



OPTICORE™: A FIRST-IN-CLASS COLONIC TARGETING TECHNOLOGY

In this article, Felipe Varum, PhD, Senior Project Lead, Pharmaceutical Development, and Roberto Bravo, PhD, Head Pharmaceutical Development – both of Tillotts – and Abdul Basit, PhD, Professor of Pharmaceutics at UCL School of Pharmacy, discuss the use of colonic targeting coating technology OPTICORE™ to deliver APIs in the treatment of ulcerative colitis (UC) patients.

The large intestine remains a relatively unexplored part of the gastro-intestinal (GI) tract in terms of drug delivery. Despite several physiological challenges that need to be overcome, it offers significant and attractive possibilities for drug product manufacturers. Delaying drug release serves multiple purposes, including protection of acid-labile drugs and protection of the stomach from irritating compounds.

Moreover, colonic targeting opens new avenues for delivery and systemic absorption of molecules that undergo degradation and/or are poorly absorbed in the upper GI tract.¹ This is due to the low levels of luminal and mucosal metabolic enzymes found in the colon, in comparison with the small intestine,^{2,3} and drugs which are substrates for intestinal cytochrome P450 enzymes (CYPs) and efflux transporters.^{4,5}

Targeting the distal part of the gut relies almost exclusively on enteric coatings (pH-sensitive polymers) based on Eudragit® S100, Eudragit® L100 (Evonik) or mixtures thereof. A range of successful drug products employing enteric coatings are available as first-line treatments for mild-to-moderate inflammatory bowel disease conditions such as UC, Crohn's disease and microscopic colitis. They include: Asacol™/Octasa®/Asacolone™/Fivasa™ (mesalazine; Tillotts Pharma/Allergan), Mezavant®/Lialda® (mesalazine; Cosmo Pharmaceuticals) and Entocort™ (budesonide, Tillotts Pharma).

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THE CHALLENGE

Dissolution of oral dosage forms coated with enteric polymers relies on pH gradients along the GI tract, which, along with other physiological characteristics, exhibit significant inter- and intra-individual variability. GI pH sharply increases from the stomach to the duodenum and



Dr Felipe Varum
Senior Project Lead,
Pharmaceutical Development
T: +41 61 935 26 75
E: felipe.varum@tillotts.com



Prof Abdul Basit
Professor of Pharmaceutics
T: +44 20 7753 5865
E: a.basit@ucl.ac.uk

UCL School of Pharmacy
29-39 Brunswick Square
London
WC1N 1AX
United Kingdom

www.ucl.ac.uk/pharmacy



Dr Roberto Bravo
Head Pharmaceutical Development
T: +41 61 935 26 32
E: roberto.bravo@tillotts.com

Tillotts Pharma
Baslerstrasse 15
CH-4310 Rheinfelden
Switzerland

www.tillotts.com

then gradually increases until the distal small intestine.

However, a luminal pH drop occurs at the ileocaecal junction due to the production of short chain fatty acids by colonic microbiota. This halts the pH increases observed in the small bowel, and results in challenges to the triggering of pH-sensitive dissolution systems in the colon. To allow complete drug release in the colon, accurate targeting and rapid coating dissolution is paramount to ensure effective delivery, even under challenging conditions of rapid transit time and significant pH drop in the colon – as often seen in patients with UC.⁶

A NOVEL SOLUTION

OPTICORE™ is a first-in-class validated colonic targeting coating technology.⁷ It comprises two trigger systems (pH and bacterial enzymes) enabled by the incorporation of Intract Pharma's Phloral® in the outer layer (Figure 1). There is also an inner layer promoting release acceleration.

The inner layer of OPTICORE™ builds on the benefits of the Duocoat® technology (Evonik) in accelerating drug release from enteric coated dosage forms.^{8,9} This layer is composed of a partially neutralised enteric polymer with a buffer salt (Figure 2). The high pH, buffer capacity and ionic strength promotes an active acceleration of the dissolution of the enteric polymer in the outer layer as soon as one of the release triggers is initiated (fail-safe feature).

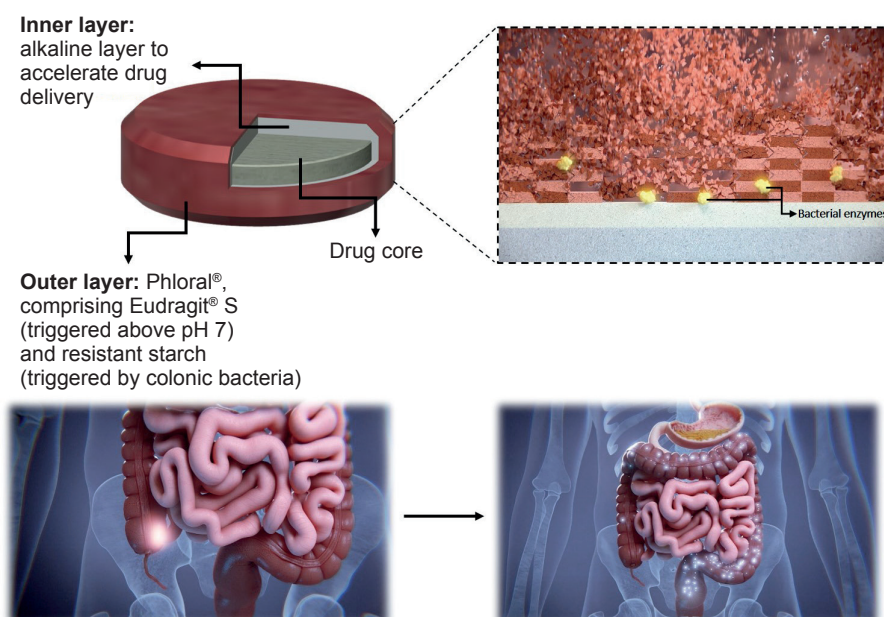


Figure 2: Schematic representation of the OPTICORE™ coating structure and tablet disintegration in the colon.⁷

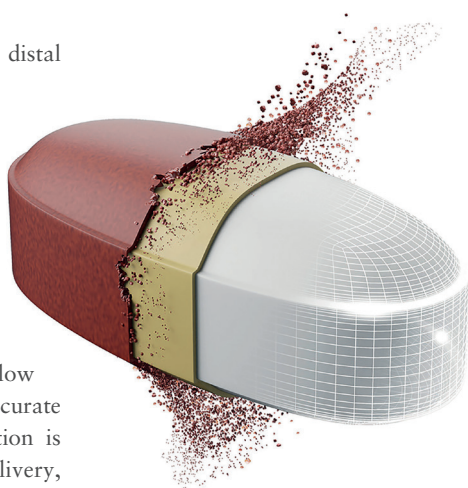


Figure 1: Schematic representation of OPTICORE™ outer layer release triggers.

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The presence of the inner layer beneath the outer layer promotes a faster drug release from OPTICORE™ coated tablets (Figure 3) in buffer simulating the luminal composition of the terminal ileum (pH 7.4 Krebs buffer) in comparison with state-of-the-art enteric coatings designed for colonic targeting (Eudragit® S, (Evonik) dissolves above pH 7).

The outer layer of OPTICORE™ comprises the two-trigger release technology Phloral®.^{10,11,12} This combines an enteric polymer, such as Eudragit® S, which is responsible for the pH-driven dissolution, and resistant starch (Figure 2). When embedded into the outer layer coating, this polysaccharide does not dissolve or swell during transit in the upper gut and resists digestion by salivary and pancreatic enzymes.

In the large intestine, where bacterial numbers are several orders of magnitude higher than in the upper gut, resistant starch can serve as a source of energy for colonic microbiota. This allows for weakening of the coating structure, acting as a second drug release trigger, even in conditions of lower luminal colonic pH and fast transit time, as often seen in UC patients.

Below the pH trigger (pH = 7) of the enteric polymer in the outer coating, drug release from OPTICORE™ coated tablets can be initiated due to the action of bacterial enzymes (Figure 3) as shown in a model of the human colon (human faecal slurry).⁷

The combination of these features provided by the outer and inner layer allows an accurate and timely release of the API in the ileo-colonic region, making it available throughout the colon (Figure 2). The versatility of the OPTICORE™ technology makes it suitable for use in any type of oral solid dosage forms such as tablets, capsules or pellets.

Optionally, an isolation layer between the drug-containing core and the inner layer may be used, particularly if the drug is acidic, which may limit the features of the inner layer in terms of enteric polymer dissolution acceleration.

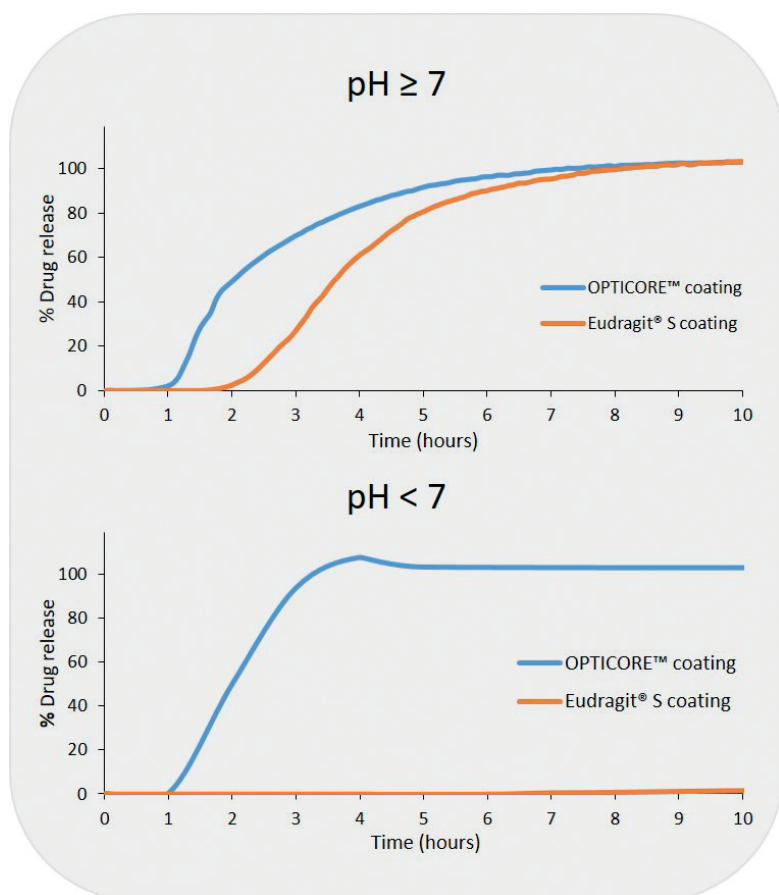


Figure 3: Drug release from OPTICORE™ coated tablets mediated by pH and by bacterial enzymes.

CLINICAL PROOF OF CONCEPT AND BENEFITS

The benefits of the dual-trigger system (Phloral®) to ensure accurate colonic targeting have been demonstrated in healthy

human subjects by means of gamma-scintigraphy¹⁰ and in *Clostridium difficile* patients who received a faecal material transplantation delivered in capsules coated with this technology.¹¹

The OPTICORE™ technology has been successfully implemented in a novel mesalazine 1600 mg drug product. Gamma-scintigraphy investigations showed accurate colonic targeting in all subjects enrolled in the study (Figure 4), allowing for a distribution of the drug along the colon to ensure sufficient local

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concentrations, both in healthy subjects and in mild-to-moderate UC patients.

OPTICORE™ coated 1600 mg tablets successfully met the primary clinical endpoints (clinical and endoscopic remission) of the largest mesalazine induction therapy Phase III study incorporating central reading.¹³ The first drug product developed based on the OPTICORE™ technology is now available from Tillotts Pharma for treating UC patients in multiple markets under the brands Asacol™ 1600, Octasa™ 1600, Yaldigo™ 1600 and Asacolone™ 1600.

CONCLUSIONS

OPTICORE™ coating technology was successfully developed by combining an alkaline inner layer with an outer enteric layer embedded with pH and enzymatic triggers. The inclusion of resistant starch to the Eudragit® S coating formulation does not impact coating robustness and the enteric properties, but is designed to allow an accelerated drug release when the pH of the luminal fluid is above seven (as in Krebs buffer pH 7.4) or below seven (as in pH 6.8 human faecal slurry). Therefore, OPTICORE™ coating technology offers significant advantages, particularly for accurate drug delivery in the colon of UC patients, even when using single-unit dosage forms, such as tablets.

ABOUT THE COMPANY

Tillotts Pharma is an international specialty pharmaceutical company with more than 300 employees in Switzerland and around the world. It markets its own products – such as Asacol™ and Entocort™ – as well as in-licensed products in around 65 countries through its affiliates within Europe and a network of gastroenterology-focused partners throughout the world. Tillotts has been part of the Japanese Zeria Group since 2009.

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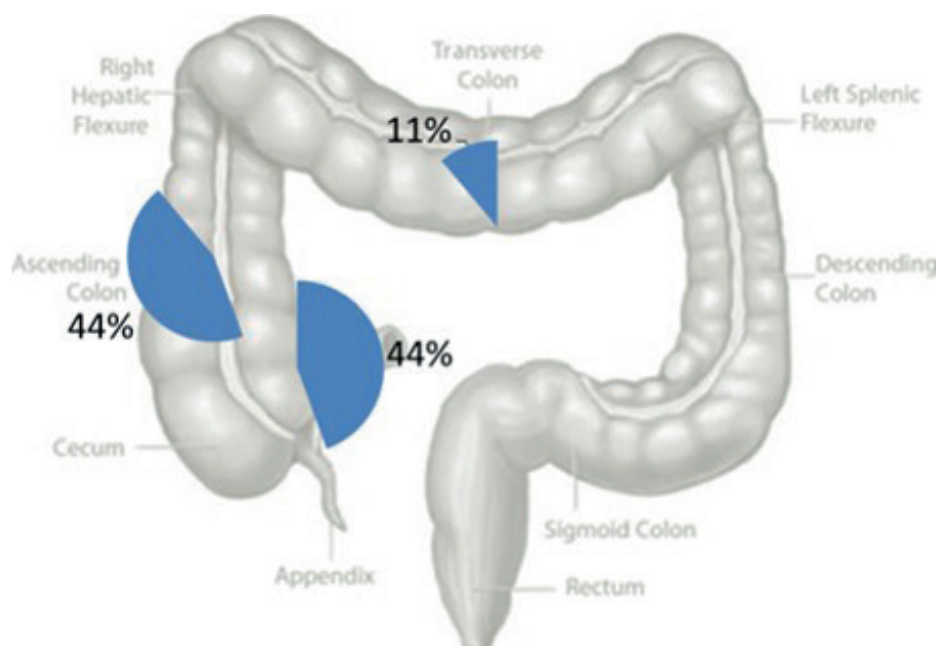


Figure 4: Representation of OPTICORE coated tablets' disintegration locations within the large intestine in human volunteers (followed by gamma-scintigraphy).

The UCL School of Pharmacy is one of the most highly rated pharmacy schools in the UK. It has more than 175 years of experience and tradition, throughout which it has retained its identity as a specialist institution dedicated to teaching and research in pharmacy and the pharmaceutical sciences. The UCL School of Pharmacy is currently rated fifth in the world by QS Rankings (Pharmacy and Pharmacology) as well as 10th in the Shanghai Ranking (Pharmacy and Pharmaceutical Science).

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ABOUT THE AUTHORS

Felipe Varum, PhD, Senior Project Lead, Pharmaceutical Development, at Tillotts Pharma. He is responsible for the end-to-end development of drug products, mostly oral dosage forms, for new clinical candidates and/or for life-cycle management purposes. His experience in the field of oral delivery and gastro-intestinal targeting spans more than 14 years. Prior to joining Tillotts Pharma, Dr Varum was enrolled at UCL School of Pharmacy, in the group of Professor Abdul Basit, as a PhD student and later as a Research Fellow.

Roberto Bravo, PhD, is Head of Pharmaceutical Development at Tillotts Pharma. He leads a team of project leaders and scientists responsible for the development of new drug products for the effective treatment of inflammatory bowel diseases. Prior to Tillotts Pharma, Dr Bravo's career started 20 years ago, when he joined F Hoffmann-La Roche and thereafter Actelion Pharmaceuticals, engaged in the physicochemical characterisation of new active compounds and in formulations to improve their oral bioavailability.

Abdul Basit, PhD, holds the position of Professor of Pharmaceutics at the UCL School of Pharmacy. He is a leading authority on oral drug delivery, digital health and innovative pharmaceutical technologies, including 3D printing. Professor Basit is a world authority on translational research; he has founded two spin-out companies (FabRx and Intract Pharma) and has invented several drug products that have entered the clinic.