The Hope for Oral Delivery of Biologics

The hope has been that biologics injectable products could be converted to oral therapies in the form of a tablet or capsule. This would greatly expand the utilization by patients and physicians, and in turn the market potential for these already valuable injectable products. In addition, from a product support perspective, patients know what to do with an oral tablet or capsule and require no training. On the other hand, injectable systems require training prior to use and ongoing technical support, which can be quite significant costs for commercial pharmaceutical organizations.

Historical Perspective

Oral delivery of biologics has been a fertile area for translational research for many years and seems to have been a very strong emphasis starting in the 1980s and early 1990s with the most popular systems under investigation being permeation enhancing technologies designed to open tight junctions for transport of macromolecules between cells. There were many failures early on with permeation enhancers, which are essentially surfactants. The failures related to using too much of the enhancers, which because of their natural ability to be good surfactants, were able to irreversibly alter the cellular membranes that they were interacting with. This resulted in much hesitancy for pharma companies to continue to pursue this avenue of research. However, the resurgence came with careful understanding of cell viability and the demonstration that tight junction opening is reversible within 30 to 60 minutes if the appropriate amounts of the enhancers are used.

It should be mentioned for completeness that other non-injectible systems, such as nasal spray, oral inhalation, buccal, sublingual, and microneedle transdermal approaches have also been evaluated extensively in parallel to the efforts on oral delivery and some products have been approved (inhaled insulin in the Pfizer/Nektar collaboration on Exubera launched in 2006 and pulled from market in 2007 for commercial reasons, and the inhaled insulin from Mannkind approved by FDA in 2014 and currently still on the market, despite modest sales) REF 1,2 While these non-injectable products are interesting and exciting for patients, the attractiveness of a tablet or capsule is still the primary hope by pharmaceutical companies due to the high familiarity by patients. Below is a representation of patient interest in delivery technologies which is a summary of many market research studies for these technologies.

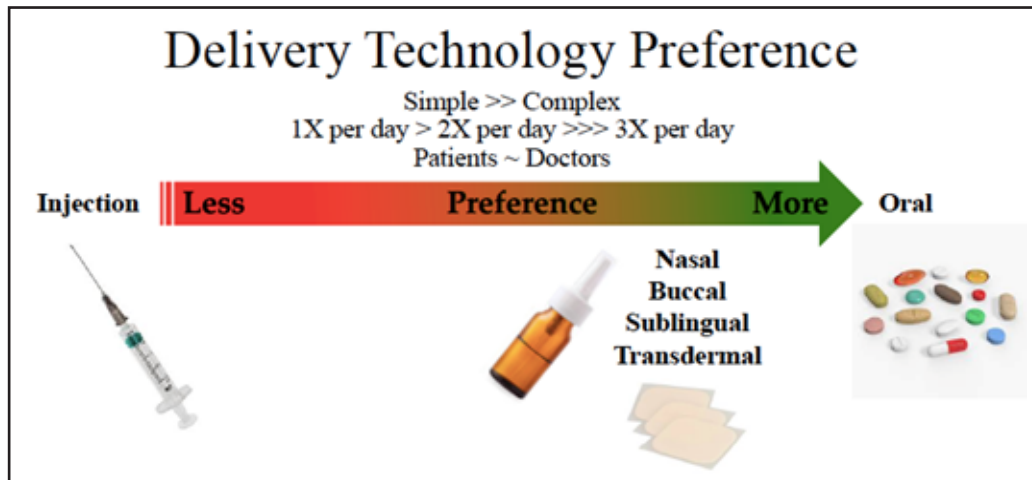**For More Information, Please Visit www.ddelabs.com**

Figure 1. Patient and Physician Preference for Usage of Delivery Technologies.

Oral Delivery Formulation Approaches

The vast majority of approaches to oral delivery of biologics have been in the use of surfactant like molecules to temporarily open the tight junctions between the cells in the epithelial layer of the GI system. The resulting bioavailability for these systems has been no more than 1 to 2% versus IV or SC injection, although this is a significant improvement over the bioavailability achieved without the permeation enhancer, which is typically less than 0.1%. These technologies work modestly for smaller peptides (1 to 4 kDa) and do not work well for proteins or antibodies. Part of the reason is the mass transport through this route is only amenable to potent molecules like peptides. A few modest successes in this area have been demonstrated but no biologics have yet reached commercial product status, despite many years of work.

One such example is a salmon calcitonin (a 34 amino acid peptide) originally developed by Novartis and Unigene in the 1990s and now in final stages of clinical development by using lauryl carnitine as enhancer (delivery technology originally promoted by Unigene and now the company Enteris Biopharma). The bioavailability compared to SC injection is between 1% and 2% for this tablet formulation. REF 3

Another near-term player to watch is the oral delivery program for semaglutide, a GLP-1 agonist with a long half-life by Novo Nordisk using the Emisphere excipient (SNAC, a hydrophobic amino acid derivative and permeation enhancer). This project was submitted to the FDA in 2019 and will test the value of an oral GLP-1 agonist in the market. The bioavailability compared to SC injection is about 0.25%. The approved SC product is a weekly injection called Ozempic, FDA approved 2017 and launched in 2018. REF 4
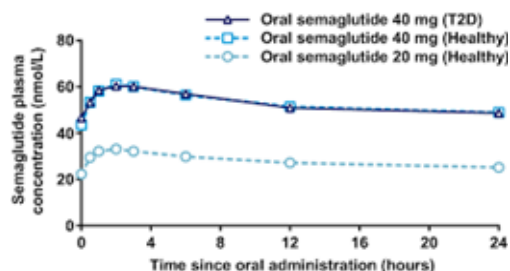
Figure 2. Semaglutide (Ozempic) weekly injection device. Semaglutide oral pharmacokinetics.

A company with one successful commercial application of their permeation enhancer tetradecyl maltoside (a component in some shampoos) is Neurelis, which has one product small molecule approved as a nasal delivery product with the enhancer (sumatriptan). Neurelis acquired Aegis in 2018 and continues to license the sugar-based surfactant as a permeation enhancer for oral and nasal applications and as an aggregation preventer for compounds such as insulin and glucagon which can fibrillate in solution. This enhancer appears to work best with small and cyclic peptides and small molecules. REF 5

Devices for Oral Delivery

A revolutionary approach to oral drug delivery was first invented and brought to reality by a very bright device engineer by the name of Mir Imran and the company Rani Therapeutics, with work first publicized in about 2010. Rani is using a sugar-based solid microneedle containing protein on a small microneedle patch that is housed within an enteric coated capsule. The device deploys within the small intestine to inject the microneedle into the wall of the gut. Preclinical data shows 50% bioavailability for insulin, human growth hormone, and interferon. Phase 1 studies were just completed with a drug-free device to demonstrate safety and phase 2 study with octreotide is ongoing in 2019. REF 6
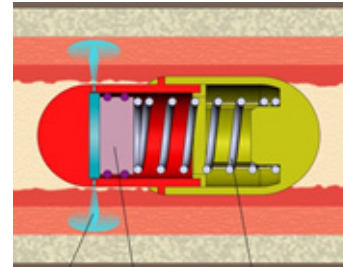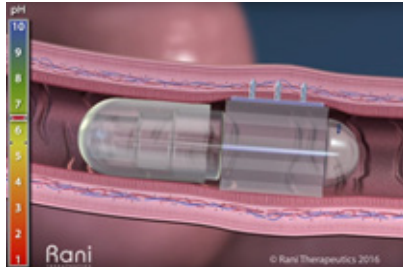
Figure 3. Engineered capsule devices for oral delivery into the gastrointestinal tract.
2a. Rani Therapeutics RaniPill™ device
2b MIT/Novo Soma™ device
2c. Baywind Bioventures Propel Biologics JetCAP™ device

Another player taking a similar approach is the group funded by MIT and Novo who are promoting their 'tortoise shell' device which is designed to orient by settling in an upright and position in the bottom of the stomach prior to deploying the microneedle. In 2019, this group also published preclinical data for insulin with about 50% bioavailability, demonstrating again the viability of this approach. REF 7

Finally, two groups are pursuing solution-based formulation approaches to inject high velocity liquid streams into the gut to achieve the same effect. The goal is to penetrate a solution of biologic drug into

the highly vascularized tissue of the gut to achieve significant bioavailability. It is anticipated that the results would be similar to the microneedle approach. One potential advantage for the systems is that higher drug loads may be achievable.

The first group is Progenity, which is funded by the company and in stealth mode with their approach. The second group is Baywind Bioventures, which is funding the Propel Biologics JetCAP technology. Stay tuned for more news in 2019 and 2020 from the solution based approach to penetrating the gut tissue. REF 8,9

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