Encap Drug Delivery

COLON-SCREEN

Drug Feasibility Screening for Oral Delivery to the Colon

Why target the colon?
Limitations of existing technologies
New technology
Proof of concept

Use of liquid filled capsules for colonic delivery
Key attributes of the PHLORAL delivery system
Colon-Screen Process

pH and bacteria sensitive coating for targeted delivery to the colon
**Why Target the Colon?**

Historically the clinical applications of oral drug delivery to the colon have been limited to the local treatment of diseases such as inflammatory bowel disease and irritable bowel syndrome. Little consideration has been given to the possibility for systemic absorption due to the physiology and environmental conditions in the colon, e.g. extremely low surface area due to lack of villi and lack of fluid. Nevertheless, other local diseases of the large intestine could benefit from topical delivery to the colonic mucosa and the potential of the colon for systemic delivery of drugs including vaccines, proteins and peptides is gaining renewed interest.

In spite of the physiological barriers in the colon, some drugs have excellent bioavailability from this region of the gastrointestinal tract, and in some instances higher than that seen in the small intestine (1). The colon also offers the advantage of lower efflux transporter levels and lower metabolic enzyme levels which improve bioavailability of some drugs (2).

The colon may also provide a suitable site for protein and peptide absorption as proteolytic levels are significantly lower than that in the small intestine and there is a relatively long transit time for drug absorption. Drug and vaccine delivery may also be exploited by the fact that the small intestine and the colon are lymphatic organs (3).

Oral delivery to the colon can also be used as an alternative to delivery by enema.

**Limitations of Existing Technologies**

Existing oral colonic systems generally involve coating the dosage unit with polymeric materials that will not normally dissolve in the low pH of the stomach or upper intestine but will dissolve in the higher pH of the lower intestine. However, these have the potential to be unreliable due to patient variability in transit times and luminal pH.

Alternative systems may exploit the increasing gastrointestinal bacterial population along the gut. Prodrugs, which rely on colonic bacterial enzymes to metabolise the inactive precursor to the active drug, are often drug or bacteria specific and have limited applicability.

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**Drug Feasibility Screening for Oral Delivery to the Colon**

**Rationale for Targeting the Colon**

- **Physiology**
  - Lower efflux transporter levels e.g. p-glycoprotein
  - Lower levels of metabolic enzymes e.g. CYP3A4

- **Disease**
  - Local diseases e.g. Inflammatory Bowel Disease, Irritable Bowel Syndrome, C. Difficile Infections, etc...
  - Wide range of drugs show good colonic absorption
New Technology

**Encap is able to offer clients a range of oral delivery systems for targeting different regions of the gastrointestinal tract**

This includes the Phloralm system licensed from the School of Pharmacy in London. This is a unique coating technology that is designed to target the release of drugs to the colon.

The new Phloralm technology represents a significant improvement in colonic delivery providing ‘fail-safe’ delivery of drug to the target site by employing two mechanisms to trigger drug release. The technology combines the bacterial and pH mediated approaches used previously for colonic delivery. The combination of these independent but complementary release mechanisms should overcome the limitations associated with the single trigger systems and improve site specificity. The technology involves the combination of a pH-sensitive polymer with resistant starch. This mixture is used as a film coating matrix, which can be applied to tablets, capsules or pellets.

Use of Liquid Filled Capsules for Colonic Delivery

One of the physiological constraints to the colonic delivery of drugs is the low volumes of fluid available for disintegration of dosage forms and subsequent dissolution. A combination of the new colonic drug targeting technology with liquid filled hard capsule technology, where the drug is delivered as a solution, suspension or self-emulsifying system can prove to be an ideal platform technology for the delivery of drugs to the colon. A further enhancement would be the development of formulations which would facilitate the delivery of proteins and peptides to the colon. Encap Drug Delivery has developed proprietary techniques which can allow the incorporation of proteins and peptides in aqueous formulations. These are resistant to proteolytic degradation as they pass through the gastrointestinal tract and allow the proteins to be delivered in their optimal conformation for biological activity.

Proof of Concept

The power of the new technology has been demonstrated in a recent study which tested tablets with the new coating versus Eudragit S coating, to assess the site of disintegration using gamma scintigraphy. The Phloral coated tablets were able to resist breakdown in the stomach and small intestine and consistent disintegration at the ileocaecal junction / large intestine was observed. This was consistent for both fasted and fed volunteers. In contrast with the Eudragit S coated tablets, for 50% of fed and 43% of fasted subjects, the dosage form failed to deliver consistently to the colon.

The success of the system is attributed to the role of starch, which is not digestible by mammalian pancreatic amylase but is readily digested by colonic bacterial enzymes. Even if the pH responsive polymer component of the film remains intact, the colonic bacterial enzymes will still digest the starch component allowing dosage form disintegration.

**The starch element therefore provides a back-up or ‘fail-safe’ for dosage form disintegration.**

Gamma Scintigraphic Study: Eight healthy volunteers – fed state

Site of release: (blue cap) Phloral (yellow cap) Eudragit S

Phloral

Eudragit S100
Key Attributes of the PHLORAL Delivery System

**Applications**

- Targeting local diseases of the colon
- Enhanced absorption of drugs in colon
- Poorly soluble APIs
- Peptides and proteins
- Cytotoxics
- Product life-cycle management
- Chronotherapy – deliver the drug when it is needed

**Advantages**

- Combination of pH and enzymatic controlled release providing fail-safe delivery
- Proprietary drug delivery technology – patent pending
- Target specific physiological sites
- Targeted delivery potentially reducing dosages and side effects
- Create unique marketing position
- Compatible with other Encap Drug Delivery innovative products e.g. Duocap™

**Processing**

- Suitable for all solid dosage forms, capsules or tablets/pellets
- Utilises internationally accepted pharmaceutical grade materials
- Aqueous based coating materials
- Standard coating techniques – easily scalable processing techniques

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**ENCEODE® Colon-Screen**

Encap now offers a feasibility package which will evaluate the potential to formulate candidate compounds in liquid fill formulations suitable for oral delivery to the colon. There are four stages to this process:

**Prototype formulations for evaluation**

Studies are conducted to determine the feasibility of formulating the drug candidate in a stable dosage form. The drug is incorporated into three vehicles which are suitable for liquid fill formulations delivering to the colon. The stability of the candidate compound in each formulation will be evaluated at 0, 2 weeks and 4 weeks.

**Assess the stability of the test compound to metabolism by colonic bacteria**

The microbiota of the large intestine has the capacity to ferment or metabolise a large variety of molecules, which has implications for drug stability and may preclude colonic delivery for certain compounds. Drugs reaching the colon by virtue of poor solubility or the use of modified release dosage forms are particularly at risk. In this study, the candidate compound stability will be investigated in buffered faecal slurry which simulates the conditions of the lower gut. At pre-determined time intervals, samples will be removed and assessed for drug and metabolites. This study can also be conducted for each prototype formulation from Stage 1.

**Dissolution testing**

Capsules will be tested to ensure coating integrity and to predict in-vivo drug release profiles for each prototype formulation. Prototype capsules must demonstrate resistance to stomach and upper GI tract and release contents into the colon.

**PK study (Optional)**

The Phloral coating is designed for use in the human colon, however it is recognised that clients may wish to generate preclinical data before progressing to human studies. In this optional study, the prototype formulation(s) will be administered to animals in a simple exploratory PK study. The data obtained will provide a quantitative measure of drug exposure in order to interpret preclinical efficacy.

**References:**

3. McConnell, E.L., Basit, A.W., Murdan, S. Colonic antigen administration induces significantly higher humoral levels of colonic and vaginal IgA, and serum IgG compared to oral administration. Vaccine 26, 639-646, 2008.

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