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Research paper

Assessing gastrointestinal motility and disintegration profiles of magnetic tablets by a novel magnetic imaging device and gamma scintigraphy

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ABSTRACT

Purpose: To validate Magnetic Moment Imaging (MMI) for the investigation of gastrointestinal transit and disintegration of solid dosage forms and to correlate the MMI findings with the corresponding gamma scintigraphic data.
Materials and methods: Three magnetic tablets (MTs) were investigated using *in vitro* and *in vivo* tests. The clinical study was a four-way, crossover study with the following arms: (a) immediate-release tablets administered in fasted state; (b) immediate-release tablets administered after 400 mL of Clinutren® ISO; (c) enteric-coated tablets administered in the fasted state; and (d) non-disintegrating tablets studied in the lightly fed state (100 mL of Clinutren® ISO).
Results: In both the *in vitro* and *in vivo* studies, tablets were detected successfully by MMI and scintigraphy. There was a good correlation between gastric residence times and positional data (in the *x*, *y* and *y*, z-axes). In addition, MMI revealed early swelling behaviour of the tablet matrix. There was excellent agreement for the disintegration times of MT(A) in the fasted arm (scintigraphy 12.0 ± 4.4 min, MMI 11.8 ± 4.4 min). In the MT(A)-fed arm, onset times determined by scintigraphy were delayed in three subjects when compared to the corresponding MMI results. Delayed disintegration was observed with MT(A) administered after food ($p < 0.01$) in both the techniques.
Conclusion: The MMI device is a reliable imaging tool for tracking the transit and disintegration of a magnetic tablet through the gastrointestinal tract.

1. Introduction

The use of the gamma camera to study novel formulations in man was reported in the late 70s [1,2] and since then it has remained the 'gold standard' imaging technique to study the *in vivo* characteristics of orally administered formulations such as tablets, capsules and multi-particulates [3–10]. Although highly utilised, the drawbacks of gamma scintigraphy include the radiation exposure to the volunteer, which minimises the number of repeat studies and restricts its use in women and children. In some countries, the use of radiation is prohibited in healthy individuals, and the instrumentation is neither portable nor widely available.

Alternative imaging techniques such as ultrasound and ^{13}C-octanoic breath tests have been validated against gamma scintigraphy for the investigation of motility and transit parameters [11,12]. These methods are used for diagnosis, but are really not adaptable for the study of dosage forms as required by the pharmaceutical scientists.

A bio-magnetic method known as Magnetic Moment Imaging (MMI) is a novel technique which is of increasing interest in clinical, physiological and pharmaceutical researches. An appropriate magnetic measuring device is used to measure the magnetic field generated from a magnetically tagged solid dosage form whilst in the gastrointestinal tract. The magnetic field generated by the magnetic dipole moment penetrates the tissue without distortions which can then be detected non-invasively from outside the body. Ferrous materials such as iron oxide (Fe_3O_4, food colourant E172) and manganese ferrite ($MnFe_2O_4$) have been used to magnetically label dosage forms and meals [23–26], and permanent magnets have also been utilised to study the physiological aspects of gastrointestinal motility [27–31].

Superconducting Quantum Interference Devices (SQUIDS) are the most highly sensitive magnetic sensors used for MMI. This technique has been used to study the behaviour of disintegrating capsules [13] and non-disintegrating capsules [14,15], and the

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oesophageal transit of dosage forms [16]. A study investigating the effects of food on plasma profiles of extended-release tablets [17] demonstrated that by combining MMI and pharmacokinetic data, real insight into gastrointestinal physiological events and delayed release of drug formulations can be obtained. The real-time imaging can also provide excellent anatomical details in a 3-dimensional plane. However, the highly sensitive SQUID sensors have a few disadvantages; they are large and are costly to be run and maintained and they need to be housed in magnetically shielded rooms to take the measurement of the tiny magnetic moment generated by the formulation against the swamping effect of the earth's magnetic field. Generally, measurements are collected with the subject in the supine position, and posture effects on transit cannot be ignored.

Alternating Current Biosusceptometry (ACB) is an imaging technique where induction coils detect variations in the magnetic field produced by the ingested magnetic material. This technique has been used to quantify pharyngeal and oesophageal transit times [18,19], to measure gastric antral contractions [20] and gastric emptying rates [21], to assess the disintegration of a magnetic tablet in the stomach [22,23], and to quantify the transit and disintegration of an enteric-coated tablet and capsule in the colon [24,25] as well as to monitor colonic motility [26]. This technique can be performed without the need for a magnetically shielded room; however, the positional co-ordinates in the *x*-, y- and *z-planes* of the magnetically labelled meal or dosage form are not separated, making comparisons between this technique and standard imaging methods difficult.

There is clearly an opportunity for a direct, alternative imaging technique to study the transit of dosage forms (both disintegrating and non-disintegrating) and to detect altered motility patterns that are apparent in many diseases. The objective of the current study was to validate the application of the MTS1000 as an instrument to measure gastrointestinal transit of oral formulations in a normal clinical setting. Various phantom and *in vitro* disintegration tests were performed to establish that different magnetic tablets could be detected by the MTS1000. A clinical study employing simultaneous use of gamma scintigraphy and MMI to monitor the behaviour of three different radio-labelled magnetic tablets was then carried out. One of the main advantages of the MMI technique is that the tumbling and real-time movement of the dosage form can be visualised. This prompted a secondary objective to investigate the effect of food in the stomach on these movements.

2. Materials and methods

2.1. Materials

All the materials used in the current study were of pharmacopoeial grade. The black iron oxide complied with the EC Directive 95/45/EC E172 specification. Other materials included acetone, isopropyl alcohol (IPA), methanol, and hydrochloric acid 37% AnalaR (Merck Eurolab, UK). Formulations for human use were prepared using clear coloured size 00 capsules made from hydroxypropyl methylcellulose (HPMC) (Vcaps®) (Capsugel, division of Pfizer Inc, UK); black iron oxide (E172) (Town End plc, Leeds, UK); Avicel PH105 (microcrystalline cellulose) (FMC Biopolymer, Belgium); magnesium stearate (Sigma–Aldrich, Germany); low-substituted hydroxypropyl cellulose (LH-21) (Shin-Etsu Chemical Co, Ltd., Japan); Primojel (sodium starch glycolate) (Univar, UK); Eudragit L100 (Degussa, Rohm Pharma Polymers, Germany); Kollidon 30 (polyvinyl pyrrolidone, PVP) (BASF Chemical Company, Germany); lactose (JML plc. Southampton, UK); Clinutren® ISO (Nestlè Clinical Nutrition UK); Citroflex-2 (triethyl citrate) (Morflex Inc, North Carolina, USA); and Ethocel standard 10 premium (ethylcellulose) (Dow Chemical Company, Michigan, USA). Technetium-99m-diethylenetriaminepentaacetic acid, [^{99m}Tc]-DTPA, was supplied by the West of Scotland Radionuclide Dispensary, Glasgow, UK.

2.2. The magnetic tracking system

The magnetic tracking system, MTS1000 (STL, Systemtechnik, Ludwig GmBH, Germany), is lightweight (2.9 kg) and portable (dimensions: 539 × 252 × 88 mm). It contains a measuring detector which consists of 72 Anisotropic Magnetoresistors sensors (AMR sensors). The sensors are arranged in a square with a third of the sensors orientated in the *x*-direction, a third in the *y*-direction and a third in the *z*-direction. This arrangement depicts that for each sensor and for each data point, magnetic dipoles three components *x*, y and *z*, two angles characterising the location and its magnetic moment can all be quantified. The fitting procedure is a novel signal processing technique that uses advanced software gradiometers according to proprietary algorithms. These algorithms allow the location, orientation and strength of the magnetic moment to be determined.

2.3. Manufacture of magnetic tablets

Three different tablets were manufactured: an immediate-release magnetic tablet, MT(A), with an *in vitro* disintegration time of 10–20 min; an enteric-coated magnetic tablet, MT(B), and a non-disintegrating magnetic tablet MT(C). The different compositions of the excipients for MTs(A–C) are listed in Table 1. Formulation batches were prepared to produce 30 tablets. All the excipients except magnesium stearate were mixed in a Turbula mixer (Glen-Creston Instruments Ltd., Middlesex, UK) for 20 min, following which the magnesium stearate was introduced to the blend and mixed for another 5 min. This was then passed through a No. 18 sieve. [^{99m}Tc]-DTPA-labelled lactose (activity 2 MBq at the time of dosing) was added to 1.51 g of the powder mix and was distributed with a spatula. This mixture was manually compressed at a pressure of 1 ton using a Spex CertiPrep Bench Press (Spex CertiPrep Ltd., Middlesex, UK). Two different punch and die sets (Penta Punch & Die Co. Ltd., Nottingham, UK) were used to produce tablets with the following dimensions: MT(A), 19 × 6 × 7 mm; and MT(B) and MT(C), 19 × 6 × 9 mm. Tablets had a density of 2.2 g/cm^3.

2.4. Coating of magnetic tablets

MT(A) was encased in a 00 HPMC capsule. MT(B) and MT(C) were spray coated using a mini-coater drier (MCD-2,Caleva Process Solutions Ltd., UK) using the coating solutions and conditions outlined in Table 2. MT(B) was coated with a PVP sub-coat prior to an enteric top coat.

2.5. Magnetisation of magnetic tablets

Tablets were magnetised in a permanent magnetic assembly for 10 min at a magnetic field strength of 0.79 Tesla (e-Magnets, UK). The magnetic field strength of the tablets was checked using a hand-held gaussmeter (Hirst Magnetic Instruments Ltd., UK).

2.6. Phantom and in vitro disintegration experiments

MMI acquisitions were recorded using the DView-MTS v5.4-1.7 software for data acquisition (sampling frequency of 100 Hz). Three regions were defined on the sensor area of the MTS1000: region I, 0–4 cm from the origin; region II, 4–8 cm from the origin; and an outermost region III, 8–12 cm from the origin. Moment and position deviations were investigated at different heights (2 cm intervals) above the sensor area in the *z-plane* until they

Table 1
The composition of the magnetic tablets: MT(A), MT(B) and MT(C).

	Iron oxide (g)	Avicel PH105 (g)	Sodium starch glycolate (g)	LH-21 (g)	Magnesium stearate (g)
MT(A)	1.0	0.45	0.05	Nil	0.01
MT(B)	1.0	0.45	Nil	0.05	0.01
MT(C)	1.0	0.5	Nil	Nil	0.01

MT(A): immediate-release magnetic tablet.
MT(B): enteric-coated magnetic tablet.
MT(C): non-disintegrating magnetic tablet.

Table 2
Caleva mini-coater/drier conditions for coating MT(B) and MT(C).

Mini-coater conditions	MT(B) 3% (w/v) PVP solution	MT(B) 1.8% (w/v) Eudragit L100 solution	MT(C) 3%(w/v) ethylcellulose solution
Fan speed (m/s)	10	6.0	12
Temperature (°C)	40	20	40
Solution delivery rate (rpm)	2.0	2.0	2.5
Nozzle height (mm)	150	140	100
Frequency (Hz)	17.5	17.5	17.5
Air pressure (bar)	0.4	0.4	0.4
Spray time (min)	15	30	60

MT(B): enteric-coated magnetic tablet.
MT(C): non-disintegrating magnetic tablet.

were no longer detected. The deviations between the actual co-ordinates and those determined by the MTS1000 were plotted.

To establish the natural variation of the magnetic moment signal during movement, a tablet was positioned on a plastic rotating arm and was manually rotated during the MMI recording. The radius of the tablet path was altered (2.2, 5 and 9 cm) in order that all the three different sensor regions were included. This was repeated at different heights above the sensor and plots of the magnetic moment signal produced.

Simultaneous studies using the MTS1000 and a gamma count rate meter (count rate meter NE4700, J&P Engineering, UK) were completed to measure the disintegration of the radio-labelled tablets: MT(A) and MT(B). Normal metal laboratory stirrers create signal distortions during the detection of a magnetic dipole by the MTS1000. Thus, a dissolution assembly was constructed using non-ferromagnetic materials (including a plastic dissolution stirrer and a glass thermostated jacketed beaker which was placed directly on the MTS1000). In all the studies of MT(A), disintegration parameters (onset and completion times and duration) were investigated using a simulated fasted medium (HCl, pH 1) and a simulated fed medium (Clinutren® ISO diluted to 60% with HCl, pH 1; resulting pH = 3.28). Tablets from a batch of MT(B) formulations were immersed in HCl, pH 1, for 2 h and thereafter in phosphate buffer, pH 6.8 (PB 6.8). In all the investigations, 500 mL of media was maintained at 37 °C and a stirring speed of 90 rpm (maximum speed of the constructed dissolution assembly) was employed.

Following an initial blank sample, 2 mL samples of the dissolution media were taken at different time intervals depending on the formulation. The time the sample was analysed was also recorded in order to correct for ^{99m}Tc decay. All decay-corrected radioactive counts and corresponding magnetic moment signals were entered into Microsoft Excel®, and plots were constructed comparing release of the radiolabel from the tablet core and decrease in the magnetic moment with time. For the radioactive measurement, onset of disintegration was determined as the midpoint between the time when 100% of the radiolabel was still in the core and the time when radioactivity was detected in the media. Further studies were performed on the non-disintegrating tablet, MT(C), to investigate coating integrity, radiolabelling and the effect of liquid immersion on the magnetic signal.

2.7. Clinical study

A single-centre four-way crossover, analyst-blind study was performed in six healthy male subjects, ages ranging from 23 to 33 years (mean: 29.5 ± 5.7 years). The mean body weight was 82.2 ± 8.5 kg and mean body mass index (BMI) was 24.3 ± 3.6. All volunteers had no history of gastrointestinal symptoms and had no metal plates in or non-removable jewellery on their body. Written informed consent was given by all volunteers before the study, and the study followed the tenets of the Declaration of Helsinki and was approved by the Glasgow Royal Infirmary Research Ethics Committee.

On arrival at the study centre on each study day, external radioactive markers were attached to the chest of each subject to allow accurate image alignment of sequential scintiscans. A small tape marker was also attached to the midline of the subject's anterior to facilitate alignment at each MMI recording. MT(A) was randomly given in the fasted state or 15 min after 400 mL Clinutren® ISO (1680 kJ). MT(B) and MT(C) were given 5 min after 100 mL Clinutren® ISO (420 kJ). All tablets were administered with 240 mL water.

In all the study arms, immediately after dosing, a 2-min anterior MMI acquisition was recorded (sampling frequency of 100 Hz, 12,000 data points). The subject then walked to another room where a 30-s anterior scintigraphic image was acquired. During the initial MMI recording the subject's tape marker was aligned to a specific position on a lettered scale system in order that the stomach was positioned within the sensor detection region. In all the subsequent measurements, the subject was asked to re-align himself to the same point on the scale. When studying MT(B) and MT(C), transit through the lower gastrointestinal tract resulted in the tablet moving outwith the sensor range. In this situation, the subject was asked to stand on a secure platform which had a height of 15.5 cm.

MMI and scintigraphic imaging schedules were dependent on the tablet studied. The maximum imaging times were 2, 6 and 8 h post-dose for MT(A), MT(B) and MT(C), respectively. Upon completion of imaging, MT(A) and MT(B) subjects received a light lunch or snack before leaving the study centre. Subjects dosed with MT(C) received lunch 6 h post-dose.

2.8. Data analysis

MMI data were analysed using Axum Mathcad v5.0 software. The magnetic moment signal was plotted for all the recordings to give information on the integrity of the tablet. Spatial positioning of the tablet within the gastrointestinal tract was determined by plotting the co-ordinates on the *x*–*y* and *y*–*z*-planes, and velocity plots were created where appropriate. From the positional plots, gastric residence times and the anatomical positioning at all time points could be determined. The appearance of the tablet in the small intestine was determined when its position dropped lower down in the *y-axis*. In conjunction with this event, there was an increased movement of the tablet away from the sensor (as observed by an increase in the *z*-axis) due to the increased anatomical depth of the duodenum compared to the stomach.

Preliminary *in vitro* disintegration studies were carried out to determine how to quantify disintegration of the tablets using MMI. It was observed that there was a slow gradual loss of up to 20% in the magnetic moment prior to the onset of disintegration

of both MT(A) and MT(B). Once the tablets started to disintegrate, there was a marked change in the gradient of the line as illustrated in Fig. 2. Typically it was noted that a rapid decrease in the magnetic moment of between 50% and 80% within a 2-min period depicted tablet disintegration.

If an event (such as gastric emptying or disintegration) occurred during the 2-min MMI recording, the actual time of the event was presented. Otherwise the times presented represent the midpoint between the acquisition at which the event was observed and the previous MMI acquisition.

Scintigraphic images were analysed using the Weblink® image analysis program. Intact tablets were visualised as a single well-defined object in scintiscans, whilst tablet disintegration was visualised by the obvious spread of the radiolabel. The time of the onset of tablet disintegration was defined as the time when the spread of the radiolabel from the tablet core was first observed. Time for the completion of disintegration was defined as the time when a distinct tablet core could no longer be identified. For the measurement of all other outcomes, the times presented were derived from the midpoint between the image at which the event was observed and the previous image.

2.9. Statistical analysis

Mean data for onset, completion and duration of disintegration measured by the two techniques were compared using paired *t*-tests. The mean onset, completion and duration of disintegration results for MT(A) in the fed and fasted states were also compared to the *in vitro* results to evaluate the possibility of a correlation using unpaired *t*-tests.

Gastric residence times, small intestinal transit times (SITTs), colon arrival times and site of disintegration, where appropriate, were compared between MMI and gamma scintigraphy.

3. Results

3.1. Phantom and in vitro disintegration experiments

Results from the *in vitro* experiments showed that the magnetisation procedure produced tablets with a magnetic flux between 0.012 and 0.014 Tesla (120–140 Gauss) and a magnetic moment of between 16 and 19 mA m^2 determined by the MTS1000. All tablets were successfully detected by the MTS1000 to a maximum height of 16 cm from the detector face. The deviations between the actual position of the tablet and those determined by the MTS1000 tended to be greater as the height above the sensor increased and also when the tablet was positioned in region III (the outer region). This is due to the sensors interrogating a greater surrounding area for the signal, which introduces a greater risk of influence and interference from distant sources. In spite of this concern, the majority of all spatial deviations were smaller than 1 cm.

Fig. 1 shows the changes in the magnetic moment during rotation of the tablet. A peak is observed for every rotation of the tablet. From 4 to 10 cm above the sensor area, the deviation in the magnetic signal due to the rotations is approximately 2.5 mA m^2. As the height between the sensor and the tablet is increased beyond 12 cm, there are greater deviations (between 6 and 10 mA m^2) in the magnetic moment signal.

Table 3 highlights the relationship between the disintegration times determined by MMI and release of the radiolabel for both MT(A) and MT(B) *in vitro*. These results show that there was a significant difference in the onset and completion times and duration of disintegration of MT(A) between the two different media. The onset of disintegration was delayed in the Clinutren® ISO media

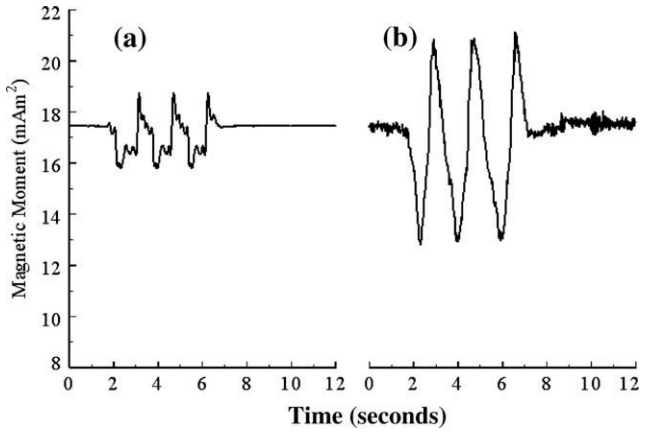

Fig. 1. The magnetic moment during manual rotation of a tablet at (a) 4 cm and (b) 16 cm above the sensor. There is an increased deviation in the magnetic moment as the tablet is rotated at a higher height away from the sensor.

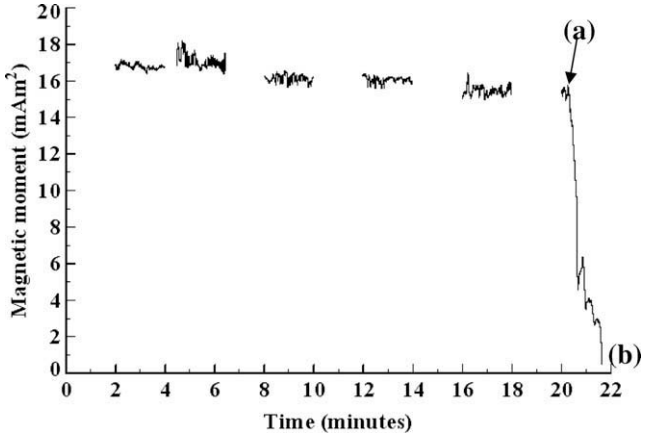

Fig. 2. Magnetic moment profile of MT(A) administered in the fasted state in subject 003; (a) the start of tablet disintegration; (b) complete disintegration is when the magnetic signal is no longer detected.

than in the acid environment; 49.0 ± 9.2 min vs 19.5 ± 6.1 min, respectively.

The coating integrity of the non-disintegrating tablet, MT(C), was tested, and tablets stayed intact for the required 8 h (time frame of clinical study day). There was no evidence of any radiolabel released from the tablet core, as determined by the scintigraphic analysis. The MTS1000 experiments showed that there was a loss of approximately 10% of the magnetic signal after 6.5 h in a fluid medium (HCl, pH 1, for first 2 h, then PB 6.8 thereafter), and this remained consistent even after 48 h.

3.2. Clinical study

MMI was able to determine the *x*-, *y*-, and z-co-ordinates of a magnetic tablet at intervals of 100 ms, enabling real-time 3D imaging in all the subjects. Five of the six subjects completed all the four study arms. Subject 4 completed three study arms, but was withdrawn from the final study arm due to the use of concomitant medication. The data from subject 4 for the three study arms that were completed were included in the subsequent data analysis.

3.3. MT(A): fasted state

All tablets disintegrated in the stomach. In four of the measurements, the onset of disintegration was observed in real time by the

Table 3
In vitro disintegration data for MT(A) and MT(B) from simultaneous MMI and gamma counts experiments.

	MMI			Radiolabel counts		
	Onset	Completion	Duration	Onset	Completion	Duration
MT(A) (fasted)	19.5 (6.1)	22.3 (5.8)	2.8 (0.3)	19.8 (6.7)	22.5 (6.1)	2.7 (0.6)
MT(A) (fed)	49.0 (9.2)	56.8 (7.8)	7.8 (7.0)	53.3 (7.2)	59.7 (7.6)	6.4 (0.6)
MT(B)	214.2 (25.9)	221.8 (23.6)	7.7 (2.5)	214.2 (25.9)	224.5 (20.7)	10.3 (5.3)

Each value represents the mean ± (standard deviation) time in minutes, $n = 3$; MT(A): immediate-release magnetic tablet and MT(B): enteric-coated magnetic tablet.

decrease in the signal during an MMI acquisition (Fig. 2). Disintegration was confirmed in the subsequent scintigraphy image by the spread of the radiolabel. The mean results for the onset of disintegration between the two techniques correlated extremely well: 11.8 ± 4.4 vs 12.0 ± 4.4 min, MMI vs scintigraphy (Fig. 3). The velocity profiles for each subject varied, and in some cases no velocity spikes were seen during the MMI recording, indicating a static tablet most likely due to the motility phase of the MMC in respect to the time of dosing. The maximum velocity of the MT(A) observed in one subject was approximately 19.5 cm/s.

3.4. MT(A): fed state

All tablets disintegrated in the stomach when administered after Clinutren® ISO. Fig. 4 shows the disintegration times of MT(A) administered after 400 mL Clinutren® ISO. A significant food effect on the onset and complete disintegration times was evident in both the techniques ($p < 0.01$ for onset, $p < 0.05$ for completion measured by MMI and scintigraphy; paired *t-tests).* In three subjects, there were large differences of 40, 50 and 32 min, respectively, in the onset disintegration times detected by the two techniques, with MMI detecting this first in all instances. In one subject, the magnetic signal had decreased to 90% of its original signal strength, yet there was no visible spread of any technetium in the scintigraphy images.

It was anticipated that altered motility patterns of the MT(A) would be observed when administered after food compared to the fasted arm. In five of the six subjects, the velocity profiles in the fed state lacked velocity spikes, indicating that the fed motility pattern of the stomach resulted in a reduced overall motility of the tablet. Intermittent velocity spikes were observed during MMI recordings in only one subject, with a maximum speed of up to 12 cm/s.

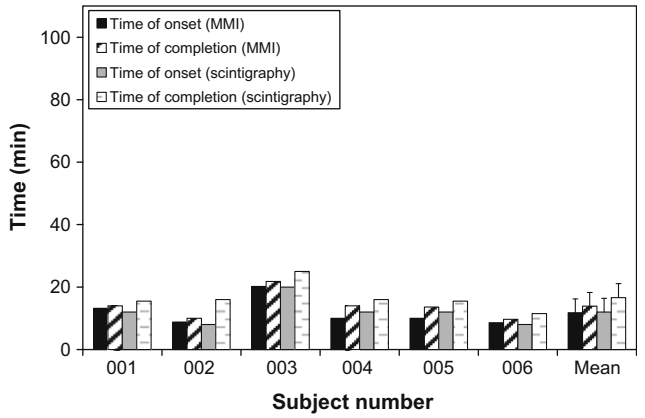

Fig. 3. Disintegration times of MT(A) administered in the fasted state which are determined by gamma scintigraphy and MMI.

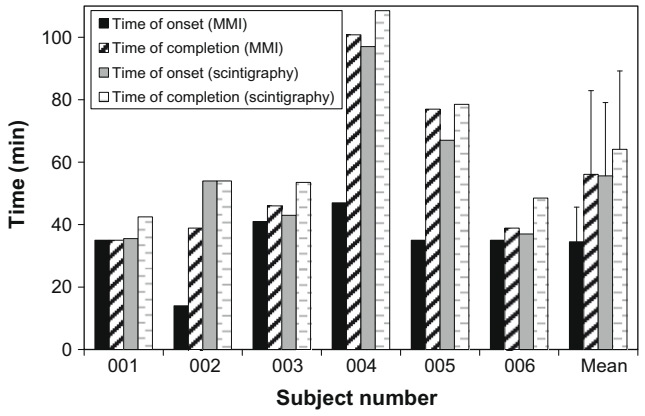

Fig. 4. Disintegration times of MT(A) administered in the fed state which are determined by gamma scintigraphy and MMI.

3.5. MT(B) and MT(C)

All MT(B) stayed intact when residing in the stomach, confirming the integrity of the enteric coating. The gastric residence times of the tablet determined by MMI corresponded with the results from gamma scintigraphy in all the subjects for both MT(B) and MT(C) (Table 4). Fig. 5 shows the onset and complete disintegration times for MT(B) for both the techniques for all the subjects. There were slight discrepancies between the onset disintegration times, but the overall agreement between the two techniques was satisfactory. There was a wide variation in the onset of disintegration after the tablet had left the stomach (ranging from 6 to 180 min).

Fig. 6 shows the localisation of the MT(B) in the *x*-, y- and *z-planes* determined by MMI and in the *x*- and y-planes determined by scintigraphy. Scintigraphy is primarily not a tool used to give anatomical detail of the lower gastrointestinal tract including loops of the intestine. MMI is excellent at showing up the phasic periods of rest and movement during intestinal transit. The movements of MT(B) through the intestines were different in each subject, but all showed distinct phases of rest, and of movement.

An obvious difference was observed in the tablet velocity when it resided in the stomach and as it moved through the intestines. Whilst in the stomach the tablet showed significant movement, seen as velocity spikes (maximum speed of 18 cm/s), which are most likely due to periods of retropulsion of the tablet in the distal stomach whilst unable to pass through the pyloric sphincter. These velocity spikes were less prominent in the small intestine (Fig. 7).

The MTS1000 successfully followed the transit of the MT(C) as it travelled through the gastrointestinal tract for the duration of the 8 h of study day. There was variation in the inter-subject transit parameters for MT(C), with only one MT(C) residing in the transverse colon at the end of the 8-h imaging time. Limited movement of the tablet was observed during the last 100 min of the imaging whilst the tablet resided in the transverse colon. This was substantiated by the extremely steady magnetic moment.

Table 4
Gastric emptying data (min) for MT(B) and MT(C). Subject 4 did not complete the study arm, MT(C).

Subject	MT(B)		MT(C)	
	MMI	Scint	MMI	Scint
1	115.0	117.0	95.0	97.0
2	115.0	117.0	95.0	97.0
3	155.5	158.5	115.5	117.5
4	86.0	88.0		
5	75.0	77.0	45.0	47.5
6	25.0	27.0	95.0	97.5
Mean	95.3	97.4	89.2	91.3
SD	44.4	44.6	26.2	26.0

MT(B): enteric-coated magnetic tablet and MT(C): non-disintegrating tablet.

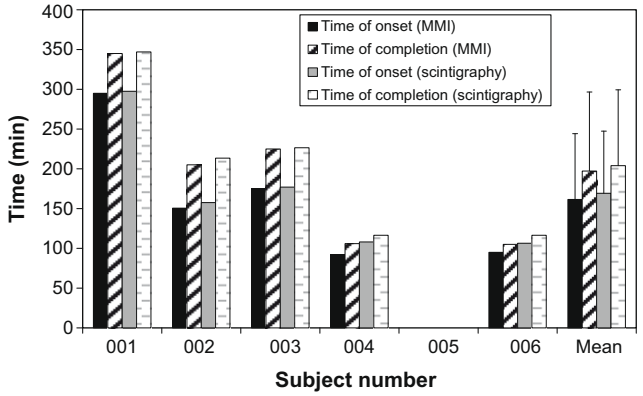

Fig. 5. Disintegration times of MT(B). The tablet did not disintegrate in subject 5 in the 6 h imaging period.

The MT(C) was not located in the descending colon or sigmoid colon at any time point. In two subjects, the MT(C) was still residing in the small intestine (terminal ileum) at the end of the 8-h imaging time. This resulted in a mean SITT of >330 ± 55 min for MMI and of 320 ± 60 min determined by gamma scintigraphy.

4. Discussion

The MTS1000 successfully recorded the transit and disintegration properties of all the magnetic tablets studied, and the produced data were comparable with the data from the scintigraphic assessment.

Data from the disintegration studies showed that the magnetic moment vs time plots can detail important information concerning the integrity of the tablet. An intact dosage form provided a permanent moment, while disintegration resulted in a complete loss of magnetic moment. The slow decrease in the magnetic moment of up to 20% in both MT(A) and MT(B) prior to disintegration is due to the disruption of the magnetic domains of the magnetic tablet by the fluid environment (*in vitro* media or gastrointestinal fluid). In MT(A), the tablet is encased inside an HPMC capsule, hence the medium which enters the capsule may penetrate the tablet core by diffusion resulting in the swelling of the tablet core. It may also wet the tablet surface causing disruption of some of the magnetic domains, and hence a decay of the overall magnetic moment.

The delay in the onset of disintegration of MT(A) using the simulated, *in vitro* fed media is in accordance with the observations of a prolonged disintegration time for rapidly disintegrating tablets in simulated fed media in the literature [33–36]. The general hypothesis is that a non-soluble film layer precipitates around the tablet core. The same delay in disintegration was observed in the clinical study.

Most of the previous MMI studies investigating the transit of dosage forms have been in the fasted state. As one of the main advantages of the MMI technique is that the tumbling and real-time movement of the dosage form can be visualised, a secondary objective of the current study was to investigate the effect of gastric contents on these movements. Clinutren® ISO was used in the *in vitro* experiments to simulate a fed medium, and was also administered in the clinical study to investigate the behaviour of tablets in different physiological states by both MMI and gamma scintigraphy. This meal was chosen as we have previously investigated the gastric emptying rates of this nutrient liquid test meal, labelled with the radiopharmaceutical technetium-99m-diethyl-

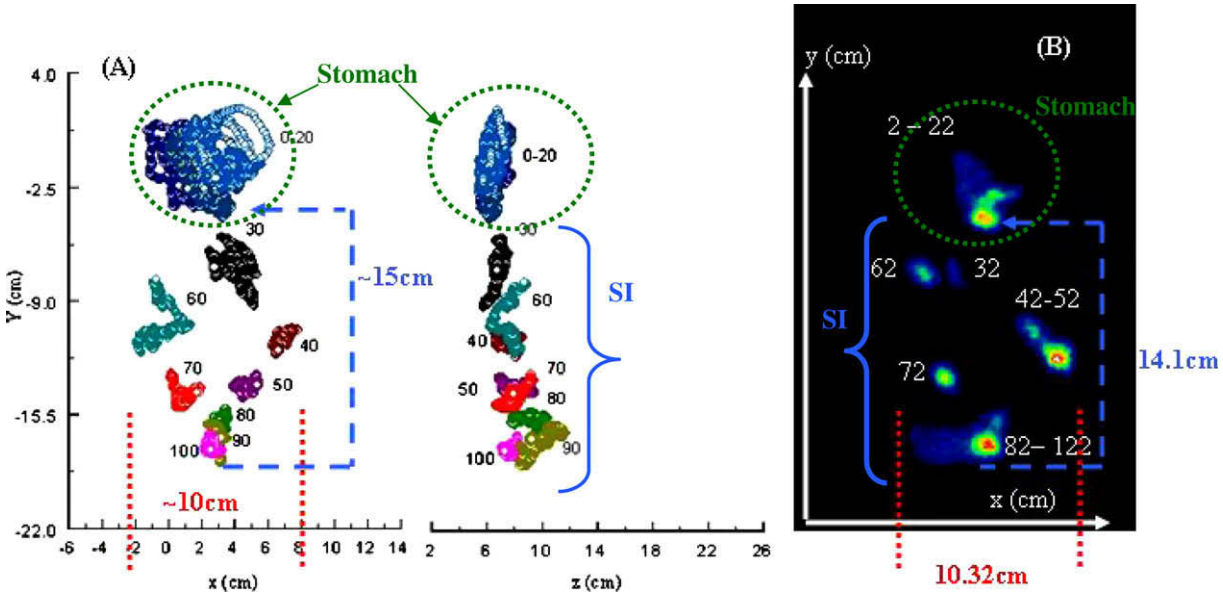

Fig. 6. (A) The localisation of MT(B) (subject 6) in the frontal view (x,y) and lateral view (z,y) determined by MMI. Disintegration occurred between the 100- and the 110-min acquisition. (B) The corresponding localisation by scintigraphy; x-, and y-planes only. Visible spread of the radiolabel was seen in the 111-min acquisition (SI = small intestine).

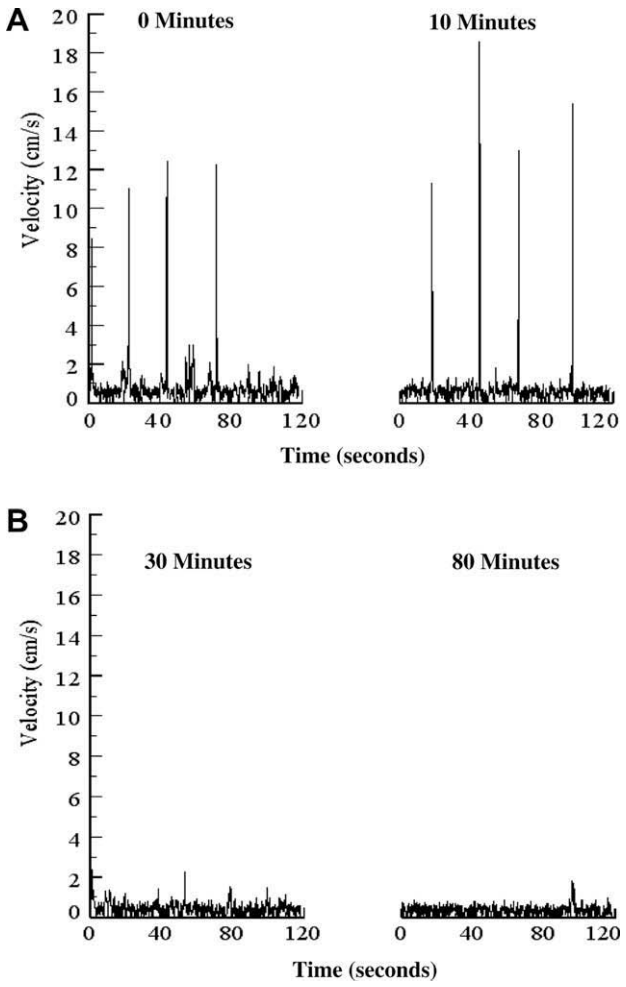

Fig. 7. The velocity of the MT(B) in subject 6 in (A) stomach and (B) the intestines (selection of time points).

enetriaminepentaacetic acid, [^{99m}Tc]-DTPA [32]. This liquid meal was tolerated well and had extremely reproducible emptying kinetics (t_{90} for 400 mL; 120 ± 13.2 min).

In the fed arm of the clinical study, there were discrepancies in the onset disintegration times, between MMI and scintigraphy, for MT(A) in three of the subjects. A possible explanation for this may be the low agitation forces in the stomach. Whilst the stomach is in a quiescent phase, the hydrodynamic dispersive forces are weak. Proteins and fatty components in Clinutren® ISO can interact with tablet constituents which may reduce the dispersion and breakup of the tablet core. This has been shown to decrease the rate of drug dissolution [33]. Clinutren® ISO could therefore affect the rate at which the radiolabel can permeate from the tablet core at low agitation forces. This was substantiated by further *in vitro* tests in the simulated fed media, using a paddle speed of 50 rpm (performed after the clinical study). The scintigraphic images failed to indicate tablet disintegration even when the onset could be observed visually in the dissolution vessel, indicating a delay in the determination of the event by scintigraphy at lower agitation speeds. These results suggest that MMI provides an earlier estimate of tablet disintegration as the magnetic moment of the tablet starts to decrease as soon as the magnetic domains are disturbed. Thus, the prolonged detection of the magnetic tablet by MMI (in subjects 2, 4 and 5) after onset could be explained by a possible food effect, lower agitation forces or a combination of both, thus allowing the majority of the tablet core to remain associated and a weak magnetic moment to be detected. The velocity profiles of the MT(A) administered after food also substantiated this theory as there was a lack of overall tablet movement in the majority of all MTS1000 recordings.

The aim of studying an enteric-coated tablet, MT(B), and a non-disintegrating tablet, MT(C), was to investigate the transit in the upper and lower gastrointestinal tract including the movement through the gut. It was hoped that we would observe the transit of MT(C) through the small and the large intestine (ascending, transverse, descending and sigmoid colon). Tablets often leave the stomach in a random and erratic fashion when given in the fasted state. However, when given after a large volume or calorific load of food, the emptying of the tablet into the duodenum can be delayed for many hours [34]. Accordingly, MT(B) and MT(C) were given after 100 mL of Clinutren® ISO in an attempt to eradicate the possible unpredictable emptying of the tablet in the fasted state and to reduce the chance of the tablet residing in the stomach for many hours.

The polymer coating on the enteric-coated tablet should simply provide a lag time for the onset of disintegration. The onset of disintegration of these tablets after they had left the stomach was extremely variable (6–180 min). Fluid volumes in the small intestine are not homogeneously distributed along the gut, and in the fasted individual can range between 50 and more than 300 mL [37]. Hence, the transit of enteric-coated tablets through watery pockets along the gut influences the performance of the enteric coat, one that is not seen in the continuous "sink" conditions of the common *in vitro* dissolution baths.

The investigations using the MT(C) highlighted that the dosage form can remain completely static in certain areas of the gastrointestinal tract. The static behaviour of the MT(C) observed in the transverse colon is an important aspect that has to be considered as the limited movement and forces experienced will affect tablet disintegration.

The average small intestinal transit time (SITT) of oral dosage forms is generally accepted in the literature as being approximately 180 ± 60 min with this transit time being unaffected by the physical form of the dosage form or the calorific value of an ingested meal. The results from this study depict a slightly longer mean SITT of the MT(C) than the accepted literature values. Clarke and colleagues [3] showed that the SITT was prolonged by an increase in size and density of pellets in a multi-particulate system, while Podczeck and co-workers [38] suggested that size may outweigh any effect of density. The prolonged SITT of the MT(C) seen in this investigation compared to those found in the literature could be due to the cumulative effect of both the large size of the dosage form (19 × 6 × 9 mm) and the high density (2.2 g/cm^3).

The ileocaecal junction (ICJ) acts to control the entry of digested food and solids from the terminal ileum to the ascending colon, and it is well accepted that dosage forms can reside at the ICJ for a period of time until the entry into the ascending colon. With the MMI instrument and our limited experience to date, it was difficult to determine a distinction between the ICJ and the ascending colon, and therefore the residence of the tablet at the ICJ or ileocaecal passages was not quantified.

Stathopoulos and co-workers [29] utilised a permanent magnet as the probe in the gastrointestinal tract over a 34-h period and measured movement using a detector incorporating Hall effect sensors. In this study, in which they combined the MMI data with CT scans from the same subject, they observed the magnetic marker moving through the ileocaecal passage. This technique is awaiting validation with the simultaneous use of widely accepted methods, and they also need to demonstrate the ability to determine a disintegrating magnetic marker to enable this to be a useful tool in the development of new dosage forms.

The depth of the gastrointestinal tract from the body surface depends on anatomical variability and also on body mass index

(BMI). Data from all the subjects in the clinical study were analysed to determine how many recordings showed the position of the magnetic tablet at a depth greater than 18 cm, as these results should be considered with caution since the positional data may not be as accurate. Of a total of 386 MMI recordings, eight measurements (2.1%) indicated that the tablet was at a depth greater than 18 cm. The magnetic moment profile during one such recording (depth of 24 cm; subject 6, 300 min acquisition, MT(C)) was investigated to determine if this was in fact a true measurement. The magnetic moment profile had large deviations (from 16 to 38 mA m^2), indicating that although the MTS1000 detected this tablet, the location at this time point may be inaccurate. In this way, any false or suspect positional data can be easily determined and commented upon.

The study design would have been improved if both anterior and posterior scintigraphic images had been acquired. Since we collected anterior scintigraphic images only, the error produced by tissue attenuation could not be corrected by the geometric mean, and hence plots of release of radiolabel from tablet core against time could not be produced. An attempt to produce these plots using the anterior data only resulted in too many sources of error due to even small movements of the tablet in the stomach and in the lower gastrointestinal tract.

One limitation of MMI when compared to scintigraphy is the lack of information that can be achieved after tablet disintegration. When this occurs in scintigraphy, the dispersion of the formulation can be determined due to the spread of the radiolabel. In MMI, once the magnetic moment is lost, no further information can be acquired. Another drawback of the present iteration of the machine is that at least 1 g of iron oxide needs to be incorporated into the dosage form to enable optimum magnetic detection. The development of a more sensitive next-generation machine currently in production will allow less iron oxide to be used, and could therefore dramatically increase the utility of this technique to the pharmaceutical and drug development industry.

In addition to tracking pharmaceutical dosage forms through the gastrointestinal tract, the information provided by the MTS1000 on tablet movement could be used to investigate motility parameters in patients with altered motility patterns. It could even have the potential to determine gastroparesis in the diabetic population by using a non-disintegrating magnetic marker (tablet or permanent magnet). In diabetics, disordered motility would be expected to be evident from data showing long periods of stagnation between movements, particularly in the upper gastrointestinal tract.

5. Conclusion

This study illustrates that the MTS1000 can detect magnetic tablet formulations successfully *in vitro* and *in vivo* throughout the gastrointestinal tract. Transit parameters, gastric residence times and disintegration parameters were established and were found to be extremely similar to those found by scintigraphy.

It appears that the MTS1000 may be a more sensitive detector of the onset of disintegration in the fed state compared to scintigraphy. This can only be applied to the disintegrating tablet studied, but is an interesting finding nonetheless. The different velocity profiles provide additional information regarding the behaviour of oral dosage forms in different areas of the gastrointestinal tract. MMI vastly widens the study population in which drug formulations and motility aspects could be studied due to the lack of an incorporated radiopharmaceutical. Studies could be performed in both females and children, and repeat studies could be carried out more frequently than authorized in scintigraphy. The portable aspect of the device is an added benefit such that it could be used in a conventional clinical setting.

The development of the second more sensitive prototype of the magnetic tracking device should allow as little as 50 mg to be integrated into a formulation without altering the dosage forms characteristics. MMI measurements could then be combined with pharmacokinetic data for insightful studies on new formulations. The non-invasive MMI technology with a more sensitive MTS1000 model could lead to an endless amount of novel research including the investigations of new formulations and gastric motility parameters in any clinical setting and in a wide range of study populations.

In conclusion, this study has shown that MMI is a technique with clear potential which could be used either as an alternative to gamma scintigraphy or in combination to maximise the data established.

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