug release in press-coated tablet formulations. In addition, the robust performance and gradual erosion of the MG tablets also demonstrated the potential of this system to be explored as platform to deliver poorly water-soluble drugs, where the mechanism of drug release is predominantly by erosion. The linearity ($r^2 > 0.92$) of the erosion rate of the MG system offers the potential of near zero-order *in vivo* release performance, which was not commonly achieved with HPMC matrix tablets [23,30,39]. The zero-order erosion profile observed in the MG system is thought to be a result of the dissolution media coming into contact with the MG tablet surface, causing L-HPC particles present there to swell and erode in conjunction with GB, therefore exposing new L-HPC particles and allowing continuation of this "active erosion" process. This erosion process would be different from hydrophilic matrix tablets, where the polymer undergoes swelling, and a distinct gel layer is formed between a swelling and an eroding front.

4. Conclusion

The current study demonstrated that the manufacturing process affects both the *in vitro* and *in vivo* erosion rate of tablets consisting of the materials intended for use as a barrier layer in a press-coated tablet formulation. Rates of erosion according to preparation method decreased in the order of direct compression > melt granulation > direct solidification. The tablet radiolabelling process was validated, thus enabling the quantification of erosion rates by scintigraphic methods. Gamma scintigraphy was also utilised successfully in this study to describe and differentiate the erosion behaviour of three types of tablets in *in vitro* and *in vivo*. *In vivo* erosion behaviour of the erodible tablet was independent of the site of location within the GI tract. Among the three different formulations, MG tablets showed the highest correlation between *in vitro* and *in vivo* erosion profile and could be used as barrier layer component of pulsatile release, press-coated tablet formulations. Furthermore, the MG tablets showed potential for delivery of water-insoluble drugs in a controlled release fashion.

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