# Evaluation of the Feasibility and Use of a Prototype Remote Drug Delivery Capsule (RDDC) for Non-Invasive Regional Drug Absorption Studies in the GI Tract of Man and Beagle Dog

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***Purpose.*** Evaluate a prototype Remote Drug Delivery Capsule (RDDC) for use in beagle dogs and human volunteers for non-invasive drug absorption studies in different regions of the gastrointestinal tract.
***Methods.*** The device was dual radiolabeled and GI transit of the RDDC was monitored by gamma scintigraphy. Beagles were used initially to demonstrate the functional utility of the device where a solution of ranitidine hydrochloride (150 mg) was non-invasively delivered to the stomach, proximal small intestine and distal small intestine. A subsequent first time in human study enrolled twelve healthy male volunteers where the intended site of release was the stomach, early small bowel, distal small bowel or colon.
***Results.*** Preliminary studies conducted in beagles indicated that the RDDC operated successfully and the onset of ranitidine serum levels were dependent on the time of capsule activation and site of drug release. Results from the human study showed that all twelve subjects swallowed the device with no discomfort. Mean gastric emptying of the RDDC was 1.50 ± 1.28 h (range = 0.25 to 4.25 h), and total small intestine transit was 4.79 ± 1.82 h (range = 2.00 to 8.25 h). The capsule was retrieved from the feces at 30.25 ± 15.21 h (range = 14.12 to 74.25 h) and there were no reported adverse events. The prototype RDDC operated successfully in nine of the twelve human volunteers and the cause for the three failures was attributed to mechanical failure while the electronics assembly performed favorably.
***Conclusions.*** This prototype remote control capsule was shown to be well tolerated and functional to use in human volunteers as well as beagles. The application of the device coupled with gamma scintigraphy has the potential to be a valuable and rapid method to non-invasively evaluate regional drug absorption in the gastrointestinal tract under conditions that are both pharmaceutically and physiologically meaningful.

**KEY WORDS:** regional drug absorption; gamma scintigraphy; remote control capsule; non-invasive.

## INTRODUCTION

The timely and successful development of novel oral drug delivery systems is partially dependent on having accurate information regarding the rate and extent of drug absorption from key segments of the gastrointestinal (GI) tract. Too often, formulation development is conducted with an incomplete understanding of the absorption characteristics of a drug from the GI tract, and consequently, specialized formulations may not meet desired criteria. This ultimately results in delays to the development of a marketable product.

The process of formulation development typically uses quality control *in vitro* tests to characterize the performance of the drug delivery system and then, by convention, has tended to extrapolate these *in vitro* results to the *in vivo* condition. For example, there has been continuous and prolonged efforts toward developing *in vivo/in vitro* correlations to predict drug absorption where one of the goals has been to reduce the need for human bioequivalence testing (2). However, the use of *in vitro* drug dissolution profiles alone has generally been unsuccessful in predicting human bioavailability *a priori* (2).

Classes of drug compounds that are known to exhibit variable absorption can benefit from more refined *in vitro* procedures like permeation studies through cultured monolayers of epithelial or endothelial cells (e.g., Caco-2 cells) which have been used to help predict *in vivo* permeability through the intestinal epithelium (3,4). This method to screen the permeation of a large number of molecules is useful in the early stage of drug development, however, these *in vitro* cell lines do not take into account the complex and variable *in vivo* processes that are present when the drug is delivered from an actual dosage form which can include a) the rate, time and GI locus of dosage form disintegration, b) the effect of pH and natural surfactants on drug solubilization, and c) competing absorption processes due to changes in gut physiology between the fed and fasted state.

*In vivo* methods using intact living systems inherently offer the drug formulator more relevant information regarding drug absorption characteristics where a variety of intubation techniques have been used to assess regional drug absorption in animals and man (5–9). The procedures typically require a naso-gastrointestinal catheter to be physically located in various regions of the GI tract and the drug solution is instilled followed by serial blood sampling to characterize pharmacokinetics and absorption from each gastrointestinal region (5–9). Although the method is very useful to determine relative *in vivo* permeability, the invasiveness of the technique has some disadvantages where the presence of a nasogastric tube has been shown to affect GI motility (10). Other available *in vivo* methods to study regional drug absorption surgically implant intestinal ports to deliver the drug to specific regions of the GI tract.

While the preceding *in vivo* methods are useful for specific objectives, these techniques can undeniably create abnormal physiologic conditions due to their invasive nature. The need to develop a pharmaceutically accurate method to study regional drug absorption was recognized nearly forty years ago when an alternative procedure to evaluate regional drug absorption was developed (11). The technique used a specially designed capsule to non-invasively release a drug at selected sites in the

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GI tract without surgery or attachment of the capsule to accessory equipment external to the body (11,12). A second remote control capsule was also reported in the literature in 1969 (13), but both of these capsules did not find extensive use after their initial report. A third remote control capsule, the High Frequency (HF) capsule, was subsequently reported (14), and has since found substantial use to evaluate the GI absorption of several drugs (15–20).

Unfortunately, the HF capsule appears to require unique operating conditions that has prohibited its routine use outside of Europe. Consequently, our desire to have a similar device readily available to couple with our sustained efforts in gamma scintigraphy (21) resulted in a collaborative effort to develop the current Remote Drug Delivery Capsule (RDDC) (22). The gastrointestinal transit of the RDDC can be monitored by gamma scintigraphy (21) and upon reaching the desired region of the GI tract, it is non-invasively opened by an external signal followed by blood samples being taken to characterize regional drug absorption.

The main objective of this first time in human study was to evaluate the feasibility and functional use of this prototype remote control capsule in human volunteers and beagles by determining if the RDDC could be successfully operated in different regions of the gastrointestinal tract. It is proposed that by using the RDDC, drug formulations can be rationally designed with respect to regional GI absorption that has been collected under pharmaceutically meaningful conditions and minimal disruption to the natural physiology. Such information provides the drug formulator an opportunity to systematically match the rate of drug release to the potential site(s) of drug absorption, thus, the drug is delivered at the right time to maximize drug absorption in a minimum number of doses. This will hopefully result in performing fewer iterations and reduce the number of failed formulations.

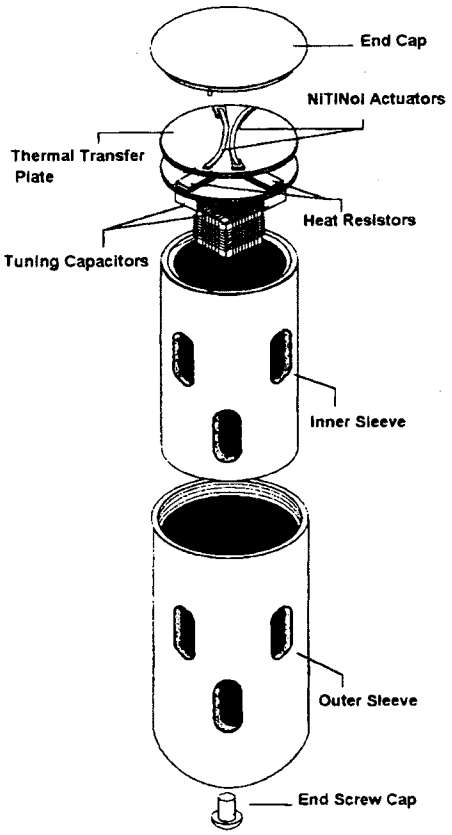


**Fig. 1.** Schematic diagram of the Remote Drug Delivery Capsule.

## MATERIALS AND METHODS

### Operation of the RDDC and Radiolabeling

The prototype RDDC is shown in Fig. 1 and consists of a large non-digestible plastic capsule (10 mm wide × 35 mm long) with a storage chamber that can contain approximately 0.8 mL of drug solution, suspension or loosely packed (water soluble) drug powder. Upon reaching the desired GI region, an external transmitter coil is situated over the anatomical area where the capsule resides and the coil sends a signal. The external signal can adequately transmit up to a distance of 10 cm which when received by the RDDC causes resistors in the electronic assembly to heat. This energy is dissipated to the thermal transfer plate and memory alloy metals depicted in Fig. 1. When a critical temperature of approximately 40°C is reached, the wires straighten to provide a mechanical force causing the inner sleeve of the capsule to rotate and the slots of the inner and outer capsule shells become aligned. After slot alignment, the drug is released and serial blood sampling characterizes drug absorption from the specific GI region.

In the current studies, the drug chamber was radiolabeled with technetium-99m DTPA (100 μCi; $t_{1/2}$ = 6 hrs) and the top end cap was radiolabeled with indium-111 chloride (20 μCi; $t_{1/2}$ = 2.8 d). Dual radiolabeling the capsule in this manner permitted the migration of $^{99m}$Tc to be visualized relative to the unreleased $^{111}$In in the capsule and ensured that the passage of the capsule could always be monitored to assess safety and capsule recovery.

### Beagle Dog Study

One of several preliminary investigations in fasted beagles evaluated regional drug absorption of ranitidine (150 mg dissolved in 0.8 mL water). Under an approved animal protocol adhering to humane treatment and principles of laboratory animal care, conscious beagles were comfortably restrained in a standing position, and situated beneath a gamma scintillation camera (Siemens BasiCam, Chicago, IL) with the camera head located over the back of the beagle. The gamma camera was equipped with a medium energy parallel hole collimator, and set for dual isotope acquisition where the pulse analyzer was tuned to the 247 keV gamma ray of $^{111}$In (15% window) and the 140 keV gamma ray of $^{99m}$Tc (8% window). Doses were administered with 60 mL of distilled water via an orogastric tube following a minimum 12 h fast and dynamic posterior images, each of one minute duration, were acquired continuously and stored on computer for permanent record and analysis. After the remote control capsule was determined to be in the gastrointestinal region of interest, the beagle was temporarily removed from the sling, and the capsule position in the GI tract was confirmed via alternate lateral and posterior imaging. The external transmitting coil was held in close contact to the beagle at the approximate location of the capsule and then turned on for a period of two minutes. Immediately after the remote

control capsule was activated, the beagle was repositioned beneath the gamma camera and dynamic posterior images were again acquired to confirm capsule opening. In this pilot study, the capsule contents were released in the stomach (n = 2), early small intestine (n = 1) and distal small intestine (n = 1).

Blood samples were initially taken at one hour intervals before capsule activation in order to confirm the absence of drug release from the unopened remote control capsule. After the capsule was opened, blood samples were taken at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 5 h post capsule activation. Serum was harvested and analyzed for ranitidine by HPLC.

### Human Study

The human study was performed as a single-center, open-label, single treatment evaluation that enrolled twelve healthy male human subjects (24–36 years, mean = 30.3 ± 3.8 yrs). Informed consent was obtained and the conduct of the study followed the tenets of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board and Radioactive Drug Research Committee at the University of Kentucky (September, 1994) and was conducted in the Nuclear Medicine Department at the University Hospital. Part of the inclusion criteria included negative stool guaiac, ability to swallow a comparably sized hard gelatin capsule (size 000), no previous gastrointestinal surgeries, regular bowel movements (at least every 48 hrs), and no known history of GI disorders or intestinal obstruction. Subjects were assigned to one four treatment groups (n = 3 for each group) where the targeted site of capsule release was the stomach, early small intestine (approximately the jejunum), distal small intestine (approximately the ileum) or colon. Active drug was not filled in the remote control capsule and administered to the study subjects in this first study so that any recorded adverse event(s) could be interpreted unambiguously; this was an important consideration due to the novelty of the device and the desire to test its safety and functionality.

### Dose Administration and *In Vivo* Gamma Scintigraphy

Capsules were administered to fasted subjects (minimum 10 h) with 240 mL of water. A gamma camera (Siemens Orbiter, Chicago, IL) was equipped with a medium energy parallel hole collimator and set for dual isotope acquisition as described in the previous section. Serial anterior views were acquired at least every 15 minutes until capsule activation. After the capsule was opened, images were acquired continuously for 30 to 60 minutes to determine the release rate of the capsule. Standard meals were eaten at 5 and 11 h post dose and later imaging timepoints were recorded hourly until colon arrival was confirmed. Intermittent images were also recorded after colon arrival until the capsule was recovered from the feces.

The recovered capsule was visually inspected for proper function of its opening mechanism and alignment of exit ports. Scintigraphic images were background and decay corrected and GI residence of the capsule in the stomach, early and distal small intestine and colon were reported as well as the time to retrieve the capsule from the feces.

## RESULTS AND DISCUSSION

### Operation of RDDC in Beagles and Ranitidine Absorption

The remote control capsule was successfully operated in all four beagles where individual ranitidine serum concentration curves are depicted in Fig. 2. The top two graphs in Fig. 2 show the results following stomach release of the RDDC where one capsule was activated at 35 minutes (beagle 1) and the other at 4.83 h post dose (beagle 2). The onset of ranitidine absorption was within 10 to 20 minutes after the RDDC was opened and coincided with entry of the released radioactive marker into the small intestine. The bottom two graphs in Fig. 2 represent capsule activation in the early small intestine (beagle 3) and distal small intestine (beagle 4). Gastric emptying of the RDDC was observed at 3.17 h for beagle 3 and the capsule was activated 30 minutes later; the onset of ranitidine absorption occurred immediately after the solution emptied from the capsule. Beagle 4 had a gastric emptying time of 3.62 h and was activated 1.63 h later when the RDDC resided in the distal small intestine. The initial onset of ranitidine absorption in beagle 4 also occurred within ten minutes after capsule activation (Fig. 2). There was no indication that the ranitidine solution leaked prior to capsule activation based on scintigraphic analysis and lack of ranitidine plasma levels prior to opening the capsule. Capsules were recovered between 33–42 h post dose and were completely opened.

### Gastrointestinal Transit of RDDC in Humans

One of the primary objectives of this first time in human study was to determine the safety and tolerance of the device. Since the remote control capsule is non-disintegrating and relatively large, it was important to demonstrate that it moved through the GI tract unimpeded. Table I lists the residence time of the capsule in the stomach, early small intestine (approximately the jejunum), distal small intestine (approximately the

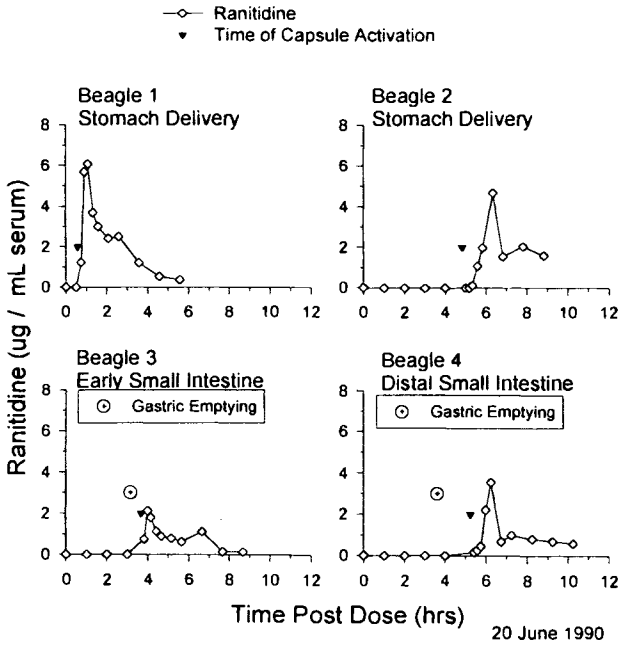


**Fig. 2.** Individual serum concentration profiles following oral administration of ranitidine solution (150 mg) in a remote control capsule to fasted beagles (-◇-). Capsules were non-invasively opened in either the stomach (n = 2), early small intestine (n = 1), or distal small intestine (n = 1). The times of gastric emptying (⊕) and capsule activation (▼) are indicated on individual graphs.

**Table I.** Gastrointestinal Residence of the RDDC (as Determined by the Indium-111 Label), Time of Capsule Activation, and Time of Recovery from Feces

| | Residence time in gastrointestinal region (h) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subject # | Stomach | Early small intestine | Distal small intestine | Total small intestine | Cecum | Colon | RDDC opened (h post dose) | RDDC recovered from feces (h post dose) |
| Stomach activation | | | | | | | | |
| 004 | 0.75 | 0.50 | 4.00 | 4.50 | 2.00 | 14.92 | 0.03 | 22.17 |
| 008 | 2.75 | 0.50 | 1.50 | 2.00 | 0.00 | 25.08 | 0.13 | 29.83 |
| 012 | 0.75 | 0.50 | 4.00 | 4.50 | 0.00 | 19.33 | 0.07 | 24.58 |
| Early small intestine activation (approximately jejunum) | | | | | | | | |
| 003 | 0.25 | 2.50 | 5.50 | 8.00 | 1.00 | 13.75 | 0.50 | 23.00 |
| 007 | 4.25 | 1.50 | 4.00 | 5.50 | 3.25 | 23.00 | 4.40 | 36.00 |
| 011 | 0.75 | 1.00 | 3.00 | 4.00 | 7.25 | 2.12 | 1.28 | 14.12 |
| Distal small intestine activation (approximately ileum) | | | | | | | | |
| 002 | 0.75 | 1.00 | 2.50 | 3.50 | 0.00 | 30.50 | 2.00 | 34.75 |
| 006 | 0.50 | 1.25 | 3.50 | 4.75 | 23.0 | 5.25 | 3.07 | 33.50 |
| 010 | 2.75 | 1.00 | 7.25 | 8.25 | 0.00 | 11.85 | 5.30 | 22.85 |
| Colon activation | | | | | | | | |
| 001 | 2.50 | 0.50 | 4.00 | 4.50 | 0.50 | 16.70 | 8.65 | 24.20 |
| 005 | 1.75 | 0.50 | 2.50 | 3.00 | 0.50 | 18.55 | 5.50 | 23.80 |
| 009 | 0.25 | 0.50 | 4.50 | 5.00 | 2.00 | 67.00 | 7.57 | 74.25 |
| Mean | 1.50 | 0.94 | 3.85 | 4.79 | 3.29 | 20.67 | n/a | 30.25 |
| SD | 1.28 | 0.60 | 1.50 | 1.82 | 6.55 | 16.60 | n/a | 15.21 |

ileum), cecum and colon. The time of capsule retrieval from the feces is listed in Table I as is the time of capsule activation.

Individual gastric residence of the remote control capsule was longer than that typically observed of other non-disintegrating oral dosage forms, for example, it is anticipated that non-disintegrating dosage forms usually empty the fasted human stomach within the first hour post dose (21,23,24). However, only seven of twelve subjects had gastric emptying times of the capsule shell less than one hour (range 0.25–0.75 hr), while the remaining five subjects had gastric emptying times greater than 1.5 h (range 1.75–4.25 hr). The mean gastric emptying time reported in Table I is 1.50 ± 1.28 h. This discrepancy suggests that because the device has a greater mass and size as compared to conventional dosage forms, a stronger gastric emptying wave may be needed to push the capsule to the dependent portion of the stomach and through the pylorus.

Once the capsule emptied from the stomach, small intestine transit time was consistent with other non-disintegrating single-unit doses previously evaluated in our laboratories. As expected, transit through the early small intestine was relatively rapid (0.94 ± 0.60 h; range 0.50–2.50 h; Table I), while the average residence time in the distal small intestine was reported as 3.85 ± 1.50 h (range 1.5–7.25 h); the overall mean transit time through the small intestine was determined to be 4.79 ± 1.82 h (range 2–8.25 h) which was comparable to other literature values (25).

Residence time of the remote control capsule in the cecum and colon was highly variable. Cecum residence ranged from 0 to 23 hours, but only subject 006 showed prolonged residence at the cecum (23 h). With the exception of one subject, all subjects defecated the capsule at or before 36 hours post dose. The prolonged colonic retention of the capsule in subject 009 was due to a limited number of bowel movements. No adverse events were reported which were considered to be associated with administration of the remote control delivery device.

## Operation of the Capsule's Opening Mechanism

The other primary objective of this study was to assess the operation of the remote control capsule in four different gastrointestinal regions. This was an important issue due to the varying depths that the capsule achieves in the body and the fact that the effective operating distance of the transmitting coil was 10 cm. Three subjects were assigned to four different treatment groups where release of the capsule targeted the colon, distal small intestine, proximal small intestine and stomach. The performance of the capsule was evaluated by the release of liquid $^{99m}$Tc-DTPA from the capsule at the appropriate time of activation and also by visual inspection of the capsule after recovering it from the feces.

Scintigraphic imaging revealed that several of the prototype capsules showed varying degrees of leakage in four of twelve subjects, however, very minimal leaking was observed in two of these subjects (less than 5% of the dose in subjects 007 and 010). It was apparent that premature leaking in these four capsules was most likely caused by a low torque reading of the capsule where the inner and outer sleeve of the capsule did not form a tight seal to make it totally impervious to the external environment.

The prototype RDDC was successfully opened at the intended time and desired gastrointestinal region in nine of twelve subjects. Of the three capsules that did not open, one capsule failed because of improper assembly of the end cap (subject 007). The other two failed capsules apparently received

an adequate external signal as indicated by straightening of the metal actuators, however, it was later determined that the torque reading of these two capsules was too high and the inner and outer capsule sleeves could not freely rotate, thus, the capsule remained closed.

It was also evident that the release of radioactive solution from the capsule was notably slower when opened in the colon. This delay was probably due to decreased fluidity and diminished gut motility in this segment of the GI tract. It should also be realized that this observation accurately depicts colonic release of a solid dosage form where dispersion in the colon is sometimes slow even after initial tablet disintegration.

## CONCLUSIONS

The prototype Remote Drug Delivery Device was shown to be both well tolerated and safe to use in normal healthy male subjects, however, some changes in the capsule design and manufacturing tolerances were deemed necessary to assure that leakage did not occur prior to its activation. The electronics and thermal transfer assembly performed favorably, but, it was suggested that activation should not be attempted if the capsule lies deeper than nine to ten centimeters into the body. The occurrence of capsule leakage has since been addressed by improving manufacturing tolerances of the inner and outer capsule sleeve and the improved capsule is now commercially available (InteliSite®, Innovative Devices, Raleigh, NC). Since these modifications have been made, we have since experienced 100% success rates in beagles (unpublished data) and greater than 90% success in human subjects [(26) and unpublished data]. These results will be reported in future publications.

The results from this first time in human study and preliminary beagle study indicated that the prototype device was functional and merited further development and could be used as a non-invasive method to map regional drug absorption in key segments of the GI tract. The device was easily radiolabeled, and was accurately tracked in the gastrointestinal tract by gamma scintigraphy when it was subsequently opened in the stomach and colon as well as in the early and distal small intestine. It is anticipated that the routine use of this system coupled with gamma scintigraphy will provide a non-invasive method to assess regional drug absorption under conditions that are both pharmaceutically and physiologically meaningful. Such data should advance the rational basis of dosage form design, and will hopefully translate to fewer failures during formulation development.

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