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Learnings From the Path to Ingestible Insulin Pills for Type 1 Diabetes Treatment,
and Future Ideas
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Abstract

Type 1 Diabetes (T1D), an autoimmune disease characterized by the destruction of insulin-producing beta cells in the pancreas, remains a significant global health challenge. The prevalence of T1D has been on an upward trend globally, affecting individuals irrespective of age, race, or socio-economic status. This rise calls for a deeper understanding and improvement in therapeutic approaches. Our research delves into the various stages of insulin delivery development, starting from the early days of animal insulin extracts to the latest innovations in pump therapy and continuous glucose monitoring systems. These advancements have not only enhanced glycemic control but also offered patients a more flexible and less intrusive lifestyle.

Typically known to be administered via regular injections of insulin boluses, Type 1 Diabetes treatments are a regular part of patients' lives, and the method of delivery – an injection which has to be taken frequently – often serves as an impediment to the treatment for reasons such as hesitance, fear of administering injections to oneself so often, mistakes made when trying to inject oneself, and more.

Recently, however, there have been breakthroughs in research attempting to make similar insulin boluses in pill/capsule form to achieve the same end goal. The problems that have stopped this method from being practiced historically include an incomplete induction of the required substances into the blood supply due to digestion, and the problem of adding said substances to a pill without side effects, and in reasonable, easy-to-swallow size. This is thus a question of both drug delivery, as well as diabetes particularly and the chemical role of insulin in its treatments.

This paper attempts to summarize the route insulin treatments for diabetes have taken since their inception to now, considering specifically the questions of drug delivery, motivations for change, and what this route illuminates for us going forward in the diabetes space as well as in drug delivery in general.

Layout

After a background on the disease in question and the role of insulin treatments for the disease, we will start by using a paper on human-centric drug delivery research to analyze the goals of drug vehicle optimization and the factors which play a role in patient willingness to use medicines based on their delivery mechanism.

We will then move onto a paper which outlines the history of insulin delivery for Diabetes treatment, particularly the developments that have been made and attempts to shift away from the traditional regular injections required as insulin boluses, as well as the challenges faced along the way.

Having set this context, we will review a paper produced jointly by MIT and Novo Nordisk on a potential oral vehicle for insulin, and the challenges faced in the development of this modern discovery. We will discuss the potential effects of this technology in the Diabetes space, as well as the potential extrapolation of this research in other fields of medicine apart from Diabetes.

Lastly, we will move onto a discussion of the impact of this research on Diabetes treatments, accessibility of said treatments, and whether this research can be applied or used as inspiration for further developments as well.

Type 1 Diabetes and the role of Insulin

Type 1 Diabetes (T1D) is a chronic autoimmune condition that primarily affects the pancreas, an organ crucial for insulin production. Insulin is a hormone that plays a vital role in regulating blood glucose levels. In T1D, the body's immune system mistakenly attacks and destroys the beta cells in the pancreas, which are responsible for producing insulin. This destruction leads to a deficiency or complete absence of insulin in the body.

The onset of T1D is most commonly in childhood or adolescence, but it can occur at any age. It's characterized by symptoms such as increased thirst, frequent urination, hunger, weight loss, fatigue, and blurred vision. These symptoms arise due to the accumulation of high levels of glucose in the blood, a condition known as hyperglycemia.

In the absence of insulin, the body is unable to effectively use glucose from food for energy. Instead, it starts to break down fat as an alternative source of energy, leading to the production of ketones. High levels of ketones can lead to diabetic ketoacidosis (DKA), a life-threatening condition that requires immediate medical attention.

Insulin therapy is the cornerstone of T1D management. Since the body cannot produce insulin, it must be administered externally. Insulin therapy aims to mimic the natural

patterns of insulin secretion by the pancreas. There are different types of insulin, categorized based on how quickly they work and how long their effects last. These include rapid-acting, short-acting, intermediate-acting, and long-acting insulins.

Patients with T1D typically require a combination of insulin types to maintain optimal blood glucose control. Rapid- or short-acting insulins are used to control blood sugar spikes during meals, while intermediate- or long-acting insulins provide a baseline insulin level. The administration of insulin can be done through multiple daily injections or an insulin pump, a device that delivers continuous subcutaneous insulin infusion.

The goal of insulin therapy is to keep blood glucose levels within a target range, as determined by a healthcare provider. This is crucial for preventing both short-term complications, like hypoglycemia (low blood sugar), and long-term complications, such as heart disease, kidney failure, nerve damage, and retinal damage, which can lead to blindness.

Managing T1D is a complex process that requires constant monitoring of blood glucose levels, careful insulin dosing, and lifestyle adjustments, including diet and exercise. Despite the challenges, advancements in insulin therapy and monitoring technologies have significantly improved the quality of life and health outcomes for individuals with T1D. However, there is still significant room for improvement when it comes to disruption of patient life and comfort.

The question of patient-centric drug delivery design in medicine

The paper "Development of an Insulin Pen as a Patient-Centric Multidisciplinary Undertaking" offers a comprehensive overview of how a human-centered approach to the design of insulin pens has significantly improved the management of diabetes. The discussion emphasizes the necessity of considering the patient's entire ecosystem when designing such devices.

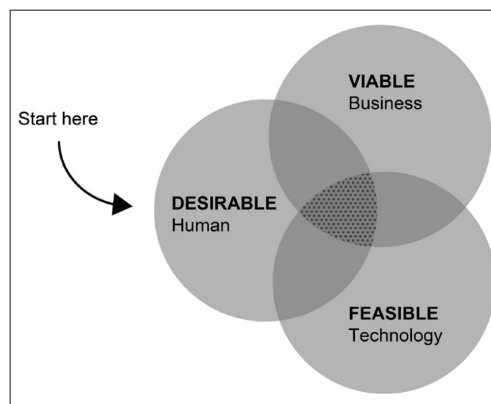


Figure 1: Human-centric design and where to start

The paper explains that human-centered design in the context of insulin pens is intended to alleviate the burden of treatment and help individuals manage their condition with as much normalcy as possible. It stresses the importance of not merely viewing individuals as patients but as users who have multifaceted lives outside their disease. This adds an element of subjectivity to an otherwise business and profitability-oriented approach of drug design which has happened historically. As seen in Figure 1, it attempts to shift the status quo from starting at the top circle, to starting at the centered one focusing on human desirability.

Using their own example of the Novo Nordisk insulin pen, which initially started out in 1985, they show how the pen design has changed through the years to the modern, latest NovoPen 6 and NovoPen Echo Plus. Despite all the changes they mention, they also emphasize the need to not change technology for the pure sake of innovation without alleviation of patient strife, which they show is translated in their technology as well, with the basic pen backbone staying the same from the very start till today.



Figure 2: Evolution of NovoPens from 1985 to 2023

It is also noteworthy how they consider adding changes like making colorful pens for child patients significant enough to describe in their pen evolution table (Figure 3), further emphasizing how viewing these changes from the lens of the patient is what must come first in all considerations. Like child patients, we also see specific catering to elderly patients – as they may have limited manual dexterity or less strength. These problems are solved through incremental changes to the traditional pen style by having shorter button travel, reduced required injection force, and larger dosage scale displays.

NovoPen Echo (2010)	<ul style="list-style-type: none"> Designed for pediatric population (available in two colors and choice of skins) Dose increments of 0.5 U Memory function End-of-dose click Short button travel to facilitate self-injection for users with little fingers 	<ul style="list-style-type: none"> In a study assessing usability and functionality among 205 children, parents, and HCPs, 80% of participants preferred NovoPen Echo to other pediatric insulin pens¹¹
FlexTouch (2013)	<ul style="list-style-type: none"> Prefilled disposable pen Large dose range (1–80 U) Large dose display Ergonomic design Low injection force required Easy touch button to facilitate device handling End-of-dose click 	<ul style="list-style-type: none"> In usability studies, patients and HCPs found FlexTouch easier to use and that it instilled more confidence than other prefilled pens¹⁸ FlexTouch was shown to deliver insulin accurately and consistently at low, medium, and high doses¹⁹
NovoPen 5 (2015)	<ul style="list-style-type: none"> Same features as NovoPen 4 Memory function 	<ul style="list-style-type: none"> Among 300 patients with diabetes, significantly more patients had increased confidence in managing their daily insulin injection when using NovoPen 5²⁰
NovoPen 6 (2019)	<ul style="list-style-type: none"> SMART insulin pen Records insulin dosing information Insulin dosing information can be viewed alongside blood glucose data, to show effects on blood glucose levels and inform diabetes management Facilitates easy transfer of insulin dosing information to other devices and HCPs Partners with compatible diabetes apps 	<ul style="list-style-type: none"> Improved insulin adherence, with fewer missed and more well-dosed mealtime injections²¹ Increased time-in-range²²

Figure 3: Incremental Changes in NovoPens from 2010 to 2019

An interesting aspect the paper highlights is the need for multidisciplinary expertise, including anthropologists, usability engineers, and medical doctors, to work alongside product development teams to incorporate patient feedback at all stages of the design process. This approach ensures that the resulting products are both functional and empathetic to the user's needs. The paper cites various examples of how this approach has been implemented, such as the consideration of dexterity issues in the elderly or the need for half-unit dosing for children, showing a deep understanding of the varying needs across different demographics.

The paper also underscores the challenge of balancing the integration of technology with usability. While technological advancements such as SMART technology in insulin pens have offered new features like dose memory and data sharing, the authors caution against letting technology dictate the design process wherever it may seem to fit. The goal is to simplify the patient's life, not complicate it with excessive data or mechanical

complexities. As the medical world progresses at an exponential rate with data sharing, the use of machine learning for personalized and catered therapeutic programs and management treatments, we must remember the prioritization of simplification throughout the process as well.

Looking forward, the paper contemplates new challenges for insulin delivery that human-centered design must address, considering the changing profiles and needs of people with diabetes. It anticipates that the evolution of drug formulations, insulin administration methods (like needle-less systems or time-release implants), and even stem cell therapies will necessitate a flexible and responsive design approach.

In summary, the paper calls for a careful balance of technical feasibility, business viability, and, most importantly, human desirability. In the views of the authors, the success of such designs is measured by their ability to blend seamlessly into the lives of users, enabling them to manage their condition effectively without it becoming the center of their existence.

The history of Insulin medicines for Diabetes with a Focus on Drug Delivery

From Banting and Best's discovery of insulin 102 years ago, in 1921, to now, insulin treatments used for people suffering from diabetes have evolved a great deal, from the actual drugs administered to the method of administration. This is summarized by Emily K. Sims et al. in the paper "100 years of insulin: celebrating the past, present, and future of diabetes therapy", which talks about how, to begin with, daily insulin injections from

glass syringes were required as treatment for all those suffering from the widely spread disease. Back then, the main challenges were in insulin extraction as well as addressing allergic reactions and unwanted side effects of the drug, and thus drug delivery and patient-centric analysis was not a priority.

This initial breakthrough of the discovery of insulin was one of the medical world's biggest milestones in the century, as it turned an 'incurable' disease to a very treatable one overnight. However, to start off, since it was being extracted from animals like pigs, and the extraction and refinement process was not as polished as today's methodology, side effects were often observed, and thus slowed down the progress of drug delivery in the starting few years.

This can be considered as the starting block from where innovation was required to make it more human-centric as well as cost-efficient for the producers and physiologically-efficient in the drug's action. It was in the 1930's that, to move away from daily required injections, long-acting insulin was researched into and discovered. Since then, the injection syringe itself, now colloquially known as a 'pen' due to the shape and self-administration, has changed considerably, making it significantly less tough to administer as opposed to regular injections from conventional medical grade glass syringes. Starting with glass syringes and moving through the development of disposable plastic syringes, insulin pens, and insulin pumps, each innovation offered improvements in ease of use, patient comfort, and more accurate dosing.

In addition to this, the extraction method shifted from initially being solely from living, large animal bodies to bacteria cloning techniques and yeast fermentation.

Advancements in insulin formulations over the decades, including the transition from animal insulin to human insulin produced via recombinant DNA technology, form a critical part of the narrative. These developments greatly reduced immunogenicity and improved patient tolerance.

Innovations were not limited to only the administration of insulin itself either: continuous glucose monitoring systems were developed in the late 1990's, which helped solve the challenge of the heterogeneity of different diabetes patients, by giving critical insights into the frequency of boluses required by the specific person being monitored. It increased reliability in the regularity of treatments administered by clinicians to patients, and laid in their own hands the judgment of delivering boluses when deemed objectively and quantitatively necessary from measurements from their own glucose levels.

Using this as a case study, it is important to note how patient needs are also constantly evolving as the discovery of better drugs and techniques do. Figure 4 shows how, where people could have been entirely wishful and 'hoping for a cure', patients nowadays are much more aware of the opportunities at the medical world's disposal, from machine learning to pump and sensor technologies, and thus require more for the patient-centric approach discussed in the previous section to be satisfied.

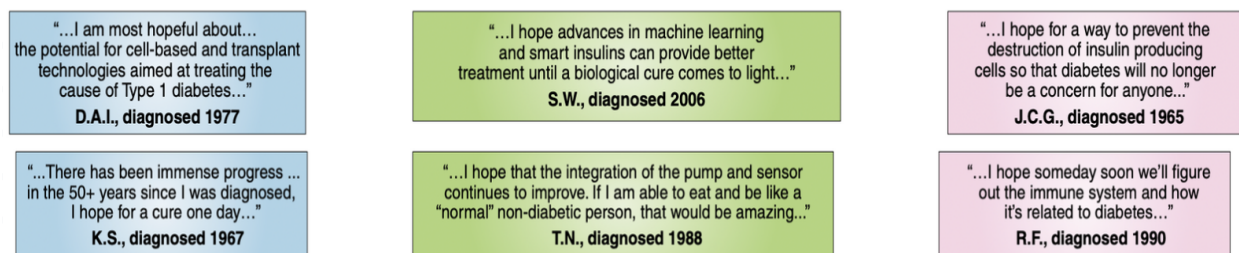


Figure 4: Patient interviews on wishes from future diabetes treatments

Not only is the method and mechanism of insulin boluses being extensively researched in hope of optimization and amelioration, but alternative treatments are also being looked into to potentially completely remove the need for a recurrent, repeated delivery of insulin to the body. The most prominent of these alternatives being researched include cell therapy, disease-modifying therapies, and technologies including artificial pancreas' and hormone pumps. However, since this paper is focusing on insulin delivery evolution and future potential, we will not go into further detail about said alternatives. It is sufficient to say that each of them are in early stages of research at the time being.

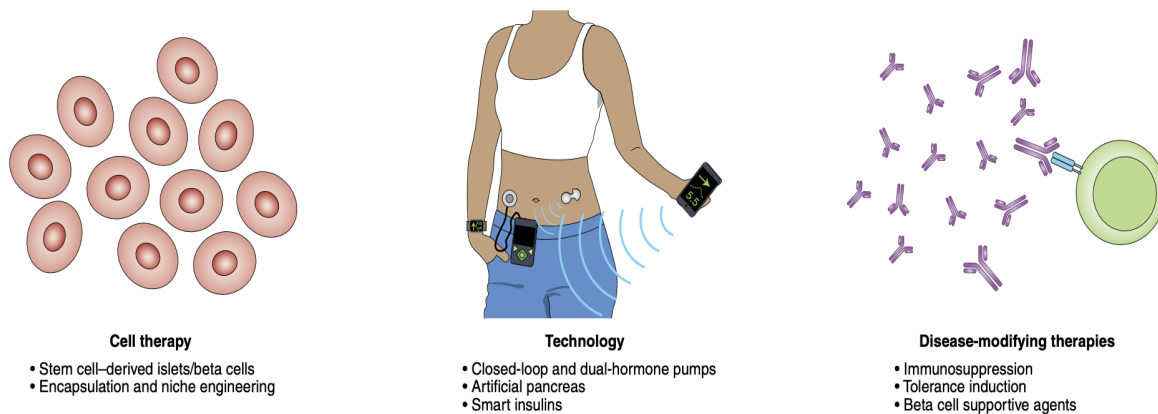


Figure 5: Alternative treatments to Type 1 Diabetes under consideration

Current Attempts at oral ingestible insulin pills

The paper “Oral insulin reloaded: a structured approach” gives examples of attempts made at oral insulin alternatives to the status quo of injectable boluses. We will be looking at a few such examples, discussing the methodology adopted and the projected outcomes and aims, with challenges faced and why they may not be viable alternatives. Finally, we will discuss the experimental design done by MIT and Novo Nordisk scientists to compare it to the other attempts and discuss possible roadblocks it could face down the road to becoming a feasible delivery mechanism.

As stated in the paper, the two major challenges which have halted oral insulin from taking over injectable insulin pens, which have practically remained the significant challenges to this switch ever since the 1930’s, are as follows: the high within-subject variability of the pharmaco-dynamic effect, and the low bioavailability requiring enormous doses as compared to subcutaneously injected insulin.

Despite these challenges, however, given how significant a breakthrough in this pursuit would be, with the prevalence of diabetes only showing an upward trend, and the hesitance and noncompliance with injectable insulin treatments across a large portion of patients, Figure 6 shows us how research in this field has only increased over the years.

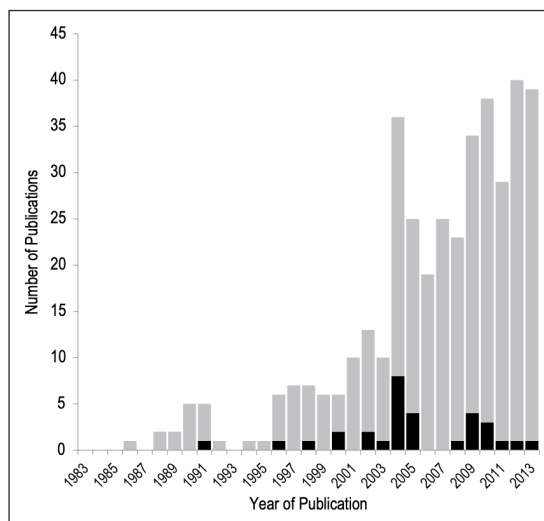


Figure 6: Number of Publications on Oral Insulin published per year

Not only would oral insulin vastly increase patient comfort and compliance with assigned treatments, it could also potentially show other advantages as compared to subcutaneous injections. Oral insulin will reach the circulation via the hepatic portal vein similar to endogenous insulin, whereas subcutaneous injections primarily induce high systemic levels of insulin, bearing a greater risk of side effects such as hypoglycemia and weight gain. This only shows more motivation and justifies the rise in research observed.

Looking at some specific examples, Biocon came up with an oral insulin compound with a polyethylene glycol side chain to improve stability and solubility, and this absorption and pharmaco-dynamic activity. However, stability meant that the pill's contents were not entirely taken into the bloodstream and thus dosage was not seen to be enough in statistically significant proportions of the testing population. Additionally, these pills had an added constraint of needing to be ingested immediately before meal intake, which

could potentially lead to side effects or inefficacy if patients were to deviate from instructions, which literature informs us to rely on.

Diabetology has also been working on its oral insulin based on their patented Axxess delivery system, based on an enteric-coated capsule filled with insulin and solubility enhancers. However, testing was unable to show clear, dose-dependent plasma insulin responses in an unequivocal manner. This was hypothesized to be due to an inadequate amount of starting insulin in the pill designed, after accounting for added loss of insulin as compared to subcutaneous injection.

Most other attempts are all early-phase, feasibility, and proof-of-concept trials with a small number of subjects tested. However, the prevalent issues within those remain the same. It is either an issue of not being able to fit enough insulin in the pills as literature informs us is required to maintain stability of insulin/glucose levels over week-long timescales, or the pills were unable to be absorbed to a great enough extent to allow the insulin within them to be operational. Orally administered therapeutic proteins must navigate extremes of pH, protease-rich environments, thick mucus layers, and cellular tight junctions before achieving systemic bioavailability.

If insulin analogues were used to increase solubility, their bioactivity was severely hampered, given that all the literature that exists is based on very specific compounds and thus does not show proof of efficacy for analogues with mutations or additional side groups introduced for added benefits. For nanoparticle-based systems to transport insulin across the intestinal barrier, the challenge was to efficiently and safely transport the insulin without alteration in its action. For pills using permeation enhancers to allow

increased absorption by the gut for a short period of time, concerns of long-term, persisting impacts on the gastrointestinal health of the individual were rightly considered and served as big halts.

SOMA - Analysis of a Potential Future for Oral Insulin

We shall now focus on a new idea proposed by a joint team of MIT professors and scientists at Novo Nordisk, outlined in a paper termed “An ingestible self-orienting system for oral delivery of macromolecules”. This paper presents a novel system for delivering large biomolecules orally. This system is inspired by the leopard tortoise's ability to reorient itself, leading to the development of the Self-Orienting Millimeter-Scale Applicator (SOMA). SOMA can autonomously position itself in the gastrointestinal tract to release drugs directly into the gastric mucosa, bypassing issues like degradation and poor absorption in the gastrointestinal tract that usually limit oral administration of biomacromolecules.

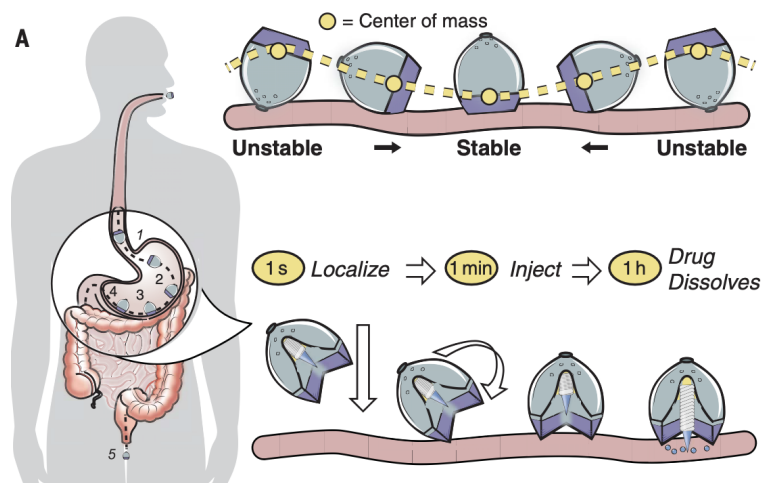


Figure 7: SOMA orienting mechanism toward stomach lining

Once in position, it then deploys milliposts fabricated from active pharmaceutical ingredients directly through the gastric mucosa while avoiding perforation. When conducting in vivo studies in rats and swine, the applicator's safety was proven, and, using insulin as a model drug, the SOMA's delivery of active pharmaceutical ingredient plasma was established, with levels comparable to those achieved with subcutaneous millipost administration.

Although the paper is vague in its title and scope, the ingestible technology proposed was considered under the lens of oral insulin bolus administration as the primary case for scientific context, material choice, and more, and it also mentions insulin as the drug to be delivered whenever discussing particular Active Pharmaceutical Ingredients (API's) to be delivered through their technology.

The design of SOMA is such that it ensures that it quickly self-oriens and remains stable in the stomach. The device uses a combination of materials to achieve a low center of mass essential for self-orientation. Its monostatic body also gives it great stability to remain in position to inject the drug required once it has stabilized in its required conformation. The paper even compares this design to a 'weeble-wobble toy'. This design was validated through simulations and in vitro studies. The drug is loaded into the SOMA in the form of a millipost, which is then deployed through the gastric mucosa.

The material used to make this pill is a combination of low-density poly-caprolactone (PCL) and high-density 316L stainless steel to produce the low center of mass needed for the SOMA to self-orient.

The decisions made in the mechanism of digestion and absorption are made in lieu of overcoming the challenges faced by biomacromolecules in surviving the harsh environment of the GI tract. This includes dealing with extreme pH levels, enzymes, and mucus barriers. The use of SOMA aims to directly insert the drug into the stomach wall, thus avoiding these barriers.

The fact that it aims to inject the API of the drug into the lining wall of the stomach makes it significantly safer as compared to intestinal walls, given that stomach walls are 4 to 6 mm thick, whereas intestinal walls range from 0.1 to 2 mm thick walls, meaning there would be a much higher risk of injury or tear if the SOMA were to attempt its perfusion there. Additionally, “gastric tissue regenerates quickly, and the fluidity of the mucous barrier seals temporary defects in the lining”.

Not only does this decision make the delivery safer, it also ensures a more efficient administration of the required API. Given the earlier stage in the digestive process of the stomach, the dose delivery time is both quicker and more predictable (since gastric emptying is recognizably and predictably modeled).

About the size of a blueberry, the capsule's small form factor also means that it passes the hurdle faced by many oral insulin pills of being too large in size to easily ingest. In tests in animals, the researchers showed that they could deliver enough insulin to lower

blood sugar to levels comparable to those produced by injections given through skin. They also demonstrated that the device can be adapted to deliver other protein drugs.

Although this design does address many of the challenges discussed above, it still raises a number of questions as to whether its tests would be able to translate seamlessly into the human body, and whether it would be able to administer as high degrees of the biomolecules required in humans as well.

First and foremost, the mechanism of using minute needles to inject the biomolecule into the stomach lining walls raises the obvious concern of leaving lasting and persistent tears, cuts, or troughs, in the stomach wall. Although its thickness, coupled with the activity of mucous membranes in the stomach, mean that this is unlikely, it can be a problem especially in patients whose stomach linings happen to produce less mucous, for example. Furthermore, the ability of SOMA to self-orient would also potentially be dependent on the time of meal intake of the patient before or with the pill, given that exaggerated movements of the stomach in churning and digesting could disrupt the orientation of the SOMA, effectively negating its entire mechanism of drug delivery. Thus, next steps definitely include further clinical testing in perhaps more extreme, dynamic stomach environments to test orientation, and testing with longer timescales to investigate whether there are any long-term effects of the repeated gastric wall injections.

However, all things considered, this paper can be used as an example as to how we can innovate to find patient-centered drug delivery techniques by adapting to challenges and taking inspiration from other species or mechanisms around us. Given the

frontmost challenge of less induction of drugs through ingested pills as opposed to subcutaneous injections, this idea navigates this by essentially designing an ingestible injection which does not depend on the digestive system to run its course for the contents of the drug to be taken into the bloodstream at varying degrees. I believe that this ties in well with the previous section about how patient-centric approaches must be at the forefront of drug delivery research.

Next Steps and Application to the Broader Question of Drug Delivery Mechanism

As far as Type 1 Diabetes goes, the paper “Oral Insulin Reloaded: A Structured Approach” deems recent efforts to shift to oral bolus administration as ‘disappointing’ and ‘slow’. However, it is imperative to note that the challenges facing shifting insulin delivery from pens to pills are substantial. That being said, with many different groups involved in research, and clinical trials picking back up after the pandemic as well, I hope that efforts continue to rise as we saw that they have been, and that a breakthrough be made to alleviate so many patients from so much discomfort.

Extrapolating this to the topic of patient-centric drug delivery in general, though, is also interesting. In any disease treatment which, as the status quo, exists as an ‘unpreferable’ technique – be that syringes or self-administered pens or frequent visits to the doctor for tests – the underlying reason is definitely our inability to conquer the challenges which stop the alternative from immediately taking over. However, at least in particular for other diseases which still depend on syringe-injectable API’s as their primary treatments, this research can provide insight into what the major challenges

faced are, and what routes can be taken to bypass them. The paper analyzed which proposed SOMA, for example, does a good job in maintaining its general applicability to the delivery of what it terms as biomolecules. In a similar vein, the other pill designs and technologies discussed, and researched for insulin treatment (given that insulin treatment is one of the most researched and profitable pharmaceutical fields thanks to the wide reach of diabetes across the United States and the world at large), also all include elements which can be extrapolated to illuminate challenges or breakthroughs in other treatments.

The question about when insulin treatments themselves will shift to oral administration does not have a reliable answer. If the initial discovery of insulin itself as a treatment is any indication, it could be very soon. Given the challenges and the time they have persisted, however, it could very well not be.

Annotated Bibliography and Citations

1. Thomas Sparre et al.: *Development of an Insulin Pen is a Patient-Centric Multidisciplinary Undertaking: A Commentary* (J Diabetes Sci Technol. 2022 May;16(3):617-622. doi: 10.1177/19322968211058707. Epub 2021 Dec 1. PMID: 34852662; PMCID: PMC9158249.)

This paper, by Novo Nordisk researchers, focuses on patient-centric drug delivery mechanisms, which shine light on the drug delivery process and philosophy as a whole, within the context of diabetes and out of it as well. It describes the goal of drug delivery research as the attempt to relieve the treatment burden of a chronic condition and help affected individuals to feel free of disease. It discusses this goal in the context of Insulin pens, initially created by Novo Nordisk, which alleviated much of the burden originally associated with Insulin injections which required medical professionals to administer them regularly to the patients, leading to inaccessibility, cost, and other concerns.

2. Emily K. Sims et al.: *100 years of insulin: celebrating the past, present, and future of diabetes therapy*

This paper provides a comprehensive roadmap of the use of insulin as a treatment for diabetes, all the way from its discovery in 1921, to its uses today and how diabetes treatment therapies have evolved in technology and philosophy. It also includes alternative treatments being researched, and delves deep into the physiological and pharmaceutical reasons for insulin's efficacy for diabetes patients.

3. Zijlstra E, Heinemann L, Plum-Mörschel L.: *Oral insulin reloaded: a structured approach*. (J Diabetes Sci Technol. 2014 May;8(3):458-65. doi: 10.1177/1932296814529988. Epub 2014 Apr 7. PMID: 24876606; PMCID: PMC4455450.)

'Oral Insulin Reloaded' provides a detailed overview of the various attempts made through the years for an oral insulin pill as an alternative to injectable insulin bolus administration. It also engages in data analysis on the overall degree of research conducted over the years on this topic. For each different company/endeavour it mentions, it included figures, the progress that the pill has made in clinical trials, as well as any blockades that it has faced. It takes a systematic approach using various forms of data analysis and historical trendsetting to show all the different attempts at oral ingestibles, pens and injections for Insulin treatments, as well as discussing the problems associated with each of these. It lays the groundwork to discuss future potential in this field very well, by comprehensively showing the main challenges in the field.

4. Alex Abramson *et al.*: *An ingestible self-orienting system for oral delivery of macromolecules*. (Science **363**,611-615(2019).DOI:10.1126/science.aau2277)

This paper from MIT, with research funded by Novo Nordisk, the National Institute of Health, the National Science Foundation Graduate Research Fellowship, Brigham and Women's Hospital, and a Viking Olaf Bjork Research Scholarship, looks at the development of an ingestible delivery vehicle which tried to counter the fact that insulin and other deliverables cannot survive passage through the stomach and gastrointestinal

tract. The problem with other ingestible vehicle attempts at delivering insulin was the insufficient levels of insulin actually being delivered to the bloodstream through the digestive system.