



TARGETING THE END GOAL: OPPORTUNITIES & INNOVATIONS IN COLONIC DRUG DELIVERY

In this article, Sejal R Ranmal, PhD, Director of Formulation, Vipul Yadav, PhD, Director of Product Development, and Abdul W Basit, PhD, Founder, all of Intract Pharma, describe recent insights into the physiology of the colon, including the increasingly recognised importance of gut flora in human health, disease and pharmaceutical treatment approaches. The authors highlight the advantages of targeting drug release to the colon, and introduce Phloral®, Intract's unique system for achieving drug release in the colon successfully and consistently.

Oral drug delivery to the colon has long been recognised to have several therapeutic advantages. Traditionally, targeting drugs to this region of the gastro-intestinal (GI) tract was viewed as a niche application, innately providing clinical benefits for localised diseases such as inflammatory bowel disease (IBD) or colorectal cancers. However, as rapidly advancing techniques in molecular biology and medical imaging have increased our knowledge of human GI physiology, the colon has emerged as an optimal site for delivery of small molecules and biopharmaceuticals. Evidently, the colon can serve as a favourable site of absorption and provide a valuable pathway for entering the systemic circulation. The emergence of revolutionary new scientific fields including microbiome therapeutics and chronotherapeutics bring promise of a new era of pharmacotherapy via the gut.

To help realise these opportunities, Intract Pharma has developed Phloral®, a dual-action technology enabling fail-safe delivery to the colon in both healthy and diseased states.

PHYSIOLOGICAL ADVANTAGES OF THE COLON

The human gut is a complex and dynamic environment with many factors influencing

the behaviour of drugs and delivery systems, including the characteristics of luminal contents (e.g. fluid volumes, pH and composition) and the function of intestinal drug metabolising enzymes and transporter systems.¹ These parameters vary in different regions of the GI tract and some can be altered by genetic factors, lifestyle and disease state. An increased understanding of these regional physiological differences continues to uncover important functions relevant to drug delivery. Leveraging the natural physiological advantages of the colon provides opportunities to optimise pharmacological effects.

The Power of the Gut Microbiome

The human gut harbours trillions of micro-organisms, collectively known as the microbiota. The density of micro-organisms increases substantially towards the distal gut with an exponential rise in the colon. The microbiota can be considered an organ in itself, with an intrinsic metabolic capacity that is implicated in the biotransformation of drugs and other xenobiotics.^{2,3,4} Degradation mediated by gut bacteria has been observed for as many as 40% of tested drugs. Despite the diversity in their chemical structures, two broad transformation patterns are most frequently observed – reduction and



Dr Sejal R Ranmal
Director of Formulation
T: +44 20 7753 5931
E: sejal.ranmal@intractpharma.com



Dr Vipul Yadav
Director of Product Development
T: +44 20 7753 5931
E: vipul.yadav@intractpharma.com



Prof Abdul W Basit
Founder
T: +44 20 7753 5865
E: abdul.basit@intractpharma.com

Intract Pharma
29-39 Brunswick Square
London
WC1N 1AX
United Kingdom

www.intractpharma.com

hydrolysis. This phenomenon can be used to an advantage in drug development through strategically designed prodrugs such as sulfasalazine, for ulcerative colitis, and the antibacterial prontosil. In other cases, it is valuable to determine the consequences of microbial metabolism of drugs and their metabolites, including effects on efficacy and toxicity.

Pioneering science is beginning to uncover the complexities of the symbiotic relationship between microbe and man, and determine its role in human health and disease.⁵ This is leading to the development of a new generation of therapeutics based on, or targeted at, the gut microbiome. This complex and dynamic ecology of over 1000 bacterial species is integral to host digestion and metabolism, defence against pathogens and interactions with both the immune and nervous systems. As such, the gut microbiome has been implicated to play a role in numerous pathologies including inflammatory diseases, diabetes, obesity, neurological disorders (including Alzheimer's disease and Parkinson's disease) and immuno-oncology.⁵ To confer their modulatory effects, many live biotherapeutic products (LBPs) and microbiome therapeutics necessitate targeted delivery to the colon where the largest contingent of gut microbiota reside. Numerous studies have also demonstrated that probiotic species are intolerant to gastric juices and the harsh environment of the stomach and small intestine.^{6,7} In contrast, an orally administered Phloral[®] coated microbial therapeutic has demonstrated improved efficacy and successful, stable engraftment of a full diversity of healthy microbiota in patients treated for recurrent *Clostridium difficile* infection.⁸

Reduced Drug Efflux Transporters and Metabolising Enzymes

The presence and function of intestinal drug transporters and mammalian drug metabolising enzymes has a profound effect on oral drug absorption, and the significance of intestinal first-pass metabolism should not be underestimated.

Recent studies employing gene expression and protein abundance techniques have established that the longitudinal expression of numerous intestinal transporters varies across the length of the human gut.⁹ In particular, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are two clinically relevant efflux transporters implicated in limiting the bioavailability of

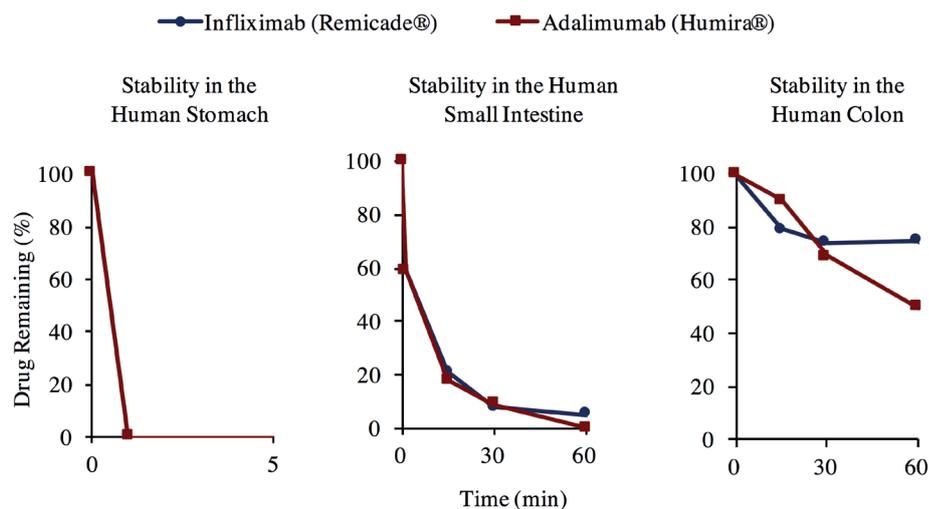


Figure 1: Stability of therapeutic monoclonal antibodies in human gastric fluids, human small intestinal fluids and human colonic fluids. Biopharmaceuticals show improved luminal stability in the colon compared with the proximal regions of the gut. Adapted from Yadav *et al* (2016).¹⁶

“Phloral[®] is the world's first and only dual-trigger coating technology which has demonstrated precise, fail-safe release in the colon in both healthy and diseased states.”

many structurally diverse drug substrates by pumping them back into the gut lumen. The mRNA expression and protein content of both P-gp and BCRP are significantly lower in the colon compared with the small intestine.¹⁰

With a few exceptions, most drug metabolising cytochrome P450 enzymes also demonstrate lower levels of expression in the colon, which can have important implications for drug effects.¹¹ For example, simvastatin, a CYP3A4 substrate, showed three times greater oral bioavailability when delivered to the distal gut (delayed-release formulation) compared with the proximal gut (immediate-release formulation).¹² Identifying and targeting the optimal site of drug absorption provides opportunities to naturally enhance oral bioavailability.

Oral delivery of biopharmaceuticals remains a “Holy Grail” in drug development, however a formidable array of physical and chemical barriers in the gut have permitted only a very small number of oral products to reach the market thus far. Poor drug stability and permeability in different regions of the gut have been major obstacles in achieving bioavailability. The proximal small intestine appears to be favourable for uptake. However, this region also presents the greatest enzymatic barrier, with lumenally secreted proteases and membrane-bound peptidases leading to significant degradation.¹³

In contrast, the colon benefits from comparatively less proteolytic activity compared with both the stomach and small intestine. Cutting-edge research utilising biorelevant human GI fluids has demonstrated that biologics, including proteins, peptides and monoclonal antibodies show significantly improved luminal stability in the colon compared with the proximal regions of the gut, as illustrated in Figure 1.^{14, 15, 16} Targeting drug delivery to the colon presents important advantages which can be used alongside complementary strategies to improve stability and permeability further (e.g. using protease inhibitors or permeability enhancers). This combined approach is likely to be the most successful in helping to realise the promise of orally administered biopharmaceuticals.

Luminal Conditions and Transit

Historically, lack of fluid volumes in the colon has been perceived as a primary limitation for targeted drug delivery. Although free fluid volumes have shown to be variable and sometimes limited,¹⁷ magnetic resonance imaging studies have shown typical filling volumes in the colon to be high, averaging over 200 mL in healthy fasted subjects.¹⁸ These modern techniques have also demonstrated that fluid volumes in the small intestine are

not homogeneously distributed but segregated in “fluid pockets” of varying volume.¹⁹ Mean small intestinal fluid levels of 50-100 mL have been reported after overnight fasting.¹⁹ As such, it is useful to evaluate drug solubility under biorelevant colonic conditions to determine the inherent behaviour of molecules in this unique environment.

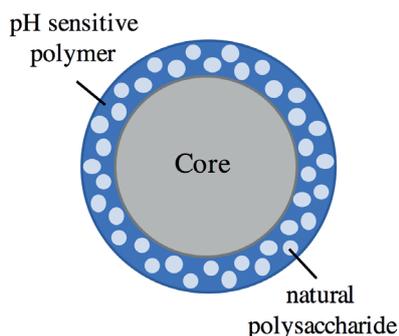
Transit times through the colon are significantly longer compared with the small bowel (on average over 24 hours *versus* four hours respectively in healthy adults), which encourages contact with absorptive surfaces and subsequently can improve drug uptake.¹¹

Transit times through the gut can also be exploited to implement a revolutionary therapeutic approach known as chronotherapy. Increasing evidence demonstrates that certain physiological functions, disease pathologies and the pharmacological effects of drugs can exhibit circadian rhythms.²⁰ Co-ordinating the timing of drug treatments with these biological effects can be used to maximise efficacy and minimise adverse effects. An orally administered formulation targeted to the colon needs to traverse the entire alimentary canal in order to reach the target site. Using this intentional time delay in absorption can facilitate effective symptom control and disease management. For example, symptoms of certain diseases such as rheumatoid arthritis, asthma and hypertension are known to manifest in the morning upon rising. Administering medicinal products at night and synchronising colon targeted release in the early hours enables patients to wake up symptom free.

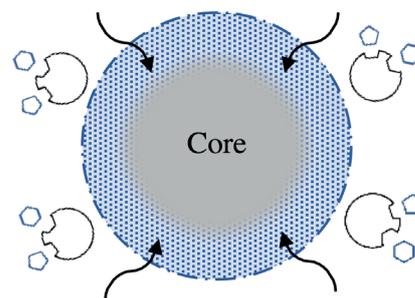
DETERMINING DRUG BEHAVIOUR IN THE GI TRACT

An increasing number of drugs in the development pipeline exhibit poor solubility, poor permeability or both. It has therefore never been more important to determine drug behaviour in specific regions of the GI tract accurately and establish optimal drug delivery strategies at an early stage. Intract has developed specialist gastrointestinal stability and permeability models as rapid and cost-effective means to evaluate drugs using biorelevant fluids and tissues from preclinical species and humans. The models have been used to evaluate the stability of numerous small molecules and biopharmaceuticals to provide unparalleled

A: Typical Dual-trigger Mechanism

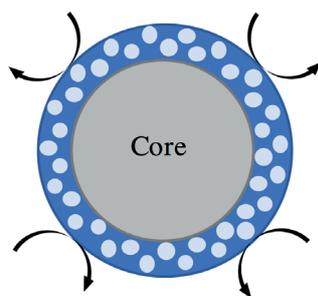


Phloral® incorporates a pH sensitive polymer and natural polysaccharide as a combination single film coating

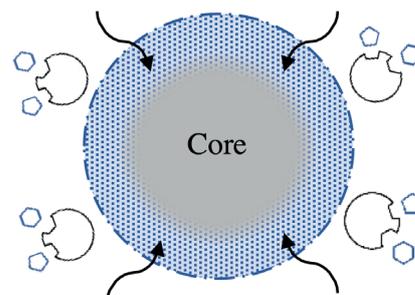


The pH sensitive polymer dissolves at a higher pH towards the colon and the polysaccharide is digested by trillions of bacteria naturally residing there

B: Fail-safe Mechanism in Subjects with a Variable Gastrointestinal pH



Even if the correct luminal pH is not reached to trigger dissolution of the pH sensitive polymer



The polysaccharide is digested by the microbiota as an independent fail-safe mechanism to guarantee release in the colon

Figure 2: Phloral’s unique dual-action mechanism exploits changes in gastrointestinal pH in combination with the enzymatic activity of the colonic microbiota as independent but complementary triggers to guarantee site-specific release.

insights into human GI behaviour, as highlighted in Figure 1.^{14,15,16,21,22}

Intract’s colon simulation model uses biorelevant inoculum, proprietary media, and a specialist anaerobic work-station to mimic the conditions of the large intestine accurately. Intract’s *ex vivo* Ussing chamber system can also be used to study the absorption and translocation of compounds across the intestinal wall from specific regions of the GI tract, including the colon. Strategic clinical collaborations provide unique access to biological fluids and tissue samples from healthy human subjects, as well as patients with GI diseases. Intract’s comprehensive knowledge and capabilities can support preclinical development and provide unique insights to improve delivery strategies for greater clinical success.

PHLORAL® FOR PRECISE FAIL-SAFE DELIVERY TO THE COLON

Despite the well-established advantages of colonic drug delivery, achieving consistent, site specific release in this region of the gut has historically proven to be a challenge. The most common approach has relied on pH sensitive polymers which are designed to dissolve at the higher pH towards the terminal ileum. However, these conventional approaches have demonstrated significant variability and failure *in vivo*, with drug release occurring prematurely or, in some cases, not at all.²³⁻²⁶ This is unsurprising given the vast inter- and intra-subject variability in critical parameters affecting formulation behaviour, including pH, fluids volumes, transit times and motility.

Phloral® is the world's first and only dual-trigger coating technology which has demonstrated precise, fail-safe release in the colon in both healthy and diseased states. This innovative system comprises of a pH sensitive polymer in combination with a natural polysaccharide that is specifically digested by the colonic microbiota (Figure 2).

The pH and enzymatic triggers work in a complementary manner to facilitate site-specific release. However in instances where the dissolution threshold of the pH responsive polymer is not reached, the polysaccharide component is independently digested by enzymes secreted by the trillions of diverse bacterial species naturally residing in the colon. This additional fail-

safe mechanism overcomes the limitations of conventional polymer coatings, as demonstrated in an *in vivo* study with human subjects.

Phloral® was evaluated against Eudragit® S, a widely used commercial pH sensitive coating. Radiolabelled tablets were coated and administered under various feeding regimens to eight healthy adults, with transit and disintegration tracked by gamma scintigraphy. All Phloral-coated tablets released in the colon whereas in the fed state, almost 40% of Eudragit® S coated tablets failed to release and were voided intact in the stool. Phloral® demonstrated 100% successful release under fed, fasted and pre-feed states (Figure 3).²⁷

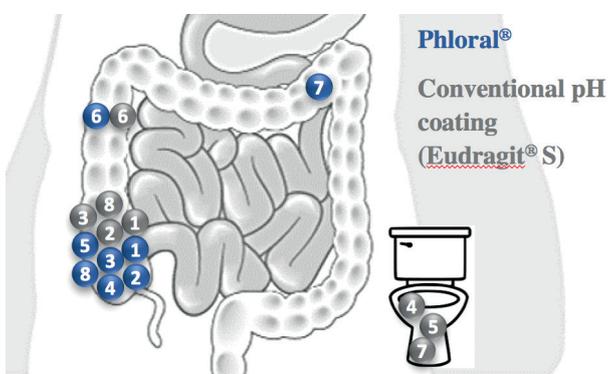


Figure 3: Phloral was evaluated against Eudragit S, a conventional pH sensitive coating, in an *in vivo* gamma scintigraphy study. Tablets illustrate the site of disintegration in 8 individual subjects in the fed state. Conventional tablets remained intact in subjects 4, 5 and 7 and passed out in the stools.

Phloral® is a patent protected technology and is available for licence exclusively from Intract Pharma. The first commercial product harnessing the power of the Phloral® technology has successfully completed phase III clinical studies, with the new once-daily formulation showing significantly improved maintenance of remission in patients with ulcerative colitis.²⁸ Other licensed products are in different stages of

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clinical development across a wide range of therapeutic indications. The technology utilises generally regarded as safe (GRAS) materials and requires conventional manufacturing equipment.

Targeted drug delivery using Phloral® provides unprecedented opportunities to exploit the natural physiological advantages of the colon to develop advanced new therapeutics with the potential to revolutionise patient care.

ABOUT THE COMPANY

Intract Pharma Ltd is a licensing and product development company offering state-of-the-art drug delivery technologies and advanced GI models for product innovation. A spin-out of University College London, Intract is centred around more than 20 years of research and innovation from the laboratory of Professor Abdul Basit.

Intract specialises in oral drug delivery and offers a range of proprietary technologies to help overcome formulation challenges and enhance product performance. Complementary to these, Intract has developed unique GI models as strategic tools to provide expert analysis of drug and formulation behaviour under physiologically appropriate conditions. Intract's drug delivery technologies have been licensed across various therapeutic indications and in-house research and development pipeline includes the preclinical evaluation of a range of products with strong scientific and commercial promise. Using specialist knowledge and experience, Intract can help establish the pathway from successful early stage preclinical development through to clinical and commercial manufacture.

ABOUT THE AUTHORS

Sejal Ranmal, PhD, is Director of Formulation at Intract Pharma and has a research background in paediatric formulation development. Before joining Intract, Dr Ranmal completed her Pharmacy degree and PhD in Pharmaceutics from University College London (UCL) School of Pharmacy, London, UK.

Vipul Yadav, PhD, is Director of Product Development and has expertise in overcoming biological barriers to achieve oral administration of biopharmaceuticals. Dr Yadav received an MSc in Drug Delivery where he researched oral peptide delivery. He then completed a PhD in Pharmaceutics at UCL School of Pharmacy exploring the biological mechanisms involved in oral delivery and intestinal uptake of anti-TNF- α monoclonal antibodies.

Abdul Basit, PhD, is Professor of Pharmaceutics at UCL School of Pharmacy. Professor Basit's research sits at the interface between pharmaceutical science and gastro-enterology, forging links between basic science and clinical outcomes. He is an international authority on oral drug delivery and absorption, and has published over 300 papers, book chapters, abstracts, and patents. He leads a large and multi-disciplinary research group, and the goal of his work is to further the understanding of GI physiology by fundamental research. He is a frequent speaker at international conferences, serves as a consultant to numerous pharmaceutical companies and is on the advisory boards of healthcare organisations, charitable bodies and scientific journals.

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