THE RISE OF COMPLEX ORAL DELIVERY SYSTEMS

In this article, María Fernández-Martos Balson, Biomedical Engineer, and Bastiaan De Leeuw, Head of Business Development, Drug Delivery, both of Cambridge Design Partnership, explore the oral delivery of biologics and the challenges that must be overcome in order to enhance bioavailability. The authors also take a look at some recently developed drug-device combinations.

After a series of failed experiments in November 1923, pathologist Geoffrey Harrison concluded that the "oral administration [of insulin] in alcohol would be so uncertain and so expensive as to be of little or no therapeutic value in diabetes mellitus in man". He published his results – and encouraged other researchers to join him in publishing their own data – with a mind to "prevent the raising of false hopes in [...] those suffering from diabetes".[1] This was a mere two years after the discovery of insulin.

Since then, peptide- and protein-based therapies have risen in prominence, representing approximately 12% of the pharmaceutical market as of 2018, and with the potential to grow substantially over the next 5-10 years.[2,3] Hundreds of biologics are now approved to treat a variety of ailments, from cancer to rheumatoid arthritis. And, since Harrison, many attempts have been made to administer such drugs in non-invasive manners, from inhalation to transdermal patches. The oral route is of particular interest for its convenience and tolerability for patients, and many recent efforts have been focused on this area.

Of course, not all therapeutic peptides would benefit from oral administration, even when achievable from a technical perspective. Robustness of delivery, patient compliance, dosing regimen and bioavailability must all be weighed up, along with the economic considerations.

From a patient perspective, it is a no-brainer: who would choose an injection if they could take a pill instead? From a business perspective, drugs may be well suited to this approach if the projected market expansion for an oral formulation outweighs the development costs and risks, as well as the projected increased cost due to any additional API that may be required to compensate for unavoidable reduced oral bioavailability.[4] To date, predominantly diabetes-associated drugs have been considered, as the mechanism is well understood and the opportunity to avoid the need for multiple daily injections is attractive.

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Yet, despite the obvious appeal and after nearly a hundred years, needles are still required. The oral delivery of biologics remains a "holy grail" – a tantalising vision and a worthy goal. In this article we will explore the challenges faced by a protein on its journey from the gastrointestinal (GI) lumen to the bloodstream and explain how ingestible devices can be used to increase oral bioavailability. The reward is self-evident. The challenge, not trivial.

THE API'S PERILOUS JOURNEY

For a therapy to be effective, the API must reach the target delivery site (in this case, systemic circulation) in sufficient concentrations. A key measure of success, then, is bioavailability: the fraction of the administered dose that reaches the bloodstream, typically expressed as a percentage. When delivered orally, proteins have extremely low bioavailability, usually less than 1%.[5] This is because their half-life in the GI lumen is short and their ability to permeate through the GI walls is limited.

The human digestive system has evolved over millions of years to break down nutrients, to eliminate waste and to protect itself. It is not a friendly environment, especially for proteins (i.e. food). To reach the bloodstream, a drug must first survive the acidic environment of the stomach, elude

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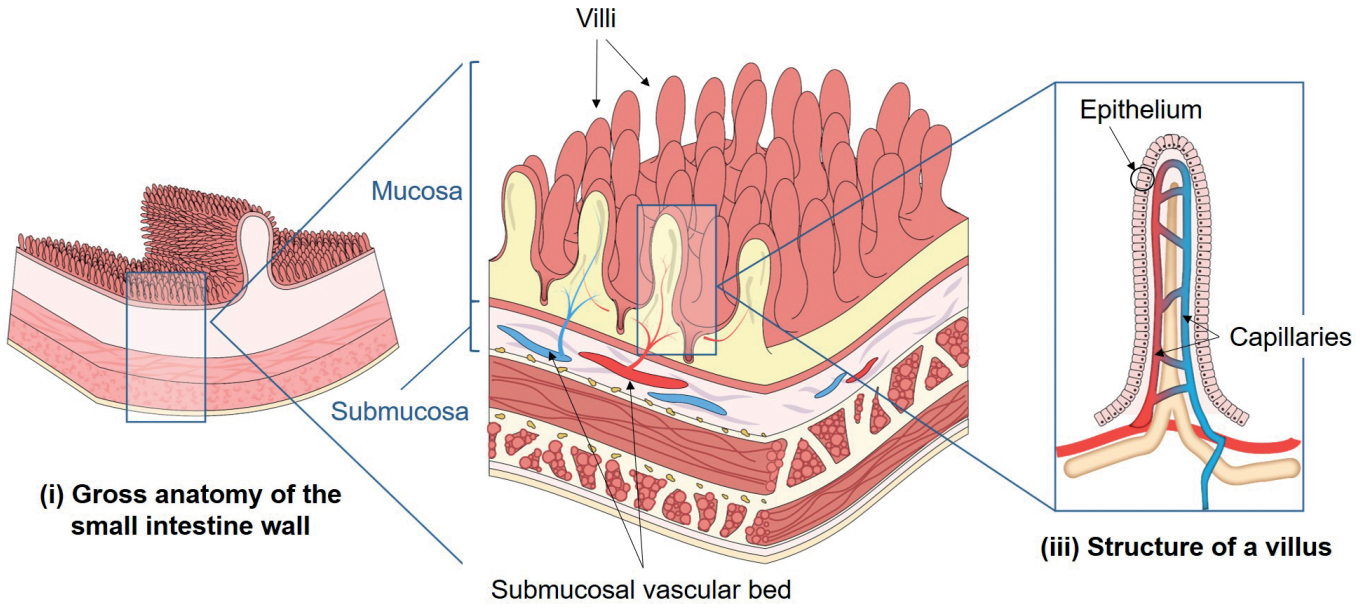

Figure 1: A cross section of the small intestine wall, highlighting the location of the submucosal vascular bed and the capillary network within the villi.

enzymatic degradation and get as far as the GI wall. Once there, the drug faces a coating of mucus and several layers of densely packed cells.

The mucus alone presents a formidable barrier. Constantly shed and secreted, it flows from wall to lumen, and from stomach to colon; drugs must diffuse upstream to reach the epithelium. It is viscous, prone to forming intermolecular bonds, and consists of a fine mesh of mucin filaments – in summary, it is very effective at preventing the passage of large, interactive molecules.[6]

For any API that makes it past the mucus the final hurdle is in the wall itself. To reach the capillaries in the villi or the vascular bed within the submucosal layer (Figure 1), the API must cross the epithelium. Epithelial cells are tightly packed and connected to one another by the aptly named tight junctions (multiprotein complexes that seal the gaps between adjacent cells). There are two main paths across this barrier (Figure 2), neither of which is easy for therapeutic peptides, as they are typically too hydrophilic to permeate through the cellular membrane and across the cells themselves (transcellular transport), and too large to pass between tight junctions (paracellular transport).[7] Overall permeability is therefore very low.

ENHANCING BIOAVALABILITY

In order to reach the bloodstream intact and in sufficient quantities, an API must successfully navigate the aforementioned obstacles. That is, the delivery system must achieve the following high-level functions:

- Protection: protect the API from chemical and enzymatic degradation in the GI lumen
- Localisation: enable the API to reach the GI wall
- Absorption: ensure transport of the API through the GI wall.

Attempts to fulfil these functions – and thus improve bioavailability – fall into two broad categories: pharmaceutical strategies (relying on reformulation and use of excipients) and mechanical strategies (relying on physical parts and mechanisms).

The pharmaceutical approach typically involves the use of enzyme inhibitors to decrease the rate of protein breakdown in the lumen (protection) and the use of permeation enhancers to improve diffusion of the drug through the epithelium (absorption), while relying on regular diffusion/advection and the increased drug half-life in the lumen for

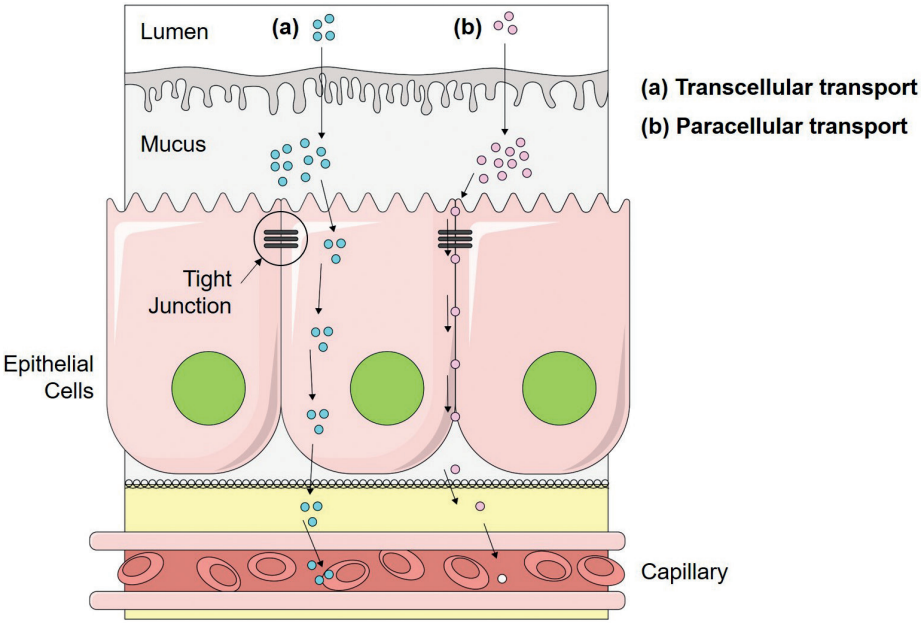

Figure 2: Two paths across the epithelium to reach systemic circulation: through the cells themselves, or between them.

"The challenge, of course, is to obtain a useful improvement in bioavailability (increasing it to 30-50%)[5] while mitigating the safety risks."

localisation. Other formulation techniques include direct chemical modification of the peptide or protein to increase permeability (e.g. PEGylation) and the use of carrier systems such as nanoemulsions and nanoparticles.[8,5]

Chemical strategies such as these have demonstrated marginal improvements in the oral bioavailability of therapeutic macromolecules, with some formulations achieving 1–2% bioavailability in clinical studies.[9] This only provides an incremental change, rather than truly enabling a shift in the attractiveness of oral administration. Moreover, the technologies deployed can carry undesirable side effects, for example some permeation enhancers may cause inflammation or allow pathogens to breach the epithelial layer, potentially leading to infections. The challenge, of course, is to obtain a useful improvement in bioavailability (increasing it to 30–50%)[5] while mitigating the safety risks. Many specific drug formulations (and some platform technologies) that aim to strike this balance are currently in development.[10]

In contrast to the purely pharmaceutical approach, device-enabled oral delivery aims to fulfil the three key functions by mechanical means. In principle, the concept is simple: the patient swallows a small device, as they would a pill. The device becomes activated once it reaches the desired location (typically the stomach or small intestine) and then, by some means, the device creates a high and localised concentration of API adjacent to the epithelium – or else it penetrates the mucosa in order to bypass the epithelium entirely and thus achieve greater bioavailability.

Physical concepts for enhanced wall penetration include the use of microneedles, ultrasound and electroporation, while a common motif to address both protection and localisation is the use of enteric materials.[9] Enteric coatings or components allow a device to pass through the acidic environment of the stomach in a dormant state, dissolving only upon reaching the higher pH of the small intestine (which then triggers the device's active state). This targeted deployment serves a double purpose: protecting the API from chemical degradation in the stomach, and bringing the drug closer to the epithelium (simply because the small intestine is much narrower than the stomach).

IN THE PIPELINE

Over the past 10 years, development efforts in this space have been shifting towards drug-device combinations. This section describes some of the more mature designs (note that this is not a comprehensive list and does not reflect the full breadth of technologies currently in development).

In an ongoing collaboration, a team of engineers from Massachusetts Institute of Technology (MIT) (US) and Novo Nordisk (Denmark) has developed several devices that show promise in preclinical studies. The self-orienting millimetre-scale applicator (SOMA) delivers a solid drug needle into the gastric mucosa. The device's shape, inspired by the leopard tortoise, ensures that the device always lands and remains on the bottom of the stomach in the upright position. Within minutes, a sugar trigger dissolves, releasing a spring that inserts the needle into the mucosa. The needle, made of up to 80% compressed insulin, dissolves over the course of one hour, releasing the API.[11]

The luminal unfolding microneedle injector (LUMI), another MIT/Novo Nordisk device, targets the small intestine instead. It consists of three legs, joined at the centre, and tipped with solid drug-loaded microneedles. Once it reaches the higher pH of the intestine, the device – initially constrained within a capsule – is deployed by a spring. The tripod unfolds in the small intestine lumen, pressing the needles into the wall, where they dissolve.[12] Proof of principle studies in pigs achieved a bioavailability of 10% and demonstrated that non-biodegradable device components were safely excreted and that there was minimal damage to the epithelium at the injection site, although long-term safety remains to be demonstrated.[13]

"Promising preclinical results, such as those of the LUMI system, demonstrate concept feasibility."

Rani Therapeutics (San Jose, CA, US) is developing a similar device. Upon reaching the small intestine, the RaniPill™ is activated. A partition between two compartments (containing dry citric acid and sodium bicarbonate respectively) dissolves, allowing the reagents to mix and produce CO_2. The gas fills a balloon, which in turn pushes a solid drug needle into the mucosa. The needle dissolves and the rest of the device is passed.[14,15] Rani's technology has attracted interest from a number of pharmaceutical companies, including Novartis (Switzerland) and Shire (now Takeda) (Japan), and they recently announced a successful Phase I study with octreotide in humans with a bioavailability claim of >70%,[16] although their data have not yet been formally published in a peer-reviewed journal.

Progenity (San Diego, CA, US) and Baywind Bioventures (San Diego, CA, US), two relatively new companies, are developing devices that aim to deliver high-velocity jets of drug solution directly through the epithelium. Both are in early development phases currently.

THE REAL CHALLENGE: SCALING UP

Promising preclinical results, such as those of the LUMI system, demonstrate concept feasibility. The next challenge is ensuring device safety and robust delivery at scale.

Typical candidate peptides for oral delivery require frequent dosing (weekly to daily) and have large target patient populations. Assuming, for example, that a once-weekly device was adopted by 5% of diabetics in the US, 80–90 million units would be required per year.[17] To be a viable therapy, the device would have to deliver the drug safely and reliably every time. It would have to be manufacturable and fillable, and fulfil its functions in tolerance cases. This is the puzzle that must be solved if oral delivery of biologics is to succeed where other non-invasive approaches have failed. Some of the key pieces are:

Miniaturisation

There is a trade-off between device size and potential payload. Drug loading should be maximised, but size is ultimately constrained by patient tolerability and the risk of intestinal obstruction. For frequently dosed

devices, the device envelope should ideally fit within a size 0 capsule (L = 21.7 mm, ø = 7.34 mm), a requirement that places a significant burden on the manufacturing process. Component features require micrometre accuracy, and manufacturers may need to develop specialist processes and equipment to handle and assemble millimetre-sized components, to fill the primary container (if delivering a liquid) or to manufacture components out of solid drug (e.g. microneedles).

Anatomy and Physiology

Not only do device tolerances matter, the device must also work reliably in spite of inter- and intra-patient variability. Human anatomy is not subject to drawing tolerances; patient's GI tracts vary significantly in shape, size and motility patterns. There are also differences between the fed and fasted states, and differences due to disease states and co-morbidities. Ensuing variations in the chemical and enzymatic makeup of the gastric and intestinal fluids, the presence or absence of chyme, peristalsis, gastric emptying times, etc, must all be taken into account.

To succeed here, device engineers must gain a deep understanding of anatomical and physiological variability in the GI tract, and of how its extremes affect each of the device functions, from localisation, though delivery, to eventual dissolution or passing.

Material Selection

Choosing the right materials can prove challenging too, as there are often conflicting requirements. There may be a need for components that store energy (e.g. springs), dissolve at certain times (e.g. triggers) and/or act as impermeable membranes (e.g. to prevent dry reagents from mixing prematurely). These requirements must all be balanced alongside manufacturability, sterilisability and patient safety.

For example, from a safety perspective, it is preferable for sharp components, such as hollow needles, to be able to dissolve in the GI tract, in order to mitigate the risk of damage to the epithelium as the device is passed. However, soluble materials can rarely hold an edge for very long in the moist environment of the GI tract. Engineers must weigh such considerations and choose wisely to ensure reliable delivery while mitigating the associated risks (and while operating in a regulatory environment that is not yet set up for this new class of devices).

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LOOKING AHEAD

Compared with 1923, we are surely closer to being able to solve the oral delivery puzzle. Basic feasibility of device-enabled delivery has been demonstrated in preclinical studies, with data supporting the potential to obtain much improved bioavailability. Whether this promise will become a commercial reality remains to be seen, but the goal is certainly worth the journey.

To get there, companies should focus on turning the technical advances that have been made so far into robust and scalable technologies, through a deep understanding of physiology, manufacturing and material selection.

ABOUT THE COMPANY

Cambridge Design Partnership is an employee-owned technology and product design partner, located in Cambridge (UK) and Raleigh, North Carolina (US). CDP provide an integrated and holistic product development capability through a highly qualified team, well equipped development labs and ISO 13485/9001 approved methods. This encompasses research and strategy, design, technology and digital innovation, product development and regulatory and manufacturing support. CDP experts are able to take combination products through a full design cycle and submission, enabling customers to launch products that are user-centric and commercially effective.

With broad experience developing devices across all forms of drug delivery, our team builds upon technological advances from various industries and sectors to develop reliable devices that can be manufactured at scale. We are well positioned to address the technical challenges posed by miniaturisation, material selection and physiological variability, critical to deliver upon the promise of oral biologics delivery.

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ABOUT THE AUTHORS

María Fernández-Martos Balson has a Masters degree in Bioengineering and Mechanical Engineering from the University of Cambridge, where she focused on the computational modelling of dynamic cell tissues, with a view to understand how tumour metastasis begins. Prior to joining CDP, Ms Fernández-Martos Balson worked in the innovation department of a leading drug delivery device manufacturer, where she contributed to a range of development projects, including the early-stage design of an intraocular injection device and the late-stage development of a gas-powered autoinjector. Since joining CDP, she has been involved in the design of subcutaneous, intratumoural and oral drug delivery devices.

Bastiaan De Leeuw has been active in the field of drug delivery for the last 20 years. Mr De Leeuw has led projects covering dry-powder formulation development, inhaler design and development, and autoinjector design and development, as well as the associated stages of clinical and regulatory evaluations. In addition, he led the initial clinical evaluation of urologic diagnostic tests at NovioGendix (the Netherlands) (now MDxHealth, Irvine, CA, US) and has worked at Focus Inhalation (Turku, Finland), Akela Pharma (Austin, TX, US), Oval Medical (Cambridge, UK) and Bespak (Norfolk, UK). Mr De Leeuw obtained his MSc Biopharmaceutical sciences at Leiden University (the Netherlands), focusing on polymeric drug delivery systems for formulation of proteins and peptides. His research there combined pharmaceutical technology and pharmacology in industry-sponsored projects.

ONdrugDELIVERY

EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Aug 2020	Industrialising Drug Delivery	PASSED
Sept 2020	Wearable Injectors	Aug 21, 2020
Sept/Oct 2020	**NEW TOPIC – INAUGURAL ISSUE!** Drug Delivery & Enviromental Sustainability	Sep 10, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 24, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 8, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
Jan/Feb 2021	Prefilled Syringes & Injection Devices	Dec 17, 2020
Feb 2021	Novel Oral Delivery Systems	Jan 7, 2021
Mar 2021	Ophthalmic Drug Delivery	Feb 4, 2021
Apr 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
Jun 2021	Connecting Drug Delivery	May 6, 2021
Jul 2021	Novel Oral Delivery Systems	Jun 3, 2021