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A novel triple-layer tablet for sustained delivery throughout GI tract - a pharmacoscintigraphic study

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PURPOSE

The ability of conventional sustained release systems to extend drug release for up to 24 hours may not translate into clinical effectiveness as most drugs are preferentially absorbed more proximally.

A novel drug delivery system has been developed, enabling drug dissolution and dispersion independent of the surrounding environment and promoting significant colonic absorption. The **Geometrically Long Absorption Regulated System** (**GLARS)** is a **triple-layered tablet**; the highly-soluble middle layer of which draws water into the tablet core rapidly while the upper and lower layers simultaneously absorb water and swell.

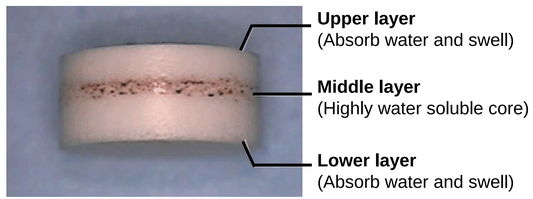

Figure 1. The GLARS tablet.

METHODS

Eight healthy male volunteers were dosed with the GLARS tablet containing 0.4 mg tamsulosin HCl and approximately 4 MBq ^{99m}Tc (measured at time of dose) 15 min after consuming 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. The tablets were radiolabelled by 'drill and fill' method, centralising the radiolabel within the tablet core.

Scintigraphic imaging and blood sampling proceeded at regular intervals to 24 h post-dose. Blood samples were centrifuged and plasma separated and frozen at -20 ° C. Images were analysed for GI transit and radiolabel release behaviour. PK samples were analysed for tamsulosin content using a validated LC-MS/MS method.

RESULTS

Figure 2 shows the key events in the GI transit of GLARS tablets in Subject 003.

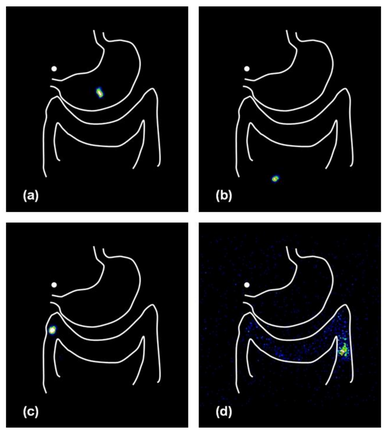

Figure 2.
(a) 60 min, tablet located in stomach
(b) 180 min, image at which gastric emptying confirmed
(c) 330 min, onset of radiolabel release, tablet in ascending/transverse colon
(d) 765 min, complete radiolabel release, tablet in descending colon

Combined interpretation of scintigraphic images and PK profiles indicate that release from the GLARS tablet commenced immediately after ingestion, as evidenced by the appearance of tamsulosin in the plasma at 1 h post-dose. A mean C_{max} of 6±3 ng/nL was achieved after 324±184 min (mean t_{max}). The mean $AUC_{0\text{-}24h}$ 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. The mean times for onset and completion of radiolabel release were 390.2±128.6 min post-dose (n=8) and 673.5±160.0 min post-dose (n=5) respectively. In seven subjects, onset of radiolabel release was observed in the colon. The only subject who showed radiolabel release onset in the stomach also had the highest C_{max} as shown in Figure 3.

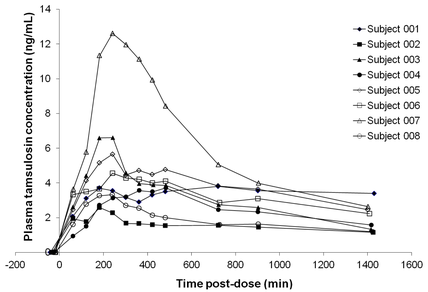

Figure 3. PK profiles of tamsulosin absorption from GLARS tablets.

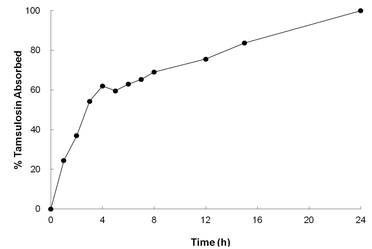

Figure 4. Mean tamsulosin absorption profile for all subjects.

Onset of radiolabel release for Subject 007 occurred at 143.0 min in the stomach. This could have been due to failure of the sealing coat applied, and correlated with the increased C_{max} due to release and absorption of a majority of the drug in the upper GI tract.

Figure 4 shows that rapid absorption occurred within the first 4 h of ingestion, reaching approximately 60%, followed by a gradual release to 24 h.

CONCLUSIONS

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