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Enteric coated timed release systems for colonic targeting

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Abstract

The gastrointestinal transit and disintegration characteristics of an enteric coated timed release formulation were investigated in a group of six healthy volunteers using the technique of gamma scintigraphy. The mean in vivo tablet disintegration time was approx. 10 h post-dose and 7.5 h after gastric emptying which was in excellent agreement with that predicted from in vitro methodology. The anatomical site of release ranged from the caecum to the descending colon and once the onset of disintegration had been detected by scintigraphy, the time for complete break up was typically in the region of 45–60 min. The enteric coated Time Clock® system therefore provides for a pharmaceutical preparation capable of drug delivery to the colon.

Key words: Timed release; Enteric coating; Gamma scintigraphy; Colon targeting

In some important situations, it would be of considerable advantage to have an oral drug delivery system that could target to the colon. This could be either for the local treatment of diseases, such as ulcerative colitis, irritable bowel syndrome (Crotty and Jewel, 1992) or to exploit the colon as a preferred region for drug absorption, possibly as a site for absorption of polypeptides (Davis, 1990). A careful analysis of the problem of peptide and protein absorption from the gastrointestinal tract suggests that the small intestine is not the preferential site for uptake (Wilding et al., 1994). Not only does the small intestine contain endogenous enzymes, but the transit time from stomach to the colon is relatively short (Davis et al., 1986). Thus, even if the drug was relatively stable in the intestines, there could be little time for its absorption. Consequently, the colon could be the preferential site for the absorption of polypeptide drugs. Although the colon has a much smaller surface area, it does have a long transit time and the level of endogenous enzymes is low. Preliminary studies indicate that the colon does indeed seem to be a potential site for oral peptide and protein delivery (Gwinup et al., 1991;, Hastewell et al., 1992; Wilding et al., 1992a). Clearly, if the colon does represent the best, or only, site for uptake of therapeutic polypeptides administered orally, then systems that have the ability to target specifically to this region will be an essential requirement (Hardy et al., 1987; Van den Mooter et al., 1992; Rubinstein et al., 1992; Lloyd et al., 1994).

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Residence time of pharmaceutical preparations in the stomach is highly variable ranging from minutes to hours depending upon the size of the preparation and whether the stomach is in the fed or fasted state (Wilding et al., 1992b). On the other hand, transit time through the small intestine is relatively consistent; in the order of 3–4 h (Davis et al., 1986). Timed release, based on a constant small bowel transit time, could be useful in providing a delayed release preparation for targeted colonic delivery (Theeuwes et al., 1993). The Time Clock® system consists of a tablet core coated with a mixture of hydrophobic material and surfactant, which is applied as an aqueous dispersion (Pozzi and Furlani, 1992). Drug release from the core of the Time Clock® system occurs after a pre-determined lag time, which depends mainly on the thickness of the hydrophobic layer and is independent of gastrointestinal pH. The preparation of the dosage form is carried out by using conventional industrial procedures and standard industrial equipment. During development of the Time Clock® system, a series of scintigraphic studies was carried out to evaluate and optimise the in vivo behaviour of the preparation (Pozzi et al., 1994). The results showed that the in vivo performance of the device was reproducible and demonstrated that the methodology for in vitro testing was a good predictor of in vivo release. However, when the primary objective was delivery to the colon, then the problem of drug release in an inopportune region of the gastrointestinal tract, caused by extended gastric residence, had to be addressed. Therefore, in order to provide greater targeting specificity for the Time Clock® system, an enteric coat was applied, which was designed to prevent dispersion of the hydrophobic layer whilst in the stomach. The objective of the scintigraphic study was to follow the gastrointestinal transit of the enteric coated Time Clock® system and to ascertain the time and anatomical position of tablet disintegration, following administration after a light breakfast.

Enteric coated Time Clock® systems, with a nominal 7 h in vitro delay in high viscosity dissolution medium (pH 7.0), were manufactured containing 2 mg of samarium oxide, enriched with the ^{152}Sm isotope (Pozzi et al., 1994). The tablets were irradiated for 4 min in a flux of 10^{12} neutrons cm^{-2} s^{-1}. Preliminary experiments had shown that trace amounts of radioactive bromine, sodium and chlorine were present in the irradiated tablets, however, the presence of these isotopic impurities did not compromise the study. Each tablet contained approx. 1.0 MBq of the gamma-emitting isotope, ^{153}Sm, at the time of administration. Six subjects were dosed with the radiolabelled preparation, 30 min after a light breakfast. Gamma camera images were recorded at frequent intervals throughout the day

The transit and disintegration characteristics of the preparation are detailed in Table 1. The mean in vivo tablet disintegration time was approx. 10 h post-dose and 7.5 h after gastric emptying. The in vivo data are in excellent agreement with that predicted from the in vitro methodology. In all six subjects, tablet disintegration oc-

Table 1
Transit and disintegration profile of an enteric coated colon targeting timed release formulation (min)

Subject	Gastric emptying	Small intestinal transit	Colonic arrival	Tablet dispersion [a]	Position of dispersion
1	103	248	351	655	caecum
2	251	168	419	656	proximal colon
3	154	267	421	655	caecum
4	123	186	319	593	proximal colon
5	87	163	250	523	descending colon
6	201	251	452	575	proximal colon
Mean	153	261	369	610	
SE	27	19	31	23	

[a] After dosing.

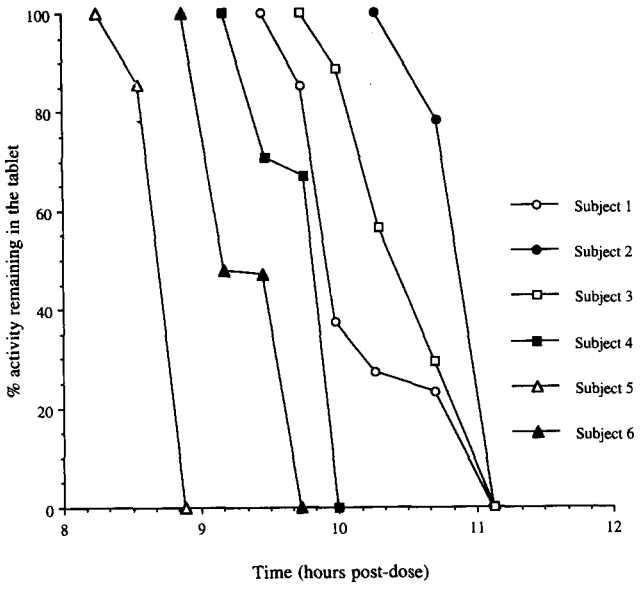

Fig. 1. Rate of disintegration for the enteric coated Time Clock® in each of the six subjects.

curred in the large bowel and was independent of residence time in the stomach. The anatomical site of release ranged from the caecum to the descending colon. Once the onset of disintegration had been noted by scintigraphy, the time for in vivo break-up/disaggregation was typically in the region of 45–60 min (Fig. 1). However, in two subjects, where onset of disintegration occurred in the caecum, tablet break up was much slower. Overall, the rate of disaggregation was more protracted in the large bowel than that reported previously for the upper gastrointestinal tract (Pozzi et al., 1994). This is presumably due to a combination of the reduced agitation conditions in the colon, coupled with an increase in the viscosity of the local micro-environment around the tablet (Macfarlane and Cummings, 1991).

The enteric coated Time Clock® system therefore provides for a new pharmaceutical preparation designed to deliver drug to the colon, which is independent of normal physiological conditions, such as pH and the digestive state of the gastrointestinal tract. However, the rationale behind all timed release devices is only valid if small intestinal transit remains constant and therefore the specificity of the systems for colonic targeting could be significantly affected by changes in motility of the gastrointestinal tract (Kellow et al., 1986).

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