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Pharmacoscintigraphy confirms consistent tamsulosin release from a novel triple-layered tablet

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ABSTRACT

Conventional modified release preparations of tamsulosin HCl have been linked to increased incidence of cardiovascular adverse events, possibly due to rapid drug peaks soon after ingestion. A 'flattened' absorption profile has been shown to reduce the occurrence of these unwanted effects while improving symptom control.

The potential of a novel triple-layered tablet to effect prolonged release and continuous absorption of tamsulosin HCl in the gastrointestinal tract was investigated in this clinical study. Gastrointestinal (GI) transit behaviour was monitored by scintigraphic imaging of technetium-labelled tablets. Drug absorption levels were simultaneously determined through pharmacokinetic analysis of blood samples.

A mean C_{max} of 6 ± 3 ng/nL was achieved after 324 ± 184 min (mean t_{max}). The mean $AUC_{0\text{-}24}$ was noted as 4359 ± 1880 ng/mL min. The mean gastric emptying and colon arrival times of the tablets were 105.2 ± 68.9 and 270.1 ± 32.0 min post-dose; giving a mean small intestine transit time of 164.9 ± 83.6 min. Variations in gastrointestinal transit did not appear to influence drug absorption.

Correlation of scintigraphic and PK data indicated that tamsulosin HCl is released steadily throughout the entire GI tract, suggesting that the mechanism of drug release is independent of GI site allowing drug release even in the low moisture environment of the colon.

1. Introduction

Oral extended delivery systems which provide constant release throughout the entire gastrointestinal (GI) tract have the potential of optimising therapeutic efficacy as well as improving patient compliance by reducing dosing frequency. The current favoured approach is that of monolithic matrix systems with uniform drug distribution throughout the dosage form.

While this technology is widely used and the polymers utilised are non-toxic and highly compatible with various drugs (Siepmann and Peppas, 2001; Ford et al., 1985, 1991; Ranga Rao et al., 1990), it is limited by its tendency to exhibit a fast initial release rate followed by a diminished release rate as dissolution progresses along the GI tract (Huang and Brazel, 2001). The reduced release rate in the distal regions of the GI tract is further compounded by the low moisture environment and viscous contents of the colon limiting fluid access to the delivery systems.

To overcome these limitations, a novel drug delivery system has been developed which enables both drug dissolution and dispersion independent of the surrounding environment; allowing consistent drug absorption even within the colon.

The Geometrically Long Absorption Regulated System (GLARS) is a triple-layered tablet comprised of upper and lower layers which absorb water and swell, plus a highly water soluble middle layer which draws water into the tablet core simultaneously (Park et al., 2011a). As the middle layer induces rapid water absorption, the penetrated water also diffuses through the upper and lower layers, causing the tablet to swell. The relatively rigid swollen matrix structure facilitates consistent *in vivo* drug release irrespective of the degree of gastrointestinal motility (Park et al., 2011b).

A suitable candidate for incorporation into this system is the selective alpha-1 antagonist, tamsulosin hydrochloride (HCl), which is used in the treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The conventional modified release formulation of tamsulosin has been shown to exhibit food and gastrointestinal transit-dependent absorption profiles. Increased serum levels (Lyseng-Williamson et al., 2002) and incidence of cardiovascular side effects (Michel

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et al., 2005a) have been noted if the medication is taken on an empty stomach compared with after a meal.

Consistent release of this drug throughout the GI tract, independent of fed/fasted state, has been shown to provide increased therapeutic benefit to sufferers of this disease, including improvement in nocturia and quality of sleep (Djavan et al., 2005) and reduced likelihood of cardiovascular adverse events (Michel et al., 2005b,c).

A clinical study was designed to investigate the *in vivo* behaviour of the tamsulosin HCl GLARS tablet using the combined approach of pharmacoscintigraphy in order to establish the link between tablet location in the gastrointestinal (GI) tract and drug absorption profile.

Gamma scintigraphy is a widely used non-invasive imaging technique that relies on capturing the emitted radiation from appropriately radiolabelled dosage forms to give information on their transit and dispersion (Davis et al., 1992). When coupled with simultaneous pharmacokinetic (PK) sampling, valuable correlations can be made between the tablet behaviour and resultant drug absorption.

To assess gastrointestinal transit, the primary variables were gastric emptying time and colon arrival time. Small intestinal transit time was calculated as the difference between gastric emptying and colon arrival times. To assess tablet disintegration, time and site of onset and complete radiolabel release were determined. PK parameters included maximum concentration observed (C_{max}), time to maximum concentration (t_{max}), and area under the curve to 24 h ($AUC_{0\text{-}24}$).

2. Materials and methods

2.1. Manufacture of GLARS tablets

The preparation process of the GLARS tablets was as reported in Park et al. (2011b). However the tablets for this study were manufactured to GMP on a pilot scale.

2.2. Radiolabelling procedures

The GLARS tablets were supplied by GL PharmTech, Korea and radiolabelled by Bio-Images Research Ltd using a 'drill and fill' method. Each GLARS tablet was drilled to 3 mm using a 1.6 mm drill bit, exactly reaching the middle layer of the tablet. This hole was filled with a milled mixture of technetium-labelled charcoal and cellulose acetate in a quantity sufficient to provide approximately 4 MBq at the target dosing time. The remainder of the hole was then filled with outer layer blend and sealed with a small amount of HPMC-based coating solution.

To compare the *in vitro* behaviour of radiolabelled and non-radiolabelled tablets, 'drilling and filling' of GLARS tablets was also conducted by substituting liquid radiolabel with 0.9% sodium chloride to produce non-radiolabelled tablets for dissolution testing. The tablets were tested in a USP Apparatus II (paddle speed 100 rpm, $37 \pm 0.5\,^{\circ}C$, 900 mL phosphate buffer pH 6.8) with the tablets located within a stationary basket assembly.

Samples were withdrawn at specific intervals and analysed for drug content by HPLC methods.

2.3. Study design and methods

This was a single-centre, open-label, single arm study in eight healthy male volunteers. The sample size for this study was selected on the basis of previous pilot studies using this imaging technique to provide descriptive data and not to support rigorous statistical analyses.

All screened volunteers gave written informed consent prior to undergoing a pre-study screening medical examination within the 28 days prior to dosing to ensure compliance with study inclusion and exclusion criteria. Male volunteers aged 18–65 years inclusive, in good general health with a body mass index in the range 18.0–29.9 kg/m^2 were eligible for inclusion in the study.

Eligible subjects attended one dosing day, receiving a single dose of a GLARS tablet, containing 0.4 mg tamsulosin HCl equivalent to 0.367 mg tamsulosin and approximately 4 MBq ^{99m}Tc (at time of dose).

On arrival at the study centre, subjects were questioned on adherence to study restrictions. These included pre-breakfast fasting for at least 10 h, of which the final 2 h required abstinence from fluids as well and avoidance of alcohol (>72 h), spicy foods (>48 h), strenuous physical activity (>24 h) and caffeine (>24 h). Subjects were also required to abstain from prescribed and over-the-counter medications for 14 days and 48 h pre-dose, respectively, unless the medication was approved by a study physician.

Prior to enrolment into the study, the subjects were required to pass both breath alcohol and urine drugs of abuse tests. Approximately 15 min prior to dosing, the subjects received a standard breakfast comprising of one scrambled egg (made with 20 mL full fat milk and 2.5 g butter), one slice of white toast with 7.5 g of butter and a cup of decaffeinated tea or coffee with 5 mL semi-skimmed milk.

At dosing, one radiolabelled GLARS tablet was taken with 240 mL chilled water.

External radioactive markers (approximately 0.01 MBq ^{99m}Tc) were taped to the chest and back to enable accurate alignment of sequential images. All scintigraphic images of the abdominal area were taken with the subject in the standing position using a Siemens E-Cam gamma camera fitted with a low-energy high-resolution collimator.

Sequential anterior and posterior abdominal images of 25 s duration each were taken immediately post-dose, then every 15 min until complete release of ^{99m}Tc from the tablet or tablet excretion was confirmed, to a maximum of 15 h post-dose. An additional image was taken at 24 h post-dose if required.

Blood samples for pharmacokinetic analysis of tamsulosin were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 12, 15 and 24 h post-dose from an indwelling cannula or by venepuncture. A pre-dose blood sample was also taken approximately 15–60 min prior to dosing.

The clinical study protocol and all amendments, participant information sheet, consent form and other study documents were approved by West of Scotland Research Ethics Committee 1 prior to study commencement. The radiation dosimetry was approved by the Administration of Radioactive Substance Advisory Committee (ARSAC). This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.

2.4. Assessment of efficacy

The scintigraphic data was analysed using the WebLink® image analysis program (Link Medical, Hampshire, UK). The times of onset and complete release of ^{99m}Tc and positional analysis were determined by qualitative assessment of the scintigraphic images by two independent, trained personnel. Precise times for transit and release of radiolabel could not be determined due to the intervals between acquisitions of images. The times presented represent the midpoint between the image at which the event was observed and the previous image.

Where complete radiolabel release times are not reported, this indicates that this event was not observed during the 15 h imaging period and the tablets were not visible in the images recorded at 24 h post-dose.

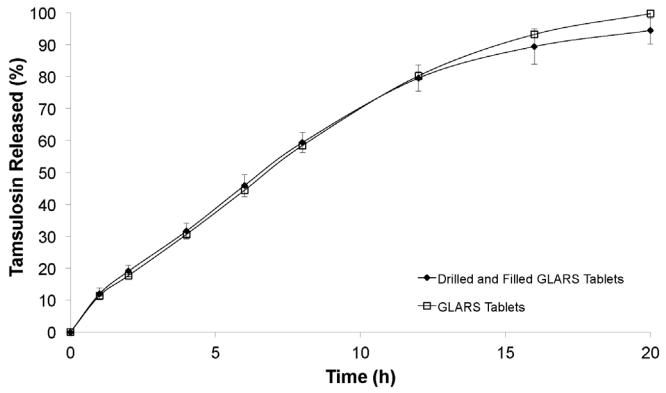

Fig. 1. Mean tamsulosin release profiles from both original and 'drilled and filled' GLARS tablets.

Blood samples were centrifuged and plasma fractions removed and frozen until shipped to GL PharmTech Corp. for analysis using a validated LC-MS/MS method.

The pharmacokinetic parameters were determined from the experimental drug concentration–time data using the non-compartment method. The maximum observed concentration (C_{max}), time at which C_{max} occurred (T_{max}), and area under the plasma concentration–time curve (AUC) were calculated using the linear trapezoidal rule from time zero to 24 h ($AUC_{0\text{-}24}$).

The fraction-absorbed calculations employed the Wagner–Nelson Method (Wagner, 1983). The percentages absorbed *vs.* time were calculated by:

$$\%\,\text{Absorbed} = \left(\frac{C(t)/Ke + \text{AUC}_{0-t}}{\text{AUC}_{0-\infty}}\right) \times 100$$

where $C(t)$ is the plasma concentration at time t, Ke is the elimination rate constant, AUC_{0-t} and $AUC_{0-\infty}$ are the area under the plasma concentration–time curve from zero to time t and infinity, respectively.

2.5. Assessment of safety/tolerability

Safety was assessed by physical examinations, vital signs, laboratory safety evaluations (blood biochemistry, haematology and urinalysis) and adverse event monitoring. Subjects were actively questioned on AEs before dosing, throughout the study day and at follow-up. AEs spontaneously reported by subjects were also noted.

3. Results

Fig. 1 shows the mean tamsulosin release profiles from both original and 'drilled and filled' GLARS tablets ($n = 12$ each). The mean drug release profile of 'drilled and filled' GLARS tablets is comparable to the original tablets with gradual release of tamsulosin observed over 20 h, with an average release at 20 h of 94% and 100% for the 'drilled and filled' and original tablets, respectively. The disparity of total drug released can be attributed to the small quantity of drug removed during the drill and fill process.

Table 1
Summary of subject demographics.

Number of subjects enrolled	8
Number of subjects completed	8
Age of subjects (mean ± SD, range)	29.0 ± 10.6, 21–52 years
Race of subjects	8 Caucasian
Height (mean ± SD)	1.75 ± 0.07 m
Weight at screening (mean ± SD)	77.4 ± 7.4 kg

All eight enrolled subjects completed the study. Table 1 summarises the demographics of the subjects. All subjects were in good general health with no significant medical history. Concomitant medications used during the study period were over-the-counter pain medication and health supplements, although these were not used within 14 days of the dosing day. All medications were approved by the study physician.

3.1. Efficacy results

3.1.1. Scintigraphy

Fig. 2 shows the key events in the gastrointestinal transit of GLARS tablets at various time points in Subject 003, including confirmation of gastric emptying, and onset and complete radiolabel release.

Gastrointestinal transit parameters, derived from scintigraphic images, are summarised in Table 2. Gastric emptying (GE) of the GLARS tablet was observed in all eight subjects during the imaging period and the mean time for GE was 105.2 ± 68.9 min. For Subject 002, gastric emptying occurred in the second image taken at 15 min post-dose. The tablets arrived in the ascending colon for all eight subjects after a mean time of 270.1 ± 32.0 min post-dose.

The mean time for small intestinal transit was 164.9 ± 83.6 min. This is in agreement with the findings of Davis et al. (1986) who have noted that the mean small intestinal transit time is 180 ± 60 min, irrespective of dosage form or fed state.

The mean times for onset and completion of release were 390.2 ± 128.6 min post-dose ($n = 8$) and 673.5 ± 160.0 min post-dose ($n = 5$), respectively. In seven out of the eight subjects, onset of radiolabel release was observed in the colon; three in the ascending colon; one in the hepatic flexure; two in the transverse colon and one in the descending colon. For the remaining subject (Subject 007), onset of radiolabel release was observed in the stomach.

Complete radiolabel release was observed in the descending colon for five subjects. For the remaining three subjects (Subjects 001, 002 and 004), complete radiolabel release was not observed within 15 h post-dose. It is likely that complete release for these subjects was also in the descending colon. Images at 24 h post-dose showed there was no tablet remaining for these three subjects.

3.2. Pharmacokinetics

A composite graph of tamsulosin profiles from all subjects is shown in Fig. 3. A mean C_{max} of 6 ± 3 ng/nL was achieved after 324 ± 184 min (t_{max}). The mean $AUC_{0\text{-}24h}$ was noted as 4359 ± 1880 ng/mL min. The shapes of the profiles were relatively similar except for the following outliers: (a) Subject 007 who displayed a C_{max} of more than double the median value and; (b) Subject 001 and Subject 003 whose t_{max} only occurred at 721 and 483 min, respectively, relatively later than the other subjects.

3.2.1. Correlation between scintigraphic and pharmacokinetic data

Interpretation of the pharmacokinetic profiles indicate that dissolution of the drug commenced immediately after ingestion which accorded with the release profiles (Fig. 1), as evidenced by the appearance of tamsulosin in the plasma even at 1 h post-dose. This was mainly due to release of the tamsulosin load within the outer layers of the tablet. Park et al. (2011b) also reported that the drug in the outer layer showed typical release profiles of a monolithic matrix whilst a time delay was observed prior to drug release from the middle layer of the GLARS tablets. Tamsulosin release continued even within the colon, as shown by the plateauing followed by gradual decrease of plasma concentration levels while the tablets were located in this region.

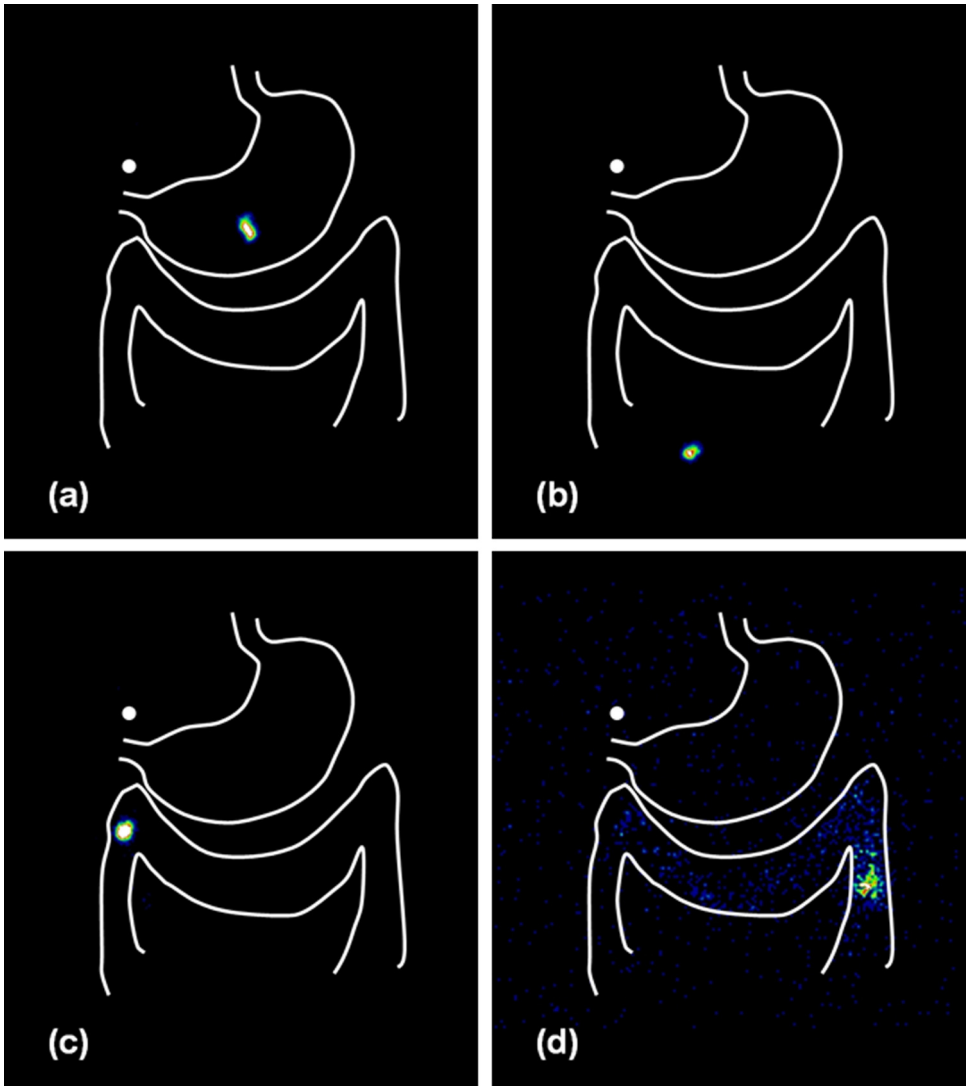

Fig. 2. Scintigraphic images of key events in the GI transit of the GLARS tablet in Subject 003: (a) 60 min, tablet located in stomach; (b) 180 min, image at which GE confirmed, tablet in small intestine; (c) 330 min (onset of radiolabel release, tablet in ascending/transverse colon) and (d) 765 min (complete radiolabel release, tablet in descending colon). Outlines of stomach and colon are drawn for visualisation only. The white circle represents the radioactive marker on the subject's chest.

Although the PK profiles of Subjects 001, 003 and 007 were different from the other subjects', this variation was not influenced by patterns of transit through the GI tract as their gastric emptying, small intestinal transit and colon arrival times were comparable to the means.

GI transit patterns did not affect absorption, as evidenced by Subject 002 who, despite exhibiting rapid gastric emptying, also displayed a similar tamsulosin absorption profile. This is a promising finding, indicating reliable drug release irrespective of GI transit behaviour.

Table 2
Gastrointestinal transit and radiolabel release parameters of GLARS tablets. (AC – ascending colon; DC – descending colon; S – stomach; TC – transverse colon; NR – not recorded, *i.e.* event not observed.).

Subject no.	GI transit parameters			Radiolabel release parameters			
	Gastric emptying time (min post-dose)	Colon arrival time (min post-dose)	Small intestinal transit time (min)	Onset (min post-dose)	Site of onset	Complete (min post-dose)	Site of complete
001	22.5	247.5	225.0	397.5	AC	NR	NR
002	8.0	322.5	314.5	577.5	AC	NR	NR
003	172.5	247.5	75.0	322.5	AC/TC	757.5	DC
004	143.0	248.0	105.0	428.0	DC	NR	NR
005	172.5	307.5	135.0	487.5	TC	652.5	DC
006	68.0	247.5	179.5	338.0	TC	712.5	DC
007	172.5	247.5	75.0	143.0	S	412.5	DC
008	82.5	292.5	210.0	427.5	AC	832.5	DC
Mean	105.2	270.1	164.9	390.2		673.5	
SD	68.9	32.0	83.6	128.6		160.0	

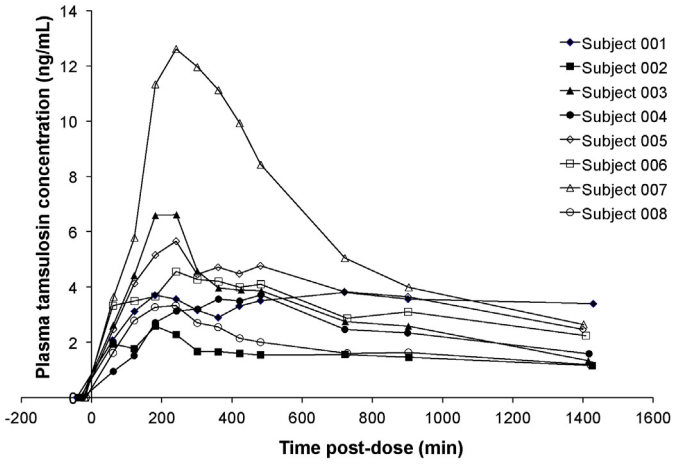

Fig. 3. PK profiles of tamsulosin absorption from GLARS tablets for all subjects.

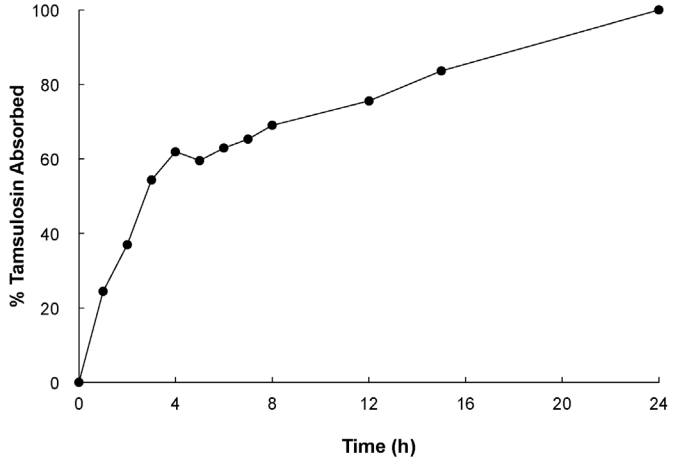

Fig. 4. Mean tamsulosin absorption profile for all subjects.

It must be noted however, that onset of radiolabel release for Subject 007 occurred at 143.0 min in the stomach. This observation for Subject 007 might have been a consequence of failure of the sealing coat applied, and was confirmed by the increased C_{max} due to release and absorption of a majority of the drug in the upper GI tract.

Fig. 4 shows a graph of mean percentage tamsulosin absorption from all subjects. The data shows that rapid absorption occurred within the first 4 h of ingestion, reaching approximately 60%, followed by a gradual release to 24 h. Scintigraphic data confirmed that the tablets reached the colon after approximately 4.5 h. This suggests that the change in absorption rate is dependent on the GI location of the tablet and that consistent tamsulosin absorption in the colon was achieved.

3.2.2. Safety/tolerability

There were four adverse events reported. All were single in episode, of mild intensity and spontaneously resolved without any intervention. Two were assessed as having no relationship to the study and the other two as unlikely to be related to the study.

4. Discussion

This extended release formulation of tamsulosin HCl was designed to potentially provide consistent release of the drug throughout the GI tract, independent of levels of moisture available for drug dissolution and diffusion. The inclusion of both gel former and gel enhancer agents was aimed at promoting water ingress and retention to enable drug release even in the distal regions of the gut, where water is limited.

The current study evaluated the drug release and GI transit behaviour of the new GLARS tablet in eight healthy subjects under lightly fed conditions utilising the combination of gamma scintigraphic imaging and PK analysis of plasma samples.

In general, with the exception of Subject 007, the shapes of the individual PK profiles were similar, showing a 'flattened' tamsulosin concentration profile (Michel et al., 2005d), similar to that observed from administration of tamsulosin using OCAS technology (Stevens and Speakman, 2006).

As with the OCAS formulation, this GLARS tablet successfully delivered tamsulosin in a controlled manner, achieving a reduced C_{max} and consistent plasma concentration over 24 h. Concurrent scintigraphic imaging data confirmed drug absorption even in the colonic regions. This supports the formulation concept that inclusion of the gel forming and gel enhancing agents can potentiate drug release in the low moisture environment of the colon.

With the exception of Subject 007 who exhibited onset of radiolabel release in the stomach at 143.0 min post-dose, onset of radiolabel release occurred in the colon between 322.5 and 577.5 min for the remaining seven subjects. This, coupled with the observation that C_{max} occurred prior to tablet arrival in the colon for six out of eight subjects, substantiates the premise that GLARS tablets swell rapidly, creating a reservoir of drug dissolution medium even as they travel into the colon.

The combined use of gamma scintigraphy and PK sampling in this study has been extremely beneficial in explaining the aberrant PK profile of Subject 007. This subject displayed a higher C_{max} in comparison to the rest of the study population which was most likely a result of premature tablet disintegration as indicated by a comparatively early onset of radiolabel release.

Although the sample size in this study was small, the findings clearly indicate the ability of the GLARS tablet in effecting an extended tamsulosin absorption profile, which could benefit patients suffering from LUTS associated with BPH.

5. Conclusions

The dual investigative approach of scintigraphic imaging and PK sampling proved to be a powerful tool in understanding the *in vivo* behaviour of GLARS tablets containing tamsulosin HCl. It was confirmed that the GLARS formulation enabled drug release and absorption to proceed in a continuous manner throughout the GI tract, even in the low moisture environment of the colon, over a 24 h period.

While it is unclear as to the actual reason for the anomalous behaviour of the tablet in one subject, the unusually high C_{max} could be explained by the information obtained from scintigraphic images. Data from all other subjects suggested that GI transit did not affect drug absorption, thereby strongly supporting the premise that tablet disintegration and consequently drug release and absorption are independent of location within the GI tract.

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