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INSPIRATIONAL NOTE

Development and approval of rybelsus (oral semaglutide): ushering in a new era in peptide delivery

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Abstract

Achieving efficacious systemic levels of orally administered peptides is incredibly challenging due to the significant barriers to their bioavailability—their stability in the gastrointestinal tract and challenge of transepithelial transit, and variable pharmacokinetics. Even so, as the generally preferred route of administration, significant research effort in academic and industrial settings has focused on enabling the systemic absorption of orally delivered peptides. Despite several decades of research, few have ever reached the market. The recent approval of Rybelsus® (oral semaglutide) by the FDA [1], the EMA [2], and the Pmda [3] represents a significant landmark in the delivery of therapeutic peptides and is the culmination of more than 30 years research and development of the drug delivery technology enabling the product—Emisphere's Eligen™ technology—and an outstanding commitment to scientific, technical, and clinical innovation by Novo Nordisk. Following years of fundamental and applied research, an innovative clinical strategy led to the aptly named PIONEER clinical programme. This included ten Phase 3 clinical trials that demonstrated the tablet formulation to be as effective as the already approved injectable form of the drug, and more effective than competitor products in terms of its blood glucose lowering effects and weight loss. Not only is this a potentially life changing medicine for diabetic patients, it holds tremendous commercial potential for Novo Nordisk, with some analysts predicting the product to reach $5 billion in peak revenues [3]. In this "Inspirational Note," we summarize some of the public domain work that led to the achievement of this significant milestone and provide commentary on its potential future impact.

Introduction

Although there are a few marketed therapeutic peptides delivered orally, the majority are injected, as significant barriers to their absorption results in extremely low, often very variable oral bioavailability [4]. Whilst injections are a very effective method to deliver poorly bioavailable drugs into the blood stream, they are relatively difficult to administer and can be painful which can result in patient anxiety. For these reasons patient adherence to the prescribed regimen can be poor, and alternative routes of delivery for proteins and peptides have been a significant area of research in both academic and industrial settings for a number of decades, with the oral route—as the generally accepted preferred route of administration—the "holy grail" [5].

By far, the most extensively investigated approach has been the combination of including an absorption enhancer in the formulation to overcome the epithelial barrier, in conjunction with an enteric coated dosage form to protect the peptide from gastric acid and pepsin, thereby targeting the small intestine with the aim of exploiting the higher absorptive surface area.

Despite the identification of a large number of absorption enhancers using in vitro and preclinical models [6], upon clinical evaluation in humans, they were often found to be less effective than predicted with few advancing to later stages or to the market [7]. This could in large part be due to the lack of equivalence between in vitro and animal models with the human gastrointestinal tract and highlights the importance of rapid clinical evaluation in humans of novel delivery systems [8]. The many failures resulted in a great deal of skepticism that a drug delivery enabled oral peptide formulation would ever make it to the market.

Rybelsus: building on 30 years of innovation

Novo Nordisk first publicly announced they were researching oral GLP-1 and insulin in 2008, after deciding to cease development of an inhaled insulin product [9]. This was a brave step, bearing in mind some of the criticism levelled

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at the commercial failure of Exubera® (Pfizer)—an inhaled insulin and the first approved non-invasive formulation of the drug—with numerous commentators attributing the failure to the patient population being accustomed to injections and therefore not seeing the added benefit of the drug delivery enabled dosage form. Even so, if any company knew the diabetic patient population and disease biology, Novo Nordisk and its scientists were undoubtedly well placed. Having been tasked with this ambitious goal Novo Nordisk's scientists were faced with two fundamental questions: Which drug molecule (active pharmaceutical ingredient (API)) should be delivered and what drug delivery technology should be used?

Selection of the API

As a general rule, companies built on a drug delivery technology (and academics) tend to use already approved APIs to develop products (or to perform their research) and in so doing demonstrate the safety, effectiveness, scalability and regulatory acceptability of their technology, or proof of scientific concept in the case of academics. This builds the foundation for a platform technology that can be used on a number of different APIs, but also reduces the development risk associated with safety and efficacy of the drug. Part of this is through necessity—such companies rarely have a drug discovery effort and APIs can be selected close to or after their patent expiry—but also they hope that the resulting product has a competitive edge provided by their technology (e.g. safety and/or efficacy and/or patient compliance). If this can be demonstrated, it should provide them with an advantage over marketed products, making the product an attractive licensing opportunity to innovator companies as part of their product lifecycle management strategy or the company itself attractive to future investors or acquirers.

For companies working in the oral peptide delivery space, this meant they generally formulated peptides with a short half-life, requiring frequent injections, or those formulated as a sustained release formulation and injected through large gauges needle—where the advantage of an oral alternative would seem to be the greatest. In fact, a number of such companies had begun development of oral GLP-1 and/or insulin products—perhaps attracted by the ready availability of the off-patent APIs, the theoretical potential for improved efficacy by delivering directly to their site of action (the liver via the hepatic portal vein) and the large and growing diabetes market [7].

Novo Nordisk's scientists however had the opportunity to take a step back and consider what the optimum properties of a molecule for oral peptide delivery might be. The company had built up world leading expertise and intellectual property in peptide design over several decades that could be exploited to maximize the chances of success of the programme. Factors such as stability of the peptide to acid or peptidase digestion and compatibility with the delivery system could be considered on a library of compounds. However, perhaps the most insightful decision made was to formulate a long-acting analogue of GLP-1. What they appreciated was that even with the best performing drug delivery system, low and variable bioavailability would be expected. By using a long-circulating peptide, clearance out of the blood stream would be lower, allowing efficacious levels to be achieved and lower variability at steady state. To our knowledge, this was the first time a long-acting peptide had been formulated in an oral drug delivery system. It is perhaps also worth pointing out that at the time (2008) Novo Nordisk had only just filed for regulatory approval for liraglutide—a long-acting GLP-1 analogue and predecessor to semaglutide—and had just initiated the Phase 2 clinical trial on semaglutide (at that point called NN9535), so neither compound was as yet approved, but the additional risk presented did not prevent Novo Nordisk from continuing with the programme [9].

Selection of the drug delivery technology

In order to select the drug delivery technology, Novo Nordisk cast their net widely using a rigorous and systematic approach to identifying and evaluating technologies and collaborating with world leaders in drug delivery on a variety of approaches, such as an oral microneedle approach with a team at MIT [10]. NovoNordisk scientists and technology scouts became fixtures on the drug delivery conference circuit, and the same year they announced their intent to develop oral formulations of GLP-1 analogues and insulin (2008), Novo Nordisk announced they were working with two of the most established oral peptide delivery technology companies at the time, Emisphere and Merrion—each of which had their own absorption enhancer technology with clinical data showing their effectiveness in humans [11, 12]. Following clinical evaluation, Novo Nordisk selected Emisphere's Eligen technology—in particular the SNAC absorption enhancer—for further development, even so later buying some of Merrion's intellectual property in 2015 [13].

Emisphere had already clinically evaluated the site of absorption of an orally delivered peptide—evaluating their 4-CNAB absorption enhancer to enable to delivery of oral insulin, comparing the absorption when the payload was delivered either to the stomach or the small intestine. The results that showed an improved glucose lowering affect from an immediate release tablet which delivered the payload to the stomach compared to delivery direct to the small intestine, an early indication that this might be a potential site of absorption for an orally delivered peptide. This was a surprising finding as the prevailing dogma at the time was that oral peptides should target the small intestine [14].

Up until this point Emisphere had performed a number of clinical studies with a number of partners using their family of absorption enhancers, some of which entered late phase clinical trials but unfortunately failed to reach the market. As discussed above, despite early clinical validation with a range of peptides, Emisphere needed to de-risk their novel excipients for potential partners and just prior to their first work with Novo Nordisk, took the decision to develop their own product—a formulation of vitamin B12 containing the SNAC absorption enhancer to enhance bioavailability [15]. The results from the development of this product, slightly ahead of oral semaglutide, would have given the Novo Nordisk team some comfort in using the novel SNAC excipient, as it would have helped provide confidence on the safety of the absorption enhancer and regulatory acceptance, and its progress was undoubtedly closely watched. Emisphere's enabled formulation of vitamin B12 utilizing the SNAC absorption enhancer was eventually launched in 2015 [16].

Understanding the mechanism of SNAC-enabled semaglutide absorption

NovoNordisk published two studies, both of which had the aim of understanding the in vivo performance of the semaglutide/SNAC-enabled tablet formulation utilizing gamma scintigraphy. The first evaluated the erosion kinetics of a radiolabelled tablet containing both the peptide and SNAC absorption enhancer, and the resulting pharmacokinetics before and after food. This demonstrated a mean time to complete tablet erosion of 85 min and a corresponding median semaglutide plasma Tmax of 90 min, which taken together with exquisite preclinical investigations performed by NovoNordisk, indicated peptide absorption was occurring in the stomach [17]. When dosed in the fed-state limited semaglutide exposure was observed in 44% of subjects and none in 56% of subjects.

The second study also utilized gamma scintigraphy to monitor the tablet erosion kinetics and resulting pharmacokinetics, but also investigated the effect of water volume administered on dosing. This also revealed complete tablet erosion within the stomach, and reduced peptide absorption when taken with a larger volume of water, which correlated with a faster gastric emptying, once more suggesting absorption of the peptide from the stomach (Figs. 1 and 2) [18]. Both of these are important findings as they could have significant implications to patient adherence and treatment success.

Discovering that semaglutide was absorbed in the stomach in human subjects was a significant finding, as up to that point the greater surface area of the small intestine was thought to hold greater advantages than avoidance of the plethora of enzymes present to digest the drug. This finding is undoubtedly one of the most surprising findings in drug delivery in recent years and presents many questions and opportunities for further research.

Researchers at Novo Nordisk performed a significant amount of further work to better understand the findings and elucidate the mechanism of action of the absorption enhancer. They concluded that SNAC maintained semaglutide in its monomeric form, facilitated transcellular absorption across the gastric epithelia, and the high concentration neutralized stomach acid and in so doing the activity of gastric pepsin to facilitate this, and this appears to be API specific [19].

The finding that the Rybelsus formulation did not promote the absorption of co-administered drugs is an important finding (clinically validated by Novo Nordisk in at least 7 drug-drug-interaction studies) both from a safety perspective and scientifically—showing that the absorption enhancer needs to be co-located with the delivered drug to exert its affects [20].

Later stage development

To obtain regulatory approval, NovoNordisk launched the aptly named PIONEER programme encompassing 10 Phase 3 clinical trials and almost 9000 diabetic patients.

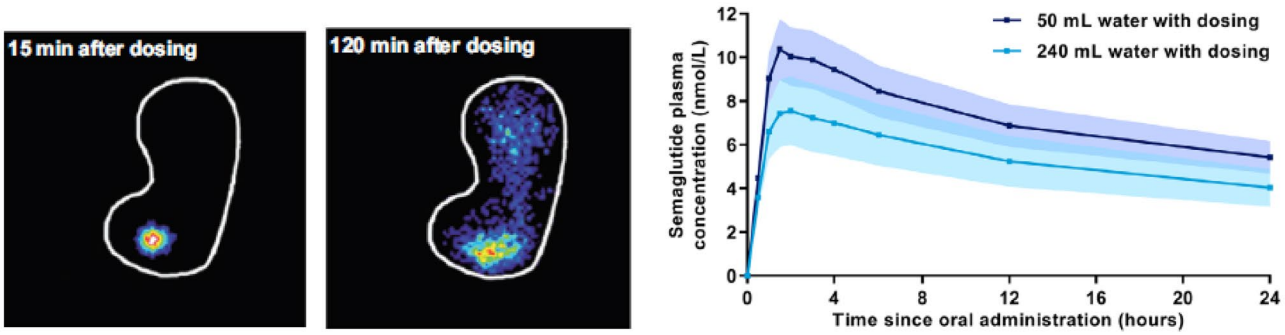

Fig. 1 Gamma scintigraphic imaging of tablet erosion in the stomach 15 min and 120 min after a single dose of 10 mg oral semaglutide containing ^{111} In labelled ion exchange resin in a representative healthy subject, and corresponding semaglutide concentration–time profile. Reproduced with permission from Baekdal et al. [18]

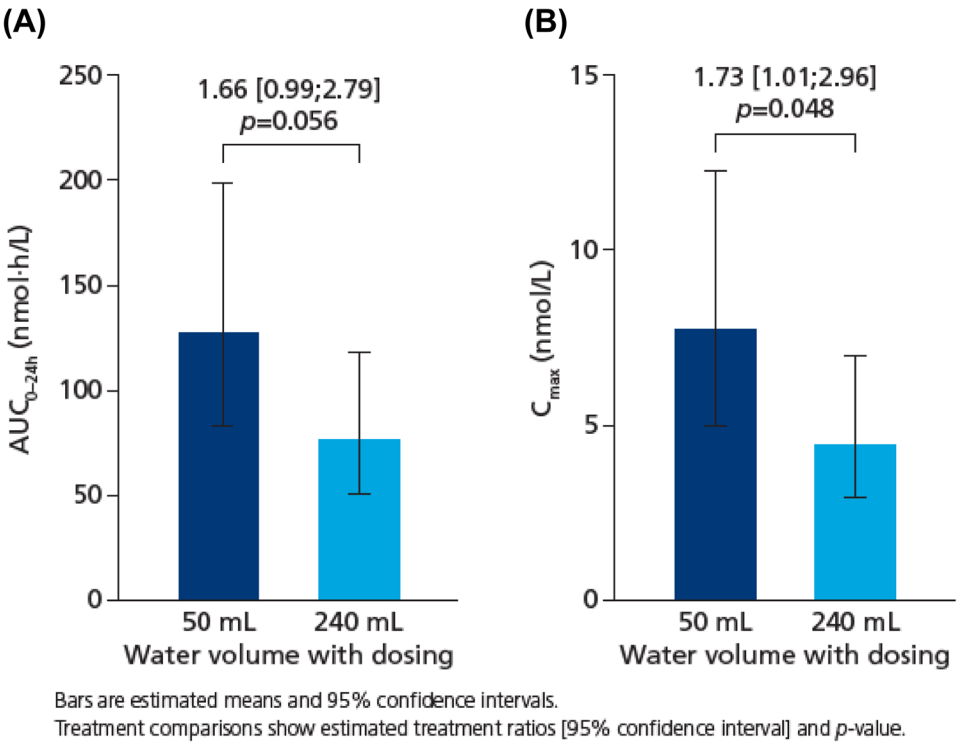

Fig. 2 Effect of water volume with dosing on **a** $AUC_{0–24\ h}$ and **b** C_{MAX} of semaglutide after a single dose of 10 mg oral semaglutide in healthy male subjects. Reproduced with permission from Baekdal et al. [18]

Furthermore, even though SNAC was shown to be effective at promoting semaglutide absorption, the bioavailability is very low—0.4–1.0% compared to 87% for the injectable form of the drug (Ozempic) [20, 21]. This meant that Novo Nordisk had to invest $2 billion alone in new manufacturing plants to supply enough API, the decision having to be made long before approval of Ozempic, demonstrating immense confidence in the drug, data on the oral formulation, and its commercial potential [22]. The results of the PIONEER programme demonstrated the oral formulation to be as effective as injection, and more effective at reducing HbA1c levels than competing products empaglifozin, sitagliptin, and weight loss than empaglifozin and liraglutide [23]. Ultimately oral semaglutide was approved by the FDA in September 2019 just 11 years after first announcing they were investigating an oral GLP-1 analogue, an amazing achievement considering the technical, clinical, and regulatory challenges faced, innovation required, and huge financial investment [20]. In November 2020, Novo Nordisk bought Emisphere Technologies for $1.8 billion to bring the drug delivery technology in-house.

The business case

The development of any new drug requires significant financial investment—magnified when a new mechanism of action or route of delivery is being explored. In the case of Ryblesus for example, significant financial investment was required—not least to enable the production of sufficient API given the low bioavailability—and the decisions for that needed to be made many years before it was certain they had a product. For Novo Nordisk, to make such investment required significant confidence in the market need and size, and a measured evaluation of the risk and the business case. This is likely to have been underpinned by their experience in the therapeutic area, robust clinical trial design and interpretation of the clinical data, and the probability of success of Ozempic (eventually approved by the FDA in 2017) [24].

However would the investment be justified? Per dose the costs of the API for Rybelsus would be far higher than for Ozempic, although it would not need a device and a sterile product. Indeed, in Novo Nordisk's "Capital Markets Day 2017" slide presentation, a unique insight is given into this with an illustrative unit cost comparison between oral semaglutide and Victoza (NovoNordisk's then approved injectable GLP-1 analogue) showing the split between API cost and delivery cost (Fig. 3) [25].

This showed that the unit cost of the oral formulation was mostly due to the cost of the API, whilst for an injectable form, the cost of the device and aseptic manufacturing predominated. Even so, the "illustrative" cost still placed the oral formulation higher than the injectable. One could imagine there being a very fine line between a positive and negative business case dependent on the cost of API, and perhaps the unsung heroes that enabled the development of the product are the peptide chemists, engineers, and scientists tasked with scaling up API production whose innovation ensured the cost of the API

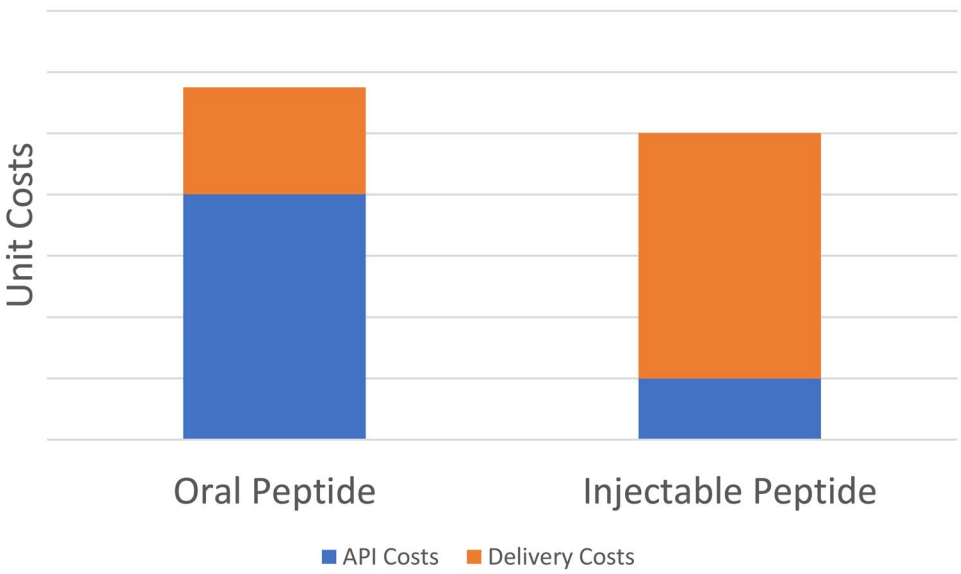

Fig. 3 Illustrative unit cost comparison of oral peptide compared to injectable form showing the contribution from API and the delivery system (tableting and packaging for oral peptide and device, formulation, filling, assembly, and packaging for injectable). Adapted from the Novo Nordisk Capital Markets Day 2017 [25]

was not so prohibitive it prevented commercial viability. It is perhaps worth noting than one would expect that by scaling up the API manufacture to meet the needs of the Rybelsus programme, the cost of goods for the API for Ozempic to be reduced, increasing that product's profitability, and in so doing de-risking the investment in API manufacturing, and the two products' development are inextricably linked. Perhaps because of this investors were later concerned Novo Nordisk might discount the price of Rybelsus in order for it to compete with other (small molecule) oral anti-diabetic medications despite [26]. On launch Rybelsus was priced similar to the injectable form, perhaps justified by its improved efficacy [27].

Future prospects for oral peptide delivery

The approval of Rybelsus is arguably the greatest innovation in peptide delivery in the last decade and was built upon years of innovation at Emisphere in development of the drug delivery technology. The persistence, dedication, and confidence of Emisphere's scientists and investors together with their scientific rigor need to be acknowledged. Many other drug delivery companies have risen and fallen in that time, and what they have achieved in conjunction with the associated innovation by Novo Nordisk is outstanding. The development of Rybelsus has stimulated similar research in almost all major pharmaceutical companies (not least Novo's competitors in the diabetes space), and many small biotechs.

This may lead to the development of more drug delivery enabled oral peptide formulations; however, the low bioavailability via the oral route will likely limit application to those where the oral route offers safety or efficacy advantages, the API cost of goods is low, or there is a large market opportunity. Furthermore, unless bioavailability can be increased much above a few single digit percent, it is likely that the first product to market for a novel API will be an injectable form. One could also imagine that a technology that could reliably increase bioavailability of semaglutide from 0.5 to 1% could make a huge impact on the cost of goods of the product making it incredibly competitive if bioequivalence could be proved. This might be achieved by designing peptides specifically for oral delivery—such as the recently published strategy by Kong et al. [28], or further advances in delivery technologies. Any increase in oral bioavailability in human subjects above that would likely enable development of oral formulations of a much wider selection of peptides—or other large hydrophilic APIs that sit outside of Lipinski's rule of 5—potentially opening up a new space of pharmacophores.

As history has proven for oral peptide delivery systems, generating data in human subjects (healthy volunteers) as quickly as possible is essential for formulations enabled with a novel drug delivery technology. Evaluating or optimizing a formulation preclinically has limited utility as animal models are at best poorly representative of human physiology and the biopharmaceutics of advanced drug delivery systems are mostly poorly understood/well characterized—unlike orally delivered small molecule drugs. For this reason, they are best explored directly in humans.

Through the development of Rybelsus, the teams at Emisphere and Novo Nordisk have not only proven the sceptics of oral peptide delivery wrong (notwithstanding that there is plenty of room for improvement and the fundamental biopharmaceutics not well understood, stimulating future work) but also innovated in numerous fields, subverted established paradigms and in so doing reinvigorated the field of oral peptide delivery, and are exemplary of innovation in its truest form—demonstrating belief, commitment, tenacity, but most of all performing exquisite science.

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