# EVALUATION OF HUMAN REGIONAL BIOAVAILABILITY TO ASSESS WHETHER MODIFIED RELEASE DEVELOPMENT IS FEASIBLE


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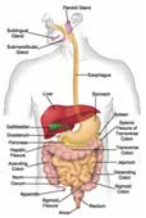
## Purpose

**Many modified release (MR) oral formulations rely on bioavailability from the distal regions of the gastrointestinal (GI) tract (i.e. the ileum and colon). Therefore, by assessing the bioavailability of a drug following delivery to the distal intestines, it is possible to determine whether MR formulation development is achievable.**

## Characteristics of the GI tract

Drug delivered *via* an oral, immediate release dosage form will usually be available for absorption from the duodenum and jejunum following formulation disintegration and drug dissolution in the stomach. These regions of the GI tract are particularly well suited to drug absorption, for example they have a large surface area.

However, the rate and extent of absorption from the proximal small intestine cannot be extrapolated to the other regions of the GI tract. Major variations in physiology from region to region have the potential to significantly alter a drug's pharmacokinetic profile and oral bioavailability.



**Regional variations in the GI tract**

- Surface area
- pH
- Fluid volume
- Gut wall enzymes
- Transporters
- Permeability
- Contractile activity
- Residence time

Single unit oral MR dosage forms administered in the fasted state travel through the proximal regions of the GI tract quickly. For approximately 4 – 5 hours after administration, drug will be delivered to the small intestine. However, thereafter the dosage form will enter the colon (Table 1). Consequently, a conventional MR formulation, requiring drug delivery for more than 3 hours will require absorption from the distal regions of the GI tract in order to be successful

| | Residence Time (hours) | |
|---|---|---|
| Region | Mean (range) | Cumulative mean |
| Stomach | 0.5 (0 – 2) | 0.5 |
| Jejunum | 1.25 (0.5 – 2) | 1.75 |
| Ileum | 1.5 (0.5 – 2.5) | 3.25 |
| ICJ | 1.25 (0 – 12) | 4.5 |
| Colon | 20 (0 – 72) | 24.5 |

Table 1: Mean GI transit times for a single unit, non-disintegrating dosage form following fasted administration (pooled data from 1985 – 2003).

## Clinical Study Design

An open-label, two-way crossover pharmacoscintigraphic study is performed in 8 to 12 healthy subjects, with a suitable washout period between administrations.

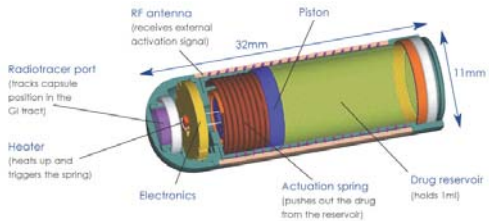
Each subject receives the drug in an immediate release format (reference) and as a bolus site-specific delivery to the colon.
Site specific delivery is achieved using the Enterion™ capsule – an engineered device which facilitates active delivery to the target site in a non-invasive manner. Administration is performed in the morning, after an overnight fast.

Following administration of the Enterion™ capsule, scintigraphic images are acquired at regular intervals (e.g. every 10 minutes) to track the location of the capsule in the GI tract. Following arrival in the region of interest (typically ileum and colon), device activation (drug release) is initiated.

Blood samples for pharmacokinetic analysis are taken immediately prior to drug release and then at regular intervals post-release.

Appropriate safety assessments are performed throughout the study

## The Enterion™ capsule




The Enterion™ capsule is a remote-controlled drug delivery device which delivers any form of a drug to targeted regions of the human GI tract.[1]

## Targeted drug delivery

A gamma-emitting radionuclide is sealed within the capsule (indium-111) and used to track the location of the capsule using gamma scintigraphy. The volunteer takes a drink containing a second gamma-emitting radionuclide (technetium-99m) which provides an outline of their stomach and colon.

When the capsule reaches the target location, the drug is actively expelled into the GI lumen. The volunteer stands inside an activation unit, which sends a electromagnetic signal that triggers the instantaneous release of the capsule contents.

## Results

The site of drug release is confirmed in real-time and by retrospective analysis of the scintigraphic images. Successful activation of the Enterion™ capsule is confirmed by the generation of a signal at the time of activation. Examination of the retrieved capsules is also performed to provide further evidence of successful drug delivery.

The plasma concentration data are analysed to generate pharmacokinetic profiles and relative bioavailability (test site *vs.* IR reference) is calculated based on AUC.

Over 130 regional drug absorption studies have been performed at Pharmaceutical Profiles. We reviewed the results from 37 of these studies. The drugs covered a range of development stages, mechanisms of action, target indications and physicochemical properties. The relative bioavailability following colonic delivery was measured and, based on the "rule of thumb" developed by Pharmaceutical Profiles, used to determine whether or not MR release development was feasible (Table 2).

Half of the studies included in this analysis (19) involved the assessment of marketed drugs, with the remainder involving drugs still in development. The trend for these two sub-groups was similar to the combined data, with the majority of drugs exhibiting relative colonic bioavailability of 60% or less. However, a very different split was observed within the 0-60% relative bioavailability bracket (Table 3).

**Table 2: Results of 37 human drug absorption studies, using the Enterion™ capsule, performed at Pharmaceutical Profiles**

| Relative bioavailability following colonic delivery | Impact on MR development | % compounds tested at PP within each category |
|---|---|---|
| < 30% | Very difficult and probably impossible using matrix formulations | 38 |
| 30% - 60% | Challenging, but should be achievable | 19 |
| > 60% | Straight forward MR development | 43 |

**Table 3: Comparison of relative colonic bioavailability for NCEs *vs* marketed drugs**

| | % compounds tested at PP within each category | |
|---|---|---|
| Relative bioavailability following colonic delivery | NCE (n=17) | Marketed (n=19) |
| < 30% | 59 | 21 |
| 30% - 60% | 6 | 32 |
| > 60% | 35 | 47 |

These data support the concept that drug development is becoming more challenging as a result of the sub-optimal physicochemical properties of new drugs entering development. They underline the need to proceed into formulation development with definitive information on bioavailability from the human GI tract.

## Conclusions

Assessment of the regional bioavailability of a drug is essential in order to understand the feasibility of achieving a modified release profile before beginning MR formulation development. Results from studies performed at Pharmaceutical Profiles confirm that MR formulation development is very difficult for approximately 60% of drugs in development.

## References


1. Wilding, IR and Prior, DV (2003). Remote controlled capsules in human drug absorption studies. *Critical Reviews in Therapeutic Drug Carrier Systems* 20(6): 405 – 431.



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