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
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.

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