Institution: University College London

Unit of Assessment: 3B - Allied Health Professions, Dentistry, Nursing and Pharmacy: Pharmacy

Title of case study: Development of more effective technologies for oral delivery of drugs via improved understanding of the physiological features of the gastrointestinal tract

1. Summary of the impact

Research by Professor Abdul Basit's group at the UCL School of Pharmacy is leading to improved treatments for ulcerative colitis and other conditions through increased knowledge of the complex physiology of the gastrointestinal tract. Improved understanding of *in vivo* drug release and uptake has allowed development of three patent-protected technologies for improved drug delivery: PHLORAL™, for release of drugs in the colon, and DuoCoat™ and ProRelease™ formulations designed to allow intact transit through the stomach followed by immediate release upon gastric emptying. These technologies are the subject of licences and ongoing development programmes, with PHLORAL™ currently in phase III clinical trials. The impact is therefore the introduction of enabling technologies that have positively influenced the drug development programmes of pharmaceutical companies.

2. Underpinning research

The research, which underpins the innovations described below, centres on understanding the chemistry and physiology of the digestive tract in relation to delivery and uptake of drugs through the oral route, which is by far the most common means to introduce drugs into the body. Our group has made a major contribution to understanding the factors (and interplay between factors) that lead to product failure or sub-optimal therapeutic effects. For example, we have identified and studied numerous intestinal parameters that can influence drug behaviour in the gastrointestinal tract, including intestinal pH, fluid volumes and composition, intestinal transit times and microbiota. These characteristics can be highly variable between individuals and within the same individual tested on different days **[1, 2, 3]**.

Overall, therefore, our work on gut physiology in relation to drug delivery has provided a knowledge base that facilitates the performance understanding and hence improvement of pharmaceutical products. More specifically, our understanding of pertinent physiological issues has led to identification of transit features that may lead to product failure or sub-optimal performance. For example, we have shown that, contrary to accepted belief, the small intestinal transit time is affected by meal intake. Food consumption was shown to significantly shorten transit time from 200 minutes to 100 minutes **[2]**. This in itself facilitates the provision of patient advice for those medications where such transit behaviour may be critical. In addition, we have established that intestinal pH is subject to marked intra- and inter-subject variability **[3]**. This in turn informs the development of pH-dependent drug delivery systems as we are now more aware of the range of gut conditions within the patient population.

This knowledge has therefore enabled us to develop delivery approaches that optimise drug release, based on a more thorough understanding of how drugs transit through the gastrointestinal tract. The key research findings that relate to the development of our new technologies include:

- Improved understanding of the factors influencing residence time (and variations thereof) in the different compartments of the gut **[1-3]**, in turn allowing us to develop delivery systems which exploit the respective time windows more effectively and realistically.

- Improved understanding of the pH environment of the stomach and small intestine **[1-6]**, in turn allowing us to develop release systems that may be more effectively and efficiently triggered by changes in pH.

- Improved understanding of the nature and behaviour of the microbiota of the colon **[1, 7-9]**,

in turn allowing us to develop colonic delivery systems with more specific and effective triggers for release.

For drugs that would otherwise be inactivated in the stomach, we have developed two novel enteric technologies that exit the stomach rapidly and thereafter release rapidly (ProRelease™ and DuoCoat™). ProRelease™, a microparticulate drug formulation, is designed to allow rapid transit through the stomach (via control of size) followed by immediate release at higher pH **[4]**. Drugs incorporated into ProRelease™ are released much more rapidly in the intestine than standard drug formulations **[4]**. DuoCoat™, a multiple-layer enteric coating technology, dissolves at a faster rate than industry-standard enteric coatings **[5]** due to our appreciation that the pH is lower in the proximal intestine than is commonly believed. In a clinical study, the mean release time of the DuoCoat™ technology, post gastric-emptying, was 28 minutes. This compared favourably with a mean time of 66 minutes for the conventional enteric coatings **[6]**.

Enteric-coated products are also used to deliver drugs to the large intestine or colon for the treatment of diseases including ulcerative colitis. However, in our studies, such coated tablets or pellets often fail to release in the colon, either failing to disintegrate at all or prematurely releasing their drug load **[3, 7]**. Further, it was shown that contrary to accepted opinion, intestinal pH alone was a poor indicator of successful tablet disintegration, with intestinal residence times and fluid volumes also playing key roles **[3]**. Observed variability in drug release using conventional carriers has led the group to develop new technologies with more reliable release characteristics. For example, research into alternative means to achieve colonic release of drugs led to recognition of the role of bacteria in degrading starch coatings and therefore enabling release in the colon **[7, 8]**. Our group identified this process, whereby the incorporation of starch into traditional film coatings leads to its degradation exclusively by colonic bacteria. This led to the development of PHLORAL™, a dual-trigger colonic delivery system, which exploits both the pH change and increase in bacterial numbers along the gastrointestinal tract, with each component acting as a failsafe to guarantee reliable and consistent targeted delivery **[9]**. Overall, therefore, our fundamental work on the effects of physiology on drug transport has led to findings which allowed us to rationally design new delivery approaches, the impact of which is described below.

3. References to the research

[1] McConnell EL, Fadda HM, Basit AW. Gut instincts: Explorations in intestinal physiology and drug delivery. Int. J. Pharm. 2008 Dec 364: 213-226. http://dx.doi.org/10.1016/j.ijpharm.2008.05.012

[2] Fadda HM, McConnell EL, Short MD, Basit AW. Meal-induced acceleration of tablet transit through the human small intestine. Pharm. Res. 2009 Feb;26(2):356-60. http://dx.doi.org/10.1007/s11095-008-9749-2

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[4] Kendall, RA, Alhnan MA, Nilkumhang S, Murdan S, Basit AW. Fabrication and in vivo evaluation of highly pH-responsive acrylic microparticles for targeted gastrointestinal delivery. Eur J Pharm Sci. 2009 Jun 28;37(3-4):284-90. http://dx.doi.org/10.1016/j.ejps.2009.02.015

[5] Liu F, Lizio R, Meier C, Petereit HU, Blakey P, Basit AW. A novel concept in enteric coating: a double-coating system providing rapid drug release in the proximal small intestine. J Control Release. 2009 Jan 19;133(2):119-24. http://dx.doi.org/10.1016/j.jconrel.2008.09.083

[6] Liu F, Basit AW. A paradigm shift in enteric coating: achieving rapid release in the proximal small intestine of man. J Control Release. 2010 Oct 15;147(2):242-5.

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[7] McConnell EL, Short MD, Basit AW. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J Control Release. 2008 Sep 10;130(2):154-60. http://dx.doi.org/10.1016/j.jconrel.2008.05.022

[8] Palmer RMJ, Newton JM, Basit AW, Bloor JR. Colonic release composition. US 2005/0220861 https://www.google.co.uk/patents/US20050220861

[9] Ibekwe VC, Khela MK, Evans DF, Basit AW. A new concept in colonic drug targeting: a combined pH and bacteria drug delivery technology. Alimentary pharmacology and therapeutics. 2008 Oct 1;28(7):911-916. http://dx.doi.org/10.1111/j.1365-2036.2008.03810.x

4. Details of the impact

Improved understanding of drug release and uptake has allowed development of three patent-protected technologies for improved drug delivery: PHLORAL™, for release of drugs in the colon, and DuoCoat™ and ProRelease™, formulations designed to allow transit through the stomach and immediate release upon gastric emptying.

PHLORAL™ arose as a result of earlier studies on a product trademarked as COLAL-PRED™ **[8]**. COLAL-PRED™ was developed with over £1m in research and licensing funding provided by Alizyme **[a]**. This technology progressed into phase III clinical trials for a product containing prednisolone metasulphobenzoate. The knowledge gained from this study led to the development of PHLORAL™ which is the world's first dual trigger colonic coating technology. The coating exploits both the pH change and increase in bacterial numbers along the gastrointestinal tract, with each component acting as a failsafe to guarantee reliable and consistent targeted delivery **[9]**. The corresponding product, which contains mesalazine as the active therapeutic ingredient, is currently in phase III trials as a treatment for ulcerative colitis. It was the subject of a patent application in 2007, which has since been granted in many territories worldwide **[b]** and has been the subject of licenses, options and contracts. The coating allows precise and consistent release of material in the colon, and may be used for the treatment of localised as well as systemic diseases (PHLORAL™ has been licensed for both purposes). In particular, a licence has been granted to Tillotts Pharma AG for treatment of ulcerative colitis using mesalazine, as the next generation of their current product Asacol™, the market-leading product for treatment of ulcerative colitis with an annual global market in excess of $600m **[c]**. Ulcerative colitis, a form of inflammatory bowel disease, affects 120,000 people in the UK, and is conventionally treated with anti-inflammatory drugs, immunosuppressants and biological therapeutics. Without successful drug delivery, surgical removal of parts of the intestine can be the only remaining option, and 25-40% of sufferers currently have all or part of their colon removed. This can also necessitate the use of stoma bags, which negatively impact quality of life. The PHLORAL™ product has entered a phase III clinical trial which will report late in 2014 **[d]**. The project has to date generated £0.75m in funding for research at the UCL School of Pharmacy and from licensing **[e]**. PHLORAL™ has additionally been licensed to Oxford Pharmascience for the delivery of statins to the colon **[f]**. This has generated more than £200,000 in research and licence revenue **[e]**. Their product (Safestat™) is designed to reduce the amount of statin that needs to be administered to the patient, thereby increasing safety as well as reducing cost **[g]**. The product is undergoing clinical development, with human trials expected late in 2013.

ProRelease™ is a microparticulate drug formulation designed to allow rapid transit through the acidic stomach environment, followed by immediate release at higher pH. Drugs incorporated into ProRelease™ are released far more rapidly than standard drug formulations. A patent was filed covering this methodology in 2004 **[h]**, and in 2009, the technology was licensed into a UK company, Kuecept Limited **[i]**. Kuecept was initially set up as a spin-out from the UCL School of Pharmacy in 2007, and currently has an annual turnover in excess of £1m, having worked on over 600 client projects since incorporation **[j]**. The license, which is restricted to provision of services to third-party clients, has resulted in early development projects for a number of drugs and generated

significant income to the UCL School of Pharmacy **[e]**.

DuoCoat™ is a multi-layer coating technology designed to rapidly dissolve in the upper small intestine. In 2007, a patent was filled in collaboration with Evonik industries **[k]**. The technology is offered for licensing through Evonik and Kuecept Limited and to date, positive proof-of-concept data has been generated with different actives **[e]**.

In summary, this family of products has had a significant impact on the development of formulations within the pharmaceutical industry, providing a clear route to much greater impact should the products be marketed for patient use. Companies have invested heavily in the development of products relating to these technologies and, in a competitive environment, have included these products in the development of their business strategies. We estimate that in total 15 pharmaceutical companies have accessed the technologies either through licensing, options or contracts to date.

5. Sources to corroborate the impact

[a] US 2003/0220861 Colonic release composition. R.M.J. Palmer, M. Newton, A. Basit, J. Bloor ("COLAL-PRED™). COLAL-PRED™ licensed to Alizyme. See press coverage: http://ww7.investorrelations.co.uk/alizyme/products/colalpred/
COLAL-PRED™ licensed to Norgine in 2008. See press coverage: http://www.grantapark.co.uk/pdf/ALIZYMELICENSESCOLAL.pdf

[b] Patent no US 2007/0243253 Colonic drug delivery formulation. A.W. Basit, V.C. Ibekwe ("PHLORAL™"): http://www.google.com/patents/US20070243253

[c] PHLORAL™ licensed to Tillotts Pharma AG. See press coverage: http://www.firstwordpharma.com/node/85129?tsid=17

[d] PHLORAL™ Phase III clinical trial 2013: https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000366-11/FI

[e] Confirmation of licence agreements and income available from Senior Business Manager, Biomedical Science, UCL Business PLC. Contact details provided.

[f] PHLORAL™ licensed to Oxford Pharmascience Group PLC. See press coverage: http://www.proactiveinvestors.co.uk/companies/news/48053/update-oxford-pharmascience-eyes-huge-opportunity-in-statins-with-ucl-deal-48053.html

[g] http://www.oxfordpharmascience.com/content/pipeline/Safestat_Atorvastatin/index.asp

[h] Patent no US 2013/101646 Method of producing microparticles. A.W. Basit, S. Murdan, R.A. Kendall ("ProRelease™") https://www.google.com/patents/US20130101646

[i] ProRelease™ licensed to Kuecept Limited. See company website: http://www.kuecept.com/prorelease/

[j] Confirmation of company establishment, turnover and project numbers available from CEO, Kuecept Limited.

[k] PCT/EP/2007/054398, Solid dosage forms comprising an enteric coating with accelerated drug release, F. Liu, A. Basit. R Lizio, HU Peterit, C Meier, M Damm http://www.google.com/patents/WO2008135090A8