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Decoupling the role of image size and calorie intake on gastric retention of swelling-based gastric retentive formulations: Pre-screening in the dog model

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ABSTRACT

Gastric retention is postulated as an approach to improve bioavailability of compounds with narrow absorption windows. To elucidate the role of image size on gastric retention and pharmacokinetics, formulations with different image sizes and swelling kinetics but similar dissolution rates were designed and imaged in dogs. Diet had a clear effect, with increasing calorific intake prolonging retention in the dog model. In contrast to clinical observations, no obvious effect of image size on gastric retention was observed in the dog, with the larger gastric retentive (GR) and smaller controlled release (CR) formulations both demonstrating similar gastric emptying. Comparable pharmacokinetic profiles were observed for the two formulations, corroborating the imaging data and providing evidence of similar in vivo dissolution rates and dosage form integrity in the dog. Food, specifically meal composition, resulted in comparable enhancements in exposure in the dog and clinic due to prolonged gastric retention. However, differentiating retention based on image size in the dog was not feasible due to the smaller pyloric aperture compared to humans. This work illustrates that the dog is capable of determining the pharmacokinetic advantage of gastric retention relative to immediate release (IR) or CR formulations, however, has limited value in differentiating between CR and GR formulations.

1. Introduction

Gastric retention has been mooted for many years as a technique by which the bioperformance of drugs with a narrow absorption window can be improved. The concept was borne from the preposition that retaining an extended release dosage form in the stomach compartment would provide sustained release of the drug from the dosage form in the stomach, maximizing absorption of those drugs which are characterized by limited or no colonic absorption. The prerequisite for considering gastric retentive (GR) technology is adequate stability of the compound under acidic conditions. Success with this strategy has been limited over the years; however, several common approaches to achieving gastric retention are under consideration including swelling-based systems, alternative geometry, floatation, high density and mucoadhesive systems (Fix et al., 1993); Klausner et al., 2003; Parikh and Amin, 2008; Waterman, 2007). Many of these technologies have not translated into clinically acceptable products, although some success has been demonstrated with Glumetza®, Proquin XR™ and Gralise all of which exhibit some degree of gastric retention when administered in the fed state (Berner and Cowles, 2006). The difficulty in achieving gastric retention lies in the physiological environment that is targeted. The mechanism of action of gastric retention devices aims to overcome the natural compulsion of the stomach to remove large, undigested material from its lumen during the Phase III migrating myoelectric complex (MMC) in the fasted state.

Floatation systems aim to achieve gastric retention by keeping material away from the pylorus, thus reducing the risk of emptying. This mechanism requires the presence of stomach contents (water or food) on which the dosage form can float. Since water empties rapidly from the stomach (half-life of emptying: 10–15 min) the requirement for food to be present in the stomach to obtain a long retention time is implied. Thus, this method of gastric retention is unlikely to show consistent success in the fasted state. Several clinical studies have been conducted with floating systems but demonstration of gastric retention is often confounded by the selection of the reference formulation (immediate release (IR) dosage form) or co-dosing with food (Oth et al., 1992), (Desai and Bolton, 1993). Clinical success has not yet been achievable under fasted conditions although floating systems administered with food can show some degree of gastric retention. Studies have shown that altering the geometry of the dosage form can result in prolonged retention as shown in the beagle dog model for ~24 h (Cargill et al.,

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1988). This is potentially related to the rigidity of the dosage form; however, similar data has not been demonstrated clinically (Fix et al., 1993).

Mucoadhesive systems are designed to adhere to the stomach mucosal membrane. The high gastric motility, continual renewal of the mucus lining and efficiency of adhesion have resulted in limited, if any, clinical promise in man. No evidence of gastric retention was demonstrated under fasted conditions with the common mucoadhesives polycarbophil and carbopol (Khosla and Davis, 1987), (Harris et al., 1990), (Jackson et al., 2001). Preclinical success has been reported; however, this may be attributed to blockage of the small pyloric sphincter with gelling material (Varum et al., 2008).

Size-increasing systems claim success by virtue of swelling to dimensions greater than those of the pyloric sphincter, thus physically preventing emptying from the stomach. It has been postulated that swelling systems need to swell to more than 15–16 mm in size (Berner and Cowles, 2006; Streubel et al., 2006) in the fasted state and more than 12–13 mm in the presence of food based on the orifice of the resting pylorus (12.8 ± 7 mm; Munk et al., 1978). Strength in at least two dimensions is an additional requirement for GR systems to prevent premature rupture of the dosage form and emptying with the housekeeper wave. Thus, it should be expected that these devices would be retained in the stomach under both fasted and fed conditions; however, clinical data demonstrating gastric retention independent of food has not been reported. Consequently, the recommendation is that GR products be administered with food to ensure maximum absorption. Clinical scintigraphy studies using a GR formulation of either metformin or furosemide revealed retention of the dosage form in the stomach for 3.9–16.8 h but only in the fed state (Gusler et al., 2003; Louie-Helm et al., 2003) with the higher fat and calorie content prolonging gastric residence (~13 h for high fat, high calorie, ~8 h for low fat, high calorie and ~4 h for low fat, low calorie). This leads us to the hypothesis that size-dependent gastric retention is likely to be mediated to a large extent by food, specifically calorie content, and not by dosage form size alone, although perhaps increasing the size improves the probability of a longer retention time. The interplay between dosage form size and calorie intake is likely essential for reliable sustained delivery of dissolved drug to the upper GI tract. Therefore, the effect of dosage unit size, calorie content and meal composition on gastric retention was explored in the dog model.

Although clinical studies are the gold-standard, dogs are routinely utilized to assess the performance of IR clinical formulations and to evaluate novel formulation technologies; however, to ensure accurate translation of formulation performance it is critical to understand species differences. Under fasted conditions gastric emptying time is comparable between dog and humans; however, prolonged gastric residence has been observed in the fed state for small non-disintegrating units ranging from 5 to 13.3 h in dogs compared to 2.6–4.8 h in humans (Davis et al., 1993). Furthermore the reduced intestinal and total transit time in dogs compared to humans (intestinal transit time: 2 h vs 3–4 h; total transit time: 6–8 h vs 20–30 h) may underpredict the performance of controlled release (CR) formulations limiting the utility of the dog model in assessing the performance of these dosage forms. However, GR formulations can theoretically be evaluated in dogs, as the dosage form is retained in the stomach, provided that the integrity of the dosage form is not compromised.

To the best of our knowledge there are no clinical studies in the literature that directly compare the gastric emptying and pharmacokinetics of a proposed GR system and a standard CR formulation under fasted conditions. A caveat to this is that although bioequivalence has been demonstrated between the GR formulation of metformin (Glumetza®) and the CR metformin product (Glucophage XR), the CR product is a swelling/gelling hydrophilic CR matrix (Timmins et al., 2005) equivalent in size (length ~21 mm after swelling for 1 h) to the GR product (length ~20 mm after swelling for 1 h) and the study was conducted under fed conditions which may confound the data interpretation (Glumetza NDA filing, 2005). This lack of data on the comparisons between a more standard CR formulation and a designed GR formulation, along with questions of the validity of the dog model for preclinical GR studies, led to the development of this study.

Table 1
Desired attributes of the gastric retentive (GR) and standard controlled release (CR) dosage forms.

Ideal attributes of a GR formulation	Attributes of a CR formulation as a comparator
• Swell to a size greater than that of the pylorus (>5 mm for the dog and >15–16 mm for humans) • Extended release (similar release rate to CR formulation) • Erodes after ~12 h • Provides similar swelling profile to a marketed GR product as an indication of being retained in the stomach	• Smaller size with minimal swelling. Ideally <5 mm for the dog and <12 mm for the clinic • Extended release (similar release rate to GR formulation) • Erodes over 12 h

The primary objective of this work was to develop a GR technology based on the swelling mechanism to guide the understanding of the relationship between the drug release rate, absorption rate and position in the gastrointestinal tract for GR and CR formulations. Formulations designed to have GR attributes based on image size or CR properties whilst providing the same extended drug release profile (Table 1) were developed and evaluated in vitro and in the dog model. Several clinical studies investigating the role of image size on gastric emptying time have been conducted under both fasted and fed conditions. A dosage unit size cut-off for gastric retention in the fed state (light and medium meal) of ~13 mm in diameter was reported by Khosla et al. (Khosla and Davis, 1990; Khosla et al., 1989). Additional supportive data from Coupe et al. (Coupe et al., 1991) in which simultaneous measurements of gastric transit using imaging and gastric motility were performed demonstrating that indigestible dosage units of ~7 mm in diameter emptied with food. Based on this information, in this study, a standard CR formulation (diameter: ~7–8 mm) and a GR formulation (18 mm × 8 mm) with similar drug release profiles were developed to explore the role of image size on gastric retention and the pharmacokinetic profile of the model drug, metformin, without different release rates confounding the data. Metformin was selected as the model compound as it is highly soluble and exhibits a narrow absorption window. More importantly, the abundance of clinical data for the immediate, controlled and GR formulations of metformin serves as a valuable comparator when developing and assessing the behavior of a novel GR formulation. Furthermore to understand the role of image size and diet composition on gastric retention, various controlled diets were evaluated. Gastric retention was assessed by radio-imaging and linked to the pharmacokinetic data. This work is intended to facilitate decoupling the role of image size and calorie content on gastric retention and to determine whether the dog is a suitable model for the evaluation of swelling-based GR dosage forms developed for the clinic.

2. Materials and methods

2.1. Materials

Methocel® K100M premium CR (hydroxypropyl methylcellulose, HPMC) was a kind gift from Colorcon (Dartford, UK), Polyox (polyethylene oxide WSR 303) was from Dowwolf Cellulosics (Germany), microcrystalline cellulose (MCC) (Avicel PH 102) was

obtained from FMC (Philadelphia, PA, USA), lactose monohydrate (Fast Flo 316) from Foremost Co. (Baraboo, WI, USA) and magnesium stearate (Type 2255) from Mallinckrodt Speciality Co. (St. Louis, MO, USA). Metformin HCl was purchased from Smruthi Organics, Ltd. (Mumbai, India). X-ray contrast threads were kindly supplied by Micropake Ltd. (Coventry, United Kingdom). Barium impregnated polyethylene spheres (BIPS) with a diameter of 1.5 mm or 5 mm were supplied by Medical I.D. systems, Grand Rapids, Michigan.

2.2. Preparation of GR and CR dosage forms

To facilitate imaging of the dosage forms, GR formulations were developed in-house with the goal of achieving similar swelling properties and release rates to that of the commercial GR reference product, Glumetza®. Powder blends were prepared by mixing the dry ingredients in a Turbula blender for 10 min, followed by 1 min lubrication with magnesium stearate. The blends were compressed using a Lloyds press at 10 mm/min to a compression pressure of 200 MPa. A caplet shaped tooling with the dimensions 18 mm × 8 mm was selected for the GR tablets, whilst for the CR tablets a concave round punch with a diameter of 8.73 mm was used.

Radio-opaque dosage forms were prepared (1) by incorporating a radio-opaque thread (2 pieces) into the center of the compressed tablet by placing short lengths of thread into tablet dies amongst the powder prior to compression or (2) by placing BIPS of 1.5 mm in diameter (3 beads) in the tablet blend prior to compression. The inclusion of radio-opaque threads or sphere in the tablets facilitated detection of the tablets using the X-ray camera and provided an indication of tablet integrity in vivo by monitoring the relative positions of the threads or beads over time.

2.3. In vitro characterization of GR and CR dosage forms

In vitro dissolution tests for the CR and GR formulations were carried out according to the United States Pharmacopeia (USP) II paddle method at 37 °C at a paddle speed of 100 rpm. The dissolution media was composed of 500 mL of simulated gastric fluid (SGF) at pH 1.2. Samples were drawn at regular time points for up to 12 h. The assay of metformin from these samples was performed using HPLC (Dionex, RFIC IonPac CS14 Column, 4 mm × 250 mm, Mobile Phase 50 mM phosphate pH 3.5; MeCN) run at 2.0 mL/min, at 255 nm and 30 °C.

To determine the swelling kinetics of the formulations, images were taken at regular intervals during dissolution using time-lapse photography (Nikon D200) under controlled lighting conditions. Image analysis was carried out using Light Box and Image-J software and the two-dimensional surface area was plotted against time to give an indication of the swelling and erosion rate over 24 h. This method restricts swelling along the base, so although it is not representative of what would happen in true USP conditions or in vivo, the method does enable comparison between dosage forms tested in a similar manner and allows ranking of formulations. Radio-labeled tablets were assessed for swelling behavior, rupture and premature drug release by comparison with non-radio-labeled tablets. No evidence of tablet rupture or significant differences in the swelling behavior was recorded indicating that the presence of the thread or BIPS did not compromise the integrity of the tablets and the radiolabeled markers were retained in the tablet for over 12 h.

2.4. In vivo assessment of GR and CR formulations

2.4.1. Pharmacokinetic studies

Six male Beagle dogs, approximately 10 kg in weight, housed in a colony located in an environmentally controlled room were used for these studies. The dogs were fed twice a day with a standard meal and had free access to water. All animal studies were conducted in accordance with a protocol approved by the Merck Institutional Animal Care and Use Committee (IACUC). Dogs allocated to a study were fasted overnight (approximately 18 h) with access to water ad libitum.

The solid dosage forms were administered in the morning with a 3.5 mL/kg water rinse via oral gavages to mimic clinical dosing conditions. The IR metformin formulation was a solution prepared in water at a concentration of 0.57 mg/mL with a final pH of 5.2. The solutions were administered via oral gavage (3.5 mL/kg) followed by an air rinse to ensure complete emptying of the dosing tube. Water was restricted for 1 h post dose and food was returned at 4 h post dosing for fasted state studies. The food effect studies were conducted by feeding the dogs, after an overnight fast, a liquidized meal containing ALPO prime cuts and Nutri-cal in various proportions to yield high, medium or low fat content meals. The calories from fat for the various meals ranged from 52% for the high fat to 33% for the medium fat meal (MFM) and 27% for the modified low fat meal. The details of the meal compositions and dosing volumes are shown in Table 2. The food was administered via oral gavage twenty five minutes prior to dosing the formulations to mimic clinical protocols and ensure that all the food was consumed. Water was restricted for 1 h post dose and then available *ad libitum*, while food was returned 8 h after dosing.

Blood samples for pharmacokinetic analysis were drawn at 0 (predose), 0.5, 1, 2, 4, 6, 8 and 24 h, collected into sodium heparin vacutainer tubes and centrifuged to separate the plasma, which was frozen until assayed. Plasma samples were analyzed for concentration of metformin using LC–MS/MS. Specifically, dog plasma was precipitated with 100% acetonitrile and diluted two fold with water prior to injecting onto the LC–MS/MS system. The linear range of the assay was 1–1000 ng/mL. Metformin and its stable labeled internal standard (D6-Metformin) were chromatographically separated using a HILIC Silica column (Waters Atlantis HILIC Silica, 2.1 mm × 50 mm, 5 μm) with a mobile phase consisting of 10 mM ammonium acetate at pH 3.5 and acetonitrile at a flow rate of 0.4 mL/min. The transitions monitored were 130–71 and 136–77 for metformin and its internal standard and peak area ratios were used to quantitate metformin concentrations. Retentions times were ~2 min for both analytes.

Pharmacokinetic parameters were determined using standard non-compartmental methods with log-linear least squares regression analysis (WinNonlin 5.2, Pharsight Corp., Palo Alto, CA, USA). Plasma metformin concentrations below the limit of quantitation (1 ng/mL) were assigned a value of zero for calculation of pharmacokinetic parameters and mean plasma concentrations. The area under the concentration versus time curves was calculated by the linear trapezoidal method during 24 h post dosing ($AUC_{0-24\,h}$). The AUC extrapolated to infinity ($AUC_{0-\infty}$) was calculated by a combination of the linear and logarithmic trapezoidal rules, with extrapolation to infinity by dividing the last measurable serum concentration by the elimination rate constant. The maximum plasma concentration, $\underline{C}_{max}$, and the time at which $\underline{C}_{max}$ occurred, T_{max}, were determined. The relative bioavailability of metformin delivered by the GR formulation and CR formulation was determined by dividing the AUC for these formulations by that of the IR metformin formulation. Deconvolution of the plasma profiles was performed using WinNonlin 5.2 IVIVC toolkit to estimate the fraction bioavailable to determine the in vivo dissolution rates and the effect of meal composition on gastric retention.

2.4.2. Radiographic studies

Radiographic studies were conducted using an X-ray control unit and tube (Eureka X-ray Tube Corporation and Genedex Corporation) and the images were analyzed using Tru DR Dicom digital

Table 2
Composition and properties of diets evaluated in the dog studies.

	High fat diet	Medium fat diet	Low fat diet	Modified low fat diet
Volume/dog	180 mL	180 mL	180 mL	45 mL
Calories from fat (%)	52%	33%	27%	27%
Total calories/dog	321 kcal	214 kcal	122 kcal	30.5 kcal
[a]Viscosity ranking	M	H	L	N.D.
Density (g/cm^3)	1.0	1.0	1.0	N.D.

[a] The meals were viscoelastic and shearing thinning over a 100× range (shear amplitude from 0.01 to 100 s^{-1}); therefore, a ranking is provided from low (L), medium (M) to high (H) instead of an absolute value.

radiography software from Sound Technologies. Radiology was used for imaging the transit of the BIPS alone and when co-dosed with either the CR or GR tablet pre-loaded with either radiopaque threads or BIPS markers (1.5 mm) from the stomach into the intestine. A similar protocol as described in Section 2.4.1 was followed for the imaging studies which were conducted in both the fasted and fed state. The dogs were manually restrained for radiography and X-ray images were taken initially, 15 min post dosing and every hour after that over a 4–5 h period or until the dosage form emptied from the stomach. Images from two perpendicular recumbence (ventral-dorsa and right lateral) positions were taken to enable accurate recording of the unit's location. Gastric emptying of the BIPS was calculated by counting the number of large (5 mm) and small (1.5 mm) BIPS units inside the stomach at each time point relative to the total number administered and the percentage of units emptied as a function of time was reported. The lag time was defined as the period during which less than 5% of the markers emptied from the stomach.

3. Results and discussion

3.1. Development and in vitro assessment of the GR and CR formulations

The theoretical ideal properties of a size-increasing/swelling gastric retention system are detailed in Table 1. In designing a swelling-based GR formulation, the time to reach the required dimensions is critical as the dosage unit should be sufficiently small to facilitate swallowing and avoid swelling or sticking in the esophagus yet achieve an appropriate size shortly after entering the stomach. Furthermore, the dosage form must erode before the next dose is administered to prevent accumulation in the stomach. The rate and extent of swelling of the novel GR formulation that would be necessary to achieve gastric retention was established based on comparisons to Glumetza®. Several placebo formulations were prepared composed of various ratios of the excipients listed in Table 3 and their swelling profiles were determined and compared to that of the benchmark GR formulation, Glumetza® (Fig. 1). Formulations containing the active compound were subsequently prepared using the composition determined in the placebo studies and substituting the lactose for metformin (500 mg). The release rate of these formulations was determined relative to that of Glumetza® and

Table 3
Composition of the active (metformin, 500 mg) and placebo gastric retentive (GR) formulations designed to perform similar to the marketed GR formulation, Glumetza®.

	Active	Placebo
Metformin	48.9%	–
Lactose	–	48.9%
Microcrystalline cellulose PH102	10.0%	10.0%
HPMC K4 M	20.3%	20.3%
PEO WSR 303	20.3%	20.3%
Magnesium Stearate	0.5%	0.5%
Weight	1000 mg	1000 mg

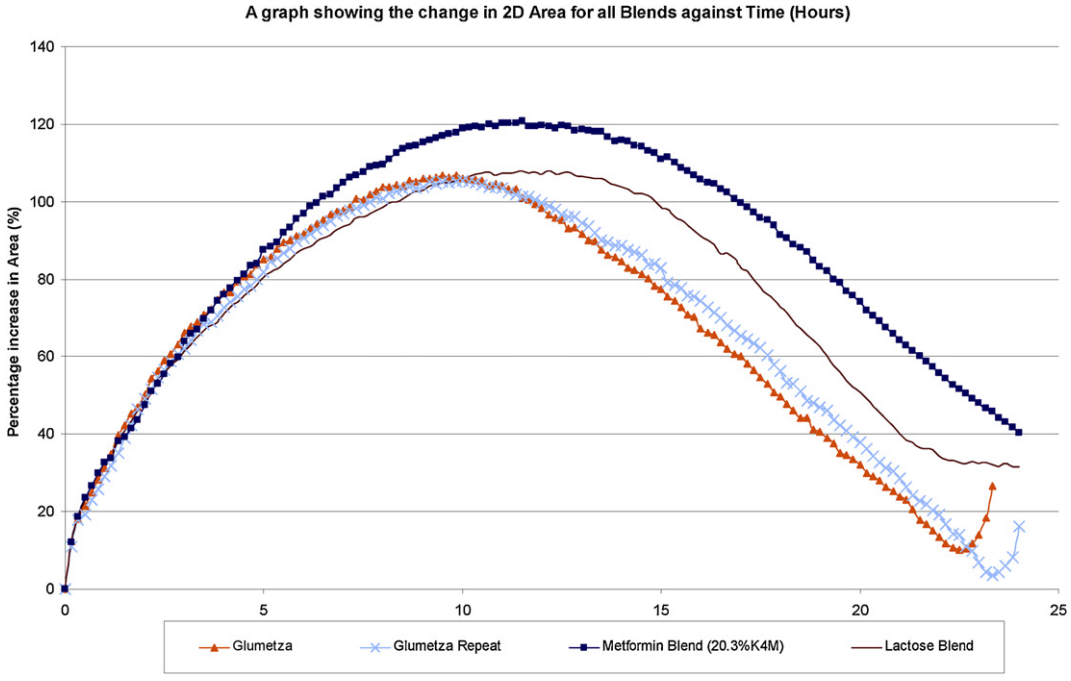

Fig. 1. Swelling profiles of active (metformin, 500 mg) and placebo gastric retentive (GR) formulations compared to that of the marketed Glumetza® product.

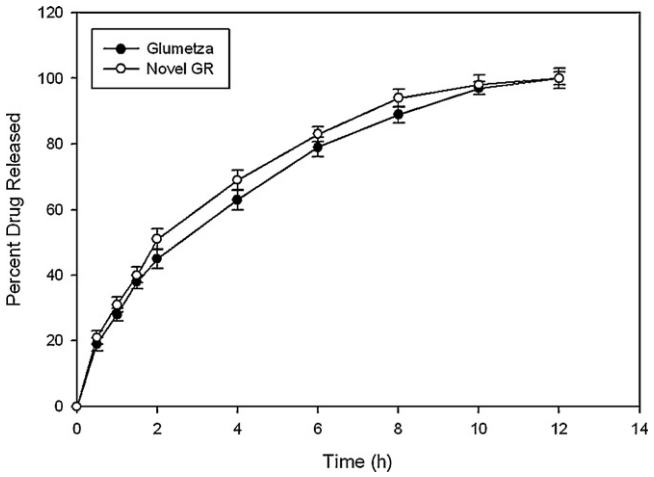

Fig. 2. Metformin drug release (500 mg dose) from the novel gastric retentive (GR) formulation compared to the marketed GR product, Glumetza in simulated gastric fluid (SGF) (pH 1.2, 500 mL).

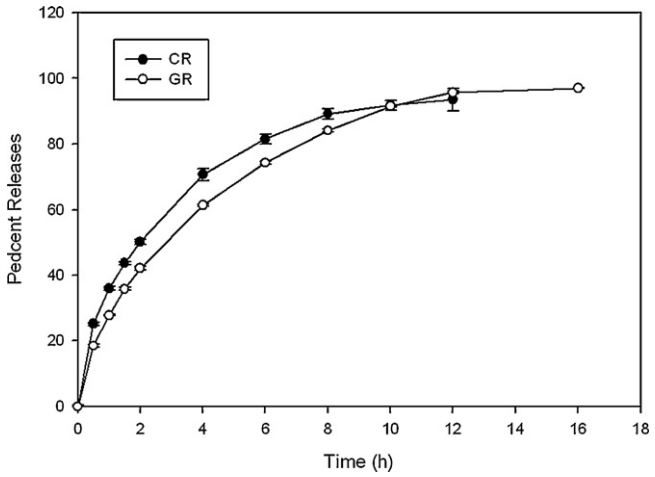

Fig. 3. Metformin drug release (20 mg dose) from the controlled release (CR) formulation relative to the gastric retentive (GR) formulation in simulated gastric fluid (SGF) (pH 1.2, 500 mL).

found to be similar (F2 similarity factor = 53; Fig. 2). Utilization of a combination of in vitro techniques and a valid comparator provided confidence that the novel formulation would demonstrate gastric retention and release drug at an appropriate rate.

As aforementioned, one of the objectives of this work was to develop a dosage form with dimensions less than the GR tablet but with comparable drug release rates by the same mechanism. This was considered essential to confirm gastric retention by enabling direct comparison of the pharmacokinetic profiles of the two formulations without dissolution rates confounding the data. Due to the higher surface area to volume ratio of the CR formulation (200 mg image size), matching the drug release profiles to the GR formulation (1000 mg image size) proved quite challenging requiring the development of several formulations. For this reason, a 200 mg image size CR formulation was the smallest size that was able to achieve adequate extension of drug release.

To evaluate the performance of the GR and CR dosage forms in the dog model, modifications to the formulation were necessary to accommodate a lower dose requirement in the dog to prevent tolerability concerns (emesis observed with 500 mg of metformin) and to facilitate preparation of a small image size CR formulation. The potency of the GR formulation was reduced from 500 mg to 20 mg of metformin by replacing the metformin with lactose (Table 4), while maintaining an image size of 1000 mg (18 mm × 8 mm × 6.3 mm). The tablet image for the CR formulation was round with a diameter of 8.73 mm and thickness of 4 mm and the same dose of 20 mg of metformin was selected (Table 4). Similar drug release profiles were obtained from the CR and GR formulations containing 20 mg of metformin (F2 = 50) confirming that the formulation composition selected achieved the objective (Fig. 3). The swelling of the adapted metformin formulation (20 mg dose) is similar to the active (500 mg dose) and placebo profiles in Fig. 1. Selected images from the swelling profile are shown in Fig. 4. Time-lapse photography was employed to visualize the swelling and erosion kinetics of the CR and novel GR formulations (Fig. 4). The diameter of the CR formulation increased by 10% over 6 h, while that of the GR formulation increased by ~20%. The height of both images doubled over 6 h; however, the GR formulation was ~2.5 times larger in volume than the CR formulation confirming that the formulations have different swelling characteristics; however, the drug release profiles are similar. It should be noted that the imaging method requires that the dosage form be fixed along the base which restricts swelling from the base. It is expected that in vivo the swelling and erosion profiles are likely to be slightly different, but this method allows for a direct comparison under controlled conditions. Table 5 summarizes the dimensions of the formulations initially and over time as they swell.

3.2. Transit of the GR and CR formulations

3.2.1. Fasted condition

The GR (1000 mg image size) and CR tablets (200 mg image size) embedded with metal threads were dosed concomitantly with small (1.5 mm diameter) and large (5 mm diameter) BIPS marker units in the fasted state in separate studies. Differential emptying of the BIPS based on size was not observed (Fig. 5) with the majority of small and large BIPS rapidly emptying 1–2 h post dosing. Interestingly the GR and CR formulations empty from the stomach within a similar time frame as that observed for the BIPS 2.0 (±0.5) h and 3 (±0.0) h, respectively, confirming that the non-disintegrating units and dosage forms are cleared from the stomach during the migrating MMC housekeeper wave that occurs every 90–120 min in dogs. Despite the large size of the GR dosage unit relative to the dog pyloric orifice it was not retained in the stomach under fasted conditions. The location of the BIPS units in the tablets relative to

Table 4
Formulation composition of the gastric retentive (GR, 1000 mg image size) and controlled release (CR) formulations (200 mg image size) containing 20 mg metformin for preclinical evaluation.

	CR	GR
Metformin	10.00%	2.00%
Avicel PH102	10.00%	10.00%
Lactose fastflo	0%	46.90%
PEOWSR303	0%	20.30%
HPMC-K4 M	79.50%	20.30%
Magnesium Stearate	0.50%	0.50%
Weight	200 mg	1000 mg

Table 5
Dimensions of the gastric retentive (GR) and controlled release (CR) formulations as imaged in the simulated USP II over time (x = diameter and y = height).

Time (h)	CR formulation 200 mg image		GR formulation 1000 mg image	
	x (mm)	y (mm)	x (mm)	y (mm)
0	8.727	3.716	18.771	5.16
4	9.478	6.388	21.916	8.943
6	9.562	7.39	22.064	10.025

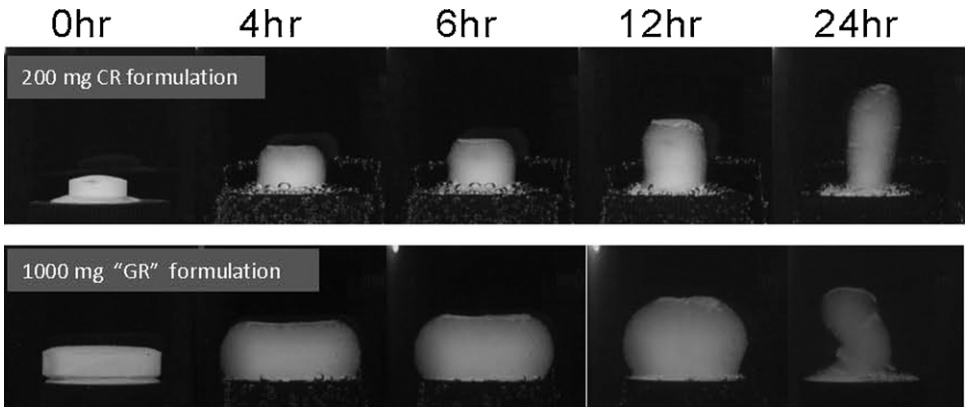

Fig. 4. Time-lapse photographs illustrating the swelling of the controlled release (CR) and gastric retentive (GR) formulations in vitro in SGF (pH 1.2, 500 mL) using USP II.

each other did not change during gastric emptying confirming that the entire dosage form emptied. To confirm that the gastric emptying of the BIPS markers was not altered specifically by the presence of the dosage forms, the small and large markers were re-dosed alone (i.e. no concomitant dosage form) in the fasted state. A similar result was observed as before with no differential gastric emptying of the markers under fasted conditions based on size and gastric emptying occurring between 1 and 3 h post dosing. Klausner et al. (Klausner et al., 2002) reported a similar observation, noting that small and large BIPS emptied simultaneously when dosed under fasted conditions.

Data on the dog pylorus is limited but studies have suggested that the *external* diameter of the pylorus is 20.1–21.5 mm in relaxation and 15.2–17.9 mm in contraction (Keinke and Ehrlein, 1983) with the difference between relaxation and contraction representing the size of the pyloric orifice (i.e. ~5 mm). This data corresponds well to the measured post-mortem value of 5.4 mm internal diameter (Ehrlein, 1988) and with in-house measurements taken during endoscopy in the fasted state (4.8–5.5 mm). During the various phases in the fasted state the pylorus is closed, only opening during the MMC phase. However, it may open transiently during the phases allowing some of the stomach contents to escape with water but mostly emptying occurs during MMC. A small number of the 1.5 mm BIPS units emptied from the stomach immediately post dosing; however, the majority of the beads emptied during the MMC. Based on the size of the pyloric orifice in dogs it is expected that dosage forms significantly larger in size would be retained in the stomach; however, this was not observed. The similar gastric emptying profiles of the BIPS and the CR and GR dosage forms

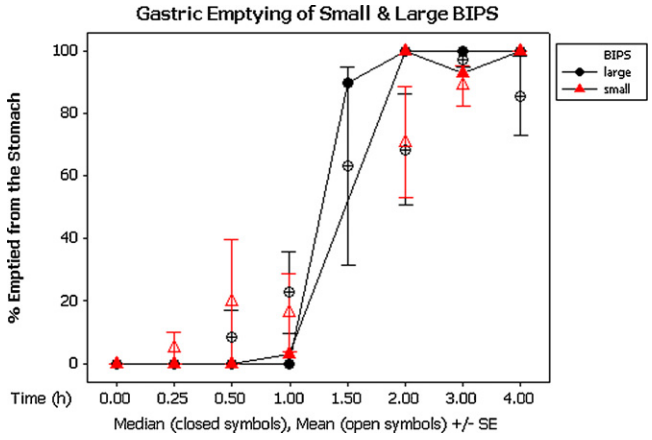

Fig. 5. Gastric emptying of small and large barium impregnated polyethylene spheres (BIPS) in the dog under fasted conditions.

appear to be aligned with the behavior of the stomach in the fasted state during which the pylorus is able to distend significantly to expel the contents of the stomach. In contrast, a study showed that a large rigid rectangular dosage form was apparently able to overcome the contractile forces during the MMC phase remaining in the dog's stomach for about 9 h; however, the administration of food 2 h post dosing may have contributed to the extended retention in the stomach (Ahmed and Ayres, 2007). Variability in gastric emptying time is expected and can be attributed to inter-individual variability between animals as well as the timing of dosing relative to the gastrointestinal motility cycle.

3.2.2. *Effect of food and meal composition on gastric emptying*

BIPS are routinely used as indicators of gastric emptying, providing quantitative information about the emptying process of solids from the stomach of small animals. The small spheres mimic the passage of food whereas the larger markers are usually used to diagnose physical obstruction (Guilford et al., 1997; Lester et al., 1999). Thus, small spheres are expected to empty *as* food, and consequently it should be expected that they empty *with* food. To confirm the reported size differentiated gastric emptying in the presence of food, the markers (1.5 mm: 30 beads, 5 mm: 10 beads) were dosed 30 min after a meal to mimic clinical protocols and radiograph images were taken until all the beads were expelled from the stomach. Previous data (Section 3.2.1) indicated that the presence of a dosage form in the stomach did not impact the gastric emptying of the BIPS; thus the CR and GR dosage forms, embedded with a radio-opaque thread, were dosed in separate experiments, but in each case were co-dosed with BIPS (5 mm, 3 beads) in the fed state. A significant delay in gastric emptying time was noted in dogs after the administration of the high fat meal (HFM); a 5–6 h lag time was observed before any gastric emptying occurred. Fig. 6a is a radiograph image which illustrates that at 5 h post dosing the BIPS and the GR dosage form containing the radio-opaque threads, are retained in the stomach resulting in a lag time. This was followed by rapid gastric emptying of BIPS and the GR dosage form over the next 2 h period as illustrated in Fig. 6b where the GR dosage form is observed in the intestine and most of the BIPS have emptied from the stomach 6 h post dosing. The emptying pattern observed in the fed state was similar to that noted in the fasted state, suggesting the return of the MMC 5 h post feeding. BIPS and the CR and GR dosage forms were only emptied from the stomach after the majority of the food had been expelled and the stomach had reverted to the fasted state.

The gastric emptying time in dogs of non-disintegrating small units under fed conditions has been reported to be generally longer than that observed in normal healthy volunteers (8 h in the dog vs

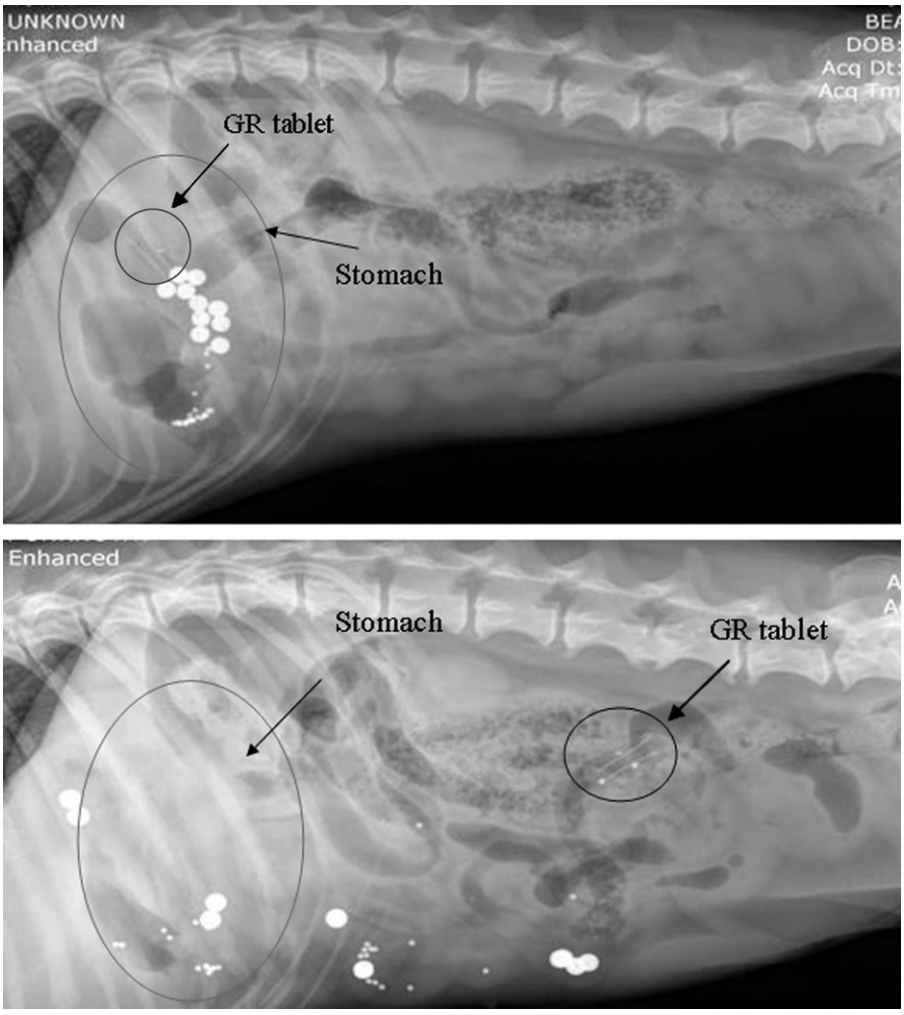

Fig. 6. Radiograph images of the gastric retentive (GR) formulation and barium impregnated polyethylene spheres (BIPS) at (a) 5 h (complete retention in the stomach) and (b) 6 h (GR tablet in small intestine) post dosing in the dog with a high fat diet.

2.5–5 h in humans); however, significant variability exists within both the clinical and preclinical data. This is potentially related to the time of administration of the dosage form relative to the meal and the time the second meal is served (Itoh et al., 1986; Khosla et al., 1989). To investigate the effect of fat and calorie content on gastric retention in the dog, two modified diets (low fat (27%), low calorie (30.5 kcal) and medium fat (33%), medium calorie (214 kcal)) were prepared (Table 2) and the lag phase and gastric emptying profile of the BIPS was evaluated. A 2 h lag time was noted with the modified low fat diet, which increased with fat and calorie content to 4 h (medium fat diet) and 6 h (high fat diet). Irrespective of the meal composition, the gastric emptying profile of the BIPS followed a similar profile to that observed in the fasted state (emptying over ~2 h). However, with the medium fat diet, the lag time observed in the dogs was similar to that noted in the clinic with a HFM (lag time of 4 h) indicating that this meal composition should provide a realistic condition to assess the formulation performance (Fig. 7). Notably, once gastric emptying of the BIPS was initiated, the profile of emptying was once again similar to that observed in the fasted state, likely heralding the return of the MMC at this point.

The observations from this study confirm the relationship between lag time and calorie content; however, it is interesting that the BIPS (1.5 mm) achieved significant food-induced gastric retention despite the small diameter relative to the proposed cut-off values measured by Meyer et al. (Meyer et al., 1985). These observations are in contrast to the data reported by Allan et al. (Allan et al., 1996) in which gradual emptying of both small and large BIPS units from the stomach over 20 h was observed with 25% of the daily calorie requirements from the Hill Prescription

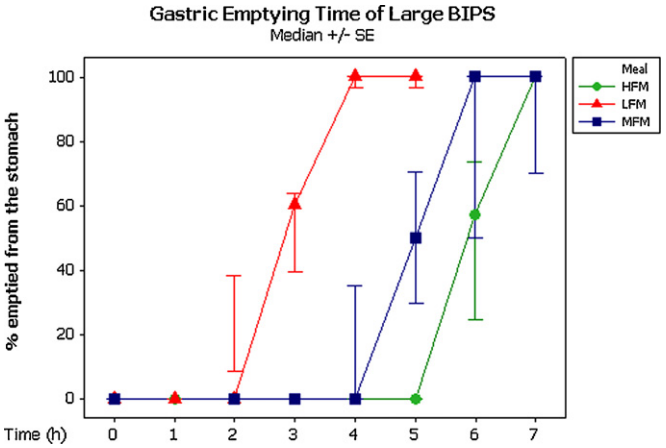

Fig. 7. Gastric emptying profiles of large barium impregnated polyethylene spheres (BIPS) when dosed with meals composed of varying fat content (HFM: high fat meal, MFM: medium fat meal, LFM: low fat meal).

Diet d/d® illustrating that particles as large as 5 mm simultaneously emptied with food in the dog. A subsequent study by Lester et al. (Lester et al., 1999) comparing gastric emptying of 1.5 mm BIPS and a radiolabeled test meal showed that gastric emptying of the BIPS was more variable with the majority of the spheres emptying during the inter-digestive phase. Both these studies suggest that the dietary composition and volume administered may affect the emptying rate of the spheres. The Hill Prescription Diet d/d® used in the above-mentioned studies has a high fiber content and is a solid diet compared to the test diets evaluated in this study. The diets selected in this study were designed to reflect those required by regulatory agencies in assessing formulation performance in humans.

The transit time of dosage units (gastric emptying) is directly related to the diameter of the unit. Transit is also related to the difference in density between the unit and media (i.e. the bigger the difference, the more likely a tablet is to be retained in the stomach) and is inversely related to the media viscosity. To better understand the differences between the gastric emptying profiles of BIPS in this study and the published results, the density and viscosity of the diets evaluated in this study were measured. The density of the BIPS was calculated to be 1.48 g/mL for the 5 mm beads and 2.54 g/mL for the 1.5 mm which is similar to the reported value of ~1.37 g/mL (Allan et al., 1996) and greater than that of the three meals evaluated (Table 2). Therefore, it is expected that BIPS will settle in the fundus of the stomach and not empty simultaneously with food despite the small dimensions of the bead relatives to that of the pylorus orifice. This highlights an interesting consideration when selecting a dog model for pre-clinical assessment of gastric retention; the postural differences between dogs and humans and the corresponding position of the stomach highlight a key difference between the pre-clinical model and man. The test meals were all viscoelastic and sheer thinning over the shear rates measured (shear amplitude from 0.01 to 100 s^{-1}) with the following ranking: MFM > HFM > low fat meal. The higher solids content in the medium fat diet compared to the HFM explains the trend observed. Previous studies in the dog model showed that increasing the diameter of a dosage unit beyond 3.2 mm whilst maintaining similar density to food slowed gastric emptying, whilst increasing the density of the dosage unit relative to that of the food delayed gastric emptying despite the small diameter of the unit (Meyer et al., 1985). The higher density of the BIPS relative to the meals appears to be more critical than the size in determining the gastric emptying rate of the BIPS.

3.2.3. Gastric transit of BIPS and the CR and GR dosage formulations

Directly comparing BIPS with the GR and CR dosage forms, across a range of meal types, illustrates that the median gastric emptying time of the small and large BIPS is statistically similar to that of the GR formulation (diameter ~18 mm) and CR formulation (diameter ~8 mm) irrespective of the meal type (Fig. 8). In some cases, a small proportion of the small BIPS was emptied with the digestible components of the meal, but invariably the majority were retained in the stomach until gastric emptying of the digestible portion was complete and were subsequently emptied during the inter-digestive phase (MMC). It was not possible to differentiate the gastric emptying of the small and large spheres or of the CR and gastric retention formulations under either fasted conditions or with selected meal compositions in the dog model. The canine pylorus appears to be more restricted with the pyloric orifice measured at 5.4 mm in the fasted state and 1.2 mm in the fed state (Ehrlein, 1988). Dosage units equal to or less than 2–3 mm in diameter appear to freely pass into the intestine, while those larger than 5 mm tend to be retained in the stomach until the onset of the housekeeper wave (Itoh et al., 1986; Meyer et al., 1985). This data

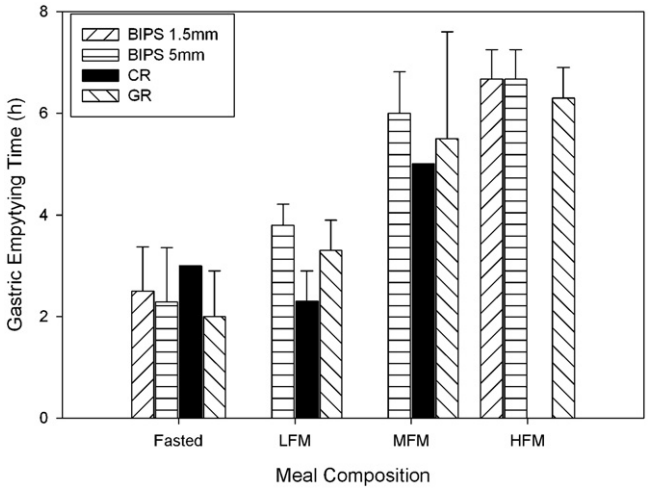

Fig. 8. Comparing gastric emptying time of small (1.5 mm) and large (5 mm) barium impregnated polyethylene spheres (BIPS), CR formulation and GR dosage forms in the dog model under various diets (HFM: high fat meal, MFM: medium fat meal, LFM: low fat meal). Data represents mean ± SD, $n = 3–6$.

confirms that in the dog model differentiation of gastric emptying rates based on size is not feasible and that gastric emptying appears to be solely mediated by the feeding status and the meal composition and volume. However, in clinical studies dosage units, 3–7 mm in diameter, are reported to freely pass through the pylorus under fed conditions (Coupe et al., 1991). Therefore, it might be anticipated that the designed CR formulation, which has a diameter in this range, would probably be emptied from the stomach in man during the fed state whilst the GR formulation is retained in the stomach until the MMC. However, since there have been examples in the literature of pellet (0.7–1.4 mm) retention in the stomach (Newton, 2010) it is postulated that this issue is much more complex, and similar trends to these observed in the dog may be observed in man.

A clear response of the fat content on gastric emptying was observed in the dog, specifically between the fasted/modified low fat content meal and the medium/high fat content meals. The gastric emptying times of swelling-based GR formulations in dogs increased from 2.0 ± 0.9 h under fasted conditions to 6.3 ± 0.58 h after a HFM, 5.5 ± 2.1 h after a MFM and 3.3 ± 0.6 h after a low fat meal (Fig. 8). A comparable response was observed in the clinic (14.3 ± 7.7 h after a HFM, 8.2 ± 7.7 h after a MFM with 30% fat and 3.76 ± 1.5 h after a low fat breakfast (Schwartz et al., 2008), (Louie-Helm et al., 2003) confirming the role of meal composition (specifically fat content) on gastric emptying times. The extended gastric retention reported in the clinic for the above formulations could be attributed to the clinical protocol followed, where food is offered to patients 4 h post dosing which prevents the stomach from returning to the inter-digestive stage during which large indigestible material can be expelled from the stomach. In fact Mojaverian summarized the effect of feeding regimens on the gastric residence time of the Heildelberg radiotelemetry capsule (7 mm × 20 mm) in humans, reporting that with frequent feeding the gastric residence time increased from ~4 h after a 500 kcal breakfast to ~6 h if lunch was provided 4 h after breakfast to 12.5 h if food/snacks were provided every 2–3 h (Mojaverian, 1996). Under fed conditions (high calorie, low fat), decreasing the diameter of a GR tablet from 13 mm to 7 mm whilst keeping the length constant (18 mm) reduced gastric retention from 12 h to 8.5 h confirming that in the clinic differential emptying based on image size is feasible (Cowles et al., 2004).

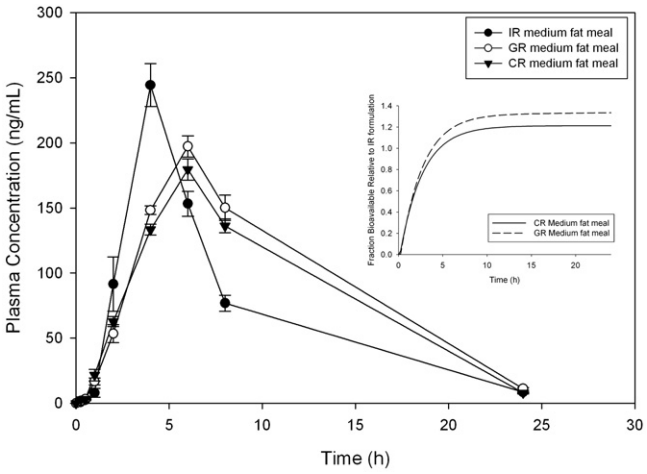

Fig. 9. Mean (±SE) plasma profiles of immediate release (IR), controlled release (CR) and gastric retentive (GR) formulations dosed with a medium fat meal (MFM) to dogs ($n = 6$). *Inset*: Metformin fraction bioavailable from the controlled release (CR) and gastric retentive (GR) formulations relative to the immediate release (IR) formulation dosed under similar fed conditions.

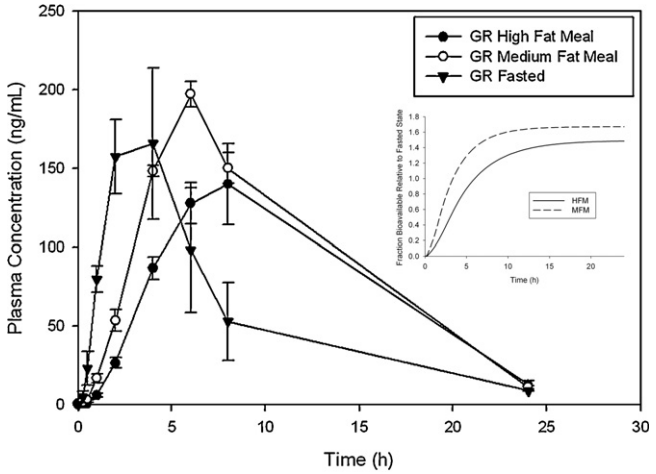

Fig. 10. Mean plasma profiles of the gastric retentive (GR) formulation in dogs under fasted, medium and high fat meal (HFM) conditions ($n = 3$). *Inset*: Metformin fraction bioavailable from the gastric retentive (GR) formulations dosed with a high fat meal (HFM) and medium fat meal (MFM) relative to the fasted state.

3.3. Pharmacokinetic evaluation of the IR, CR and GR formulations

Imaging data is valuable in determining whether a formulation is retained in the stomach or prematurely released into the small intestine; however, achieving the desired pharmacokinetic profile demonstrates true success of a GR formulation. For successful implementation of GR, greater absorption of the drug should theoretically be achievable with a retained modified release dosage form over one that is not retained and which spends time in areas of low absorption (i.e. the colon). To illustrate this, the CR and gastric retention formulations were dosed in the dog and the pharmacokinetic parameters were determined. The effect of meal composition was also assessed by comparing the pharmacokinetics under fasted, medium and HFMs. This data was generated concurrently with imaging data, as the hypothesis was that any difference in gastric retention achievable by the CR compared to the GR formulations would be translated into pharmacokinetic differences. However, given that the transit data from the imaging studies (Fig. 8) was not significantly different between the CR and GR dosage forms, it could be speculated that no pharmacokinetic difference would be observed assuming similar dosage form integrity and in vivo release rates between the formulations. Conversely, differences in the feeding regimens (and hence gastric retention times) may translate to pharmacokinetic differences.

The mean plasma concentration–time profiles for the IR, CR and GR formulations dosed with a MFM in dogs are illustrated in Fig. 9. Broader profiles with a slower increase in plasma concentration were noted for the GR and CR formulations compared to the IR formulation confirming controlled dissolution of metformin. Table 6 summarizes the mean pharmacokinetic parameters for the formulations dosed under a MFM. As expected, the CR and GR formulations exhibited comparable pharmacokinetic behavior when dosed with a MFM (relative AUC (GR/CR): 1.1, relative $\underline{C}_{max}$ (GR/CR): 1.1) confirming similar gastric retention as observed with imaging, despite significant differences in the image size. Both formulations provided a significantly higher exposure (20–30%, $p < 0.01$) and reduced $\underline{C}_{max}$ (20–30%, $p < 0.05$) compared to the IR formulation due to the narrow absorption window for metformin and slower release of the active from the GR and CR dosage forms retained in the stomach. Comparable observations between immediate and GR formulations were reported in the clinic with a 14% increase in exposure and 25% reduction in $\underline{C}_{max}$ for the GR formulation relative to an IR formulation (Gusler et al., 2003).

A critical design feature of GR formulations is the ability to withstand strong contraction forces in the stomach. Mechanical forces in the stomach are known to be more aggressive (1.5–1.9 N; Kamba et al., 2002) than those experienced in a dissolution vessel and significantly higher in the dog (Laulicht et al., 2010; Klausner et al., 2002); therefore, it is possible that the formulation may not remain intact in the stomach altering the in vivo release rate and affecting the pharmacokinetic profile. The in vitro release profiles show CR over 12 h for both the CR and GR formulations (Fig. 3). To confirm that the formulations did not prematurely rupture in the stomach and release drug over 12 h as designed, the pharmacokinetic profiles of the GR and CR formulations were deconvoluted against the IR formulation to obtain the in vivo input profiles of metformin from these formulations. The fraction bioavailable relative to the IR formulation over time is similar for the GR and CR formulations demonstrating in vivo dissolution over ~8 h which correlates with the imaging data (gastric retention of the unit for ~6 h) and confirms no loss of dosage form integrity (Fig. 9, inset).

To explore further the utility of the dog model in assessing the in vivo performance of GR formulations, which are commonly dosed with food, the role of calorie content and meal composition on gastric emptying and the pharmacokinetic profile was determined. Dosing the GR formulation with food in the dog provided a 30% and 60% increase in exposure, with comparable $\underline{C}_{max}$ values to the fasted state and a delay in T_{max} ranging from 4 h to 8 h for the medium and HFMs, respectively. Metformin was detected in the plasma 15 min post dosing irrespective of the fat and calorie content indicating that gastric emptying of metformin occurred as part of the fed state motility and not the MMC. No lag time was observed with any of the meal since the meals were blended to a smooth paste with small particles thus eliminating the time required for trituration. Generally lag times represent the trituration time for particle size reduction to 1–2 mm.

The meal composition did not significantly impact ($p > 0.5$) the extent to which exposure was increased in dogs (Table 7) with a HFM not showing an increase in exposure over the MFM. However, the rate of absorption was slower in the presence of a HFM (Fig. 10). The increase in exposure with the GR formulation under fed conditions in dogs, in conjunction with the imaging data which shows gastric retention for 5–6 h with a MFM or 6–7 h with a HFM highlights the beneficial role of the feeding status on gastric retention.

Table 6
Mean (±SE) pharmacokinetic parameters of metformin (20 mg) from the immediate release (IR), controlled release (CR) and gastric retentive (GR) formulations dosed to dogs fed a medium fat meal.

Formulation	AUC (ng × h/mL)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(GR/CR)}$ $AUC_{(IR)}$	$C_{max(GR/CR)}$ $C_{max\ (IR)}$
IR	1699.61 ± 68.11	244.31 ± 16.5	4 (4–4)	1.0	1.0
GR	2225.07 ± 102.39	197.29 ± 8.12	6 (6–6)	1.31	0.81
CR	2027.47 ± 71.75	179.45 ± 8.04	6 (6–6)	1.19	0.73

Table 7
Mean (±SE) pharmacokinetic parameters of metformin (20 mg) of the gastric retentive (GR) and immediate release (IR) formulations in the fasted and fed conditions.

		AUC (ng × h/mL)	C_{max} (ng/mL)	T_{max} (h)	AUC(fasted) AUC(fed)	C_{max} (fasted) C_{max} (fed)
GR formulation	Fasted	1380.90 ± 344.37	187.58 ± 35.07	4 (2–6)		
	Medium fat meal	2225.07 ± 102.39	197.29 ± 8.12	6 (6–6)	1.69	1.05
	High fat meal	1834.26 ± 279.54	148.9 ± 19.1	8 (6–8)	1.33	0.79
IR formulation	Fasted	2227.85 ± 323.03	502.65 ± 43.8	1 (1–2)		
	Medium fat meal	1699.61 ± 68.11	244.31 ± 16.45	4 (4–4)	0.76	0.42
	High fat meal	1807.42 ± 165.02	212.81 ± 20.6	4 (2–4)	0.81	0.49

In short, retaining the dosage form for >3.5 h in the stomach can lead to at least a 30% improvement in exposure in the dog model as observed with metformin. Published clinical data confirming the effect of food and meal composition on metformin exposure follows a similar trend to that observed in the dog model; however, the effect of fat content on exposure was more obvious with a 70% and 35% increase in exposure noted for a high and MFM compared to the fasted state (Schwartz et al., 2008). Patients are therefore advised to take GR formulations with meals to ensure retention of the dosage form in the stomach and optimal exposure. The smaller sample size in preclinical studies compared to clinical studies may be responsible for the lack of differentiation between feeding conditions. To estimate the impact of the fat content on gastric emptying time, deconvolution of the GR formulation dosed with a medium and HFM against the fasted state was performed (Fig. 10 inset). The fractional input for the MFM was slightly shorter than for the HFM (8–10 h vs 15 h) corroborating the imaging data in which slightly longer gastric retention was observed with the HFM.

Interestingly, the imaging data and the corresponding pharmacokinetic data illustrate that the GR formulation in the fasted state behaves as a standard CR formulation would, emptying from the stomach within 2 h and releasing drug over an extended period of time as it transits through the gastrointestinal tract (Fig. 11).

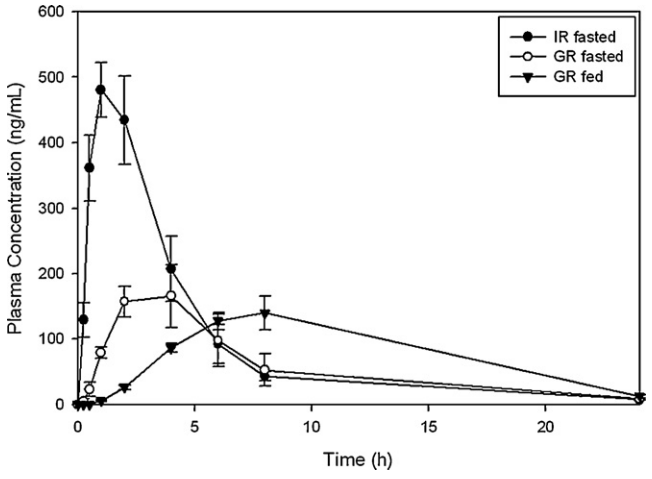

Fig. 11. Mean plasma profiles of the immediate release (IR) formulation in fasted dogs, gastric retentive (GR) formulation in fasted dogs (behaves like a controlled release (CR) formulation) and the gastric retentive (GR) formulation in the fed state ($n = 3$).

Therefore, comparing the behavior of the GR formulation in the fed versus fasted state provides an assessment of the benefits of gastric retention over CR (60% increase in exposure, similar C_{max}) for a compound with a narrow absorption window (Fig. 11). Furthermore compared to the IR formulation under fasted conditions (Table 6), a 60% decrease in exposure and 40% loss in C_{max} were observed with the GR formulation in the fasted state confirming the poor colonic absorption of metformin. Similar observations have been noted clinically with conventional CR dosage forms providing a lower C_{max} but also resulting in a loss in exposure compared to the IR formulation. In contrast the exposure and C_{max} decreased by ~25% and 60%, respectively, when the IR formulation was dosed with a high or medium fat containing meal compared to the fasted condition. This is expected for a BCS Class III compound (Table 7). A similar trend was observed in the clinic for the IR formulation (Sambol et al., 1996) with a HFM (40% reduction in C_{max} and 25% loss in exposure), confirming the utility of the dog model in assessing the effect of food on the performance of a soluble IR and GR formulation.

4. Conclusion

In the majority of published studies designed to demonstrate gastric retention, the reference formulation is an IR formulation which has a faster dissolution profile compared to the GR formulation and as such differences observed in the pharmacokinetic data are confounded by the dissolution rate and therefore can not be clearly attributed to gastric retention. In the animal studies discussed in this paper a non-disintegrating CR formulation with a similar in vitro release profile to that of a novel swelling-based gastric retention formulation was designed and evaluated in vitro by comparing the degree of swelling and drug release rate to that of a known GR formulation, Glumetza®. The CR comparator was designed to be significantly smaller and not swell appreciably to ensure passage through the pylorus and minimize its gastric residence time.

In the dog model it was not possible to differentiate the gastric emptying time of the small (1.5 mm) and large (5 mm) BIPS as well as the controlled and GR formulations under fasted and the same feeding conditions; however, there was a clear effect of diet on gastric emptying time. The GR formulation in the fasted state essentially behaves like the conventional CR formulation and a comparison of the pharmacokinetic performance of the GR formulation in the fasted and fed state provides an indication of the benefit of gastric retention especially for a drug with a narrow absorption window. The dog model is not predictive of

differentiating the gastroretentive performance of oral CR matrix/GR dosage forms of different image sizes in the presence of food likely due to the smaller pyloric aperture and vertical fundus orientation compared to humans. However, this model is capable of assessing the performance of GR/CR formulations relative to the IR formulation under fed conditions as it demonstrates differential pharmacokinetics. The impact of changes in the fat content of a meal on the pharmacokinetics was not apparent potentially due to the small sample size.

This work suggests that contrary to the size-increasing mechanism of gastric retention observed in the clinic, size of the dosage form in the dog model is not a critical factor in the fasted state and that similar gastroretention, or lack thereof, can be achieved with non-disintegrating formulations of different sizes. Diet was identified as the critical determinant of gastroretention in this example, as also reported in the clinic for Glumetza® and Proquin XR™. Optimal gastric retention can hence be achieved by modulating the size/swelling rate of the dosage form together with the erosion rate, the density of the formulation relative to the stomach contents and the composition of the meal. It is acknowledged that additional clinical studies coupled with imaging would be required to fully investigate the size-increasing theory of gastric retention based on the size of pylorus orifice in the fed state relative to that of the CR formulation.

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