Biotechnological Advances in GLP-1 Receptor Agonists: Development, Optimization, and Market Dynamics

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Abstract. Glucagon like peptide-1 (GLP-1) receptor agonists are consequential when managing obesity and type 2 diabetes mellitus (T2DM). They regulate blood glucose level and body weight by simulating the function of natural GLP-1. Through interaction with GLP-1 receptors, GLP-1 agonists activate adenylate cyclase and further trigger downstream cascades such as protein kinase A and RAPEGEF4. This could ultimately inhibit the release of glucagon, and at the same time proliferating insulin, which would then lead to decelerated emptying of gastric system and accelerated sense of satiety. In recent years, advances in biopharmaceutical engineering, such as protein engineering and peptide synthesis, have improved the pharmacokinetic properties of GLP-1 agonists, including prolonging half-life, enhancing stability, and reducing dosing frequency, thereby improving patient compliance. In addition, innovation in biotechnology has driven the development of GLP-1 and biosimilar drugs. The current mainstream delivery methods include subcutaneous injection and oral medication, while new delivery systems such as nanoparticles and microneedle patches further optimize the stability and bioavailability of drugs. This article reviews the latest biotechnology progress, optimization methods, production processes, market trends and future trends of GLP-1 receptor agonists, aiming to provide insights into the future development of GLP-1 agonists in diabetes management, and explore their potential applications in personalized medicine and combination therapy.

Keywords: GLP-1 receptor agonists; Type 2 diabetes; Protein engineering; Drug delivery systems; Biosimilars.

1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists are important in the management of weight control and T2DM. As synthetic analogs, these agonists would respond to food intake and be released, acting like natural GLP-1 hormones. GLP-1 agonists interact with GLP-1R and then activate adenylate cyclase (AC), which would then convert ATP to cyclic adenosine monophosphate (cAMP). This will further activate protein kinase A (PKA) and Rap guanine nucleotide exchange factor (RAPGEF4 or EPAC2) [1]. GLP-1 could ultimately inhibit the release of glucagon, and at the same time proliferating insulin, which would then lead to decelerated emptying of gastric system and accelerated sense of satiety. Glycemic control is augmented and weight loss is targeted, which would make GLP-1 receptor agonists an ideal therapeutic option for patients with T2DM and in need of weight management. Prevalent intake methods are subcutaneous injection and oral medicine. Current major GLP-1 agonists include liraglutide, semaglutide, and dulaglutide, each with different pharmacokinetic profiles and dosing regimens.

Recent developments in biopharmaceutical engineering demonstrate the efficacy enhancement potential of GLP-1 agonists, while improving patient adherence and expanding therapeutic applications. These advances such protein engineering, formulation technology, and amino acid modifications could lead to longer half-lives of the medicines, thereby less dosing frequency, and stronger resistance against degradation. The biotechnological advancements also facilitate the development of biosimilars, which rely on the study of GLP-1 analogs.

This essay aims to review the latest advancements in the biotech landscape that influence the development, design, production, and market dynamics of GLP-1 receptor agonists. The discussion will cover the prevalent biotechnology methods and optimisation, manufacturing process, current market and regulations, as well as future trend. This review aims to offer insights into how ongoing

research and development may shape the future of GLP-1 receptor agonists and their impact on diabetes management by integrating latest research and industry trends.

2. GLP-1 Technology Introduction

The development of GLP-1 agonists represents a major advancement in treating T2DM and obesity. Leveraging various biotechnological methods, GLP-1 agonists can be strengthened using technologies such as recombinant DNA, protein engineering, and peptide synthesis, to create more effective therapeutic agents. Recombinant DNA technology involves the insertion of gene expressing GLP-1 into a plasmid vector, followed by introduction into host cells, typically bacteria or yeast. These host cells would then express the GLP-1 peptide, which allows for production on a large scale. Applying recombinant DNA technology ensures that the produced peptides are identical to the naturally occurring GLP-1. Protein engineering could potentially enhance pharmacological properties of GLP-1 agonists. Through modifications of the amino acid sequence of GLP-1, pharmaceutical companies have already developed analogs that have stronger stability, longer half-life, or better affinity. Some usual improvements include substitution to reduce susceptibility to enzymatic degradation, creating long-acting GLP-1 agonists and thus reducing dosing frequency. Solid-phase peptide synthesis (SPPS) is another method frequently used in the development of GLP-1 agonists, which contributes to precise assembly of peptide chains and creation of modified GLP-1 analogs with enhanced properties. SPPS facilitates the intake of non-natural amino acids, thus improving the pharmacokinetic and pharmacodynamic profiles of the peptides.

Biologics including peptide-based drugs like GLP-1 agonists are significantly different from small molecule drugs. Whereas small molecules generally have lower molecular weights and are often synthesized through chemical processes, biologics are larger and more complex molecules derived from living organisms. This allows biologics to interact with biological systems in more sophisticated ways, leading to enhanced specificity and efficacy. In the case of GLP-1 receptor agonists, the peptide nature is crucial for correctly expressing physiological effects of GLP-1, including stimulating insulin secretion and inhibiting glucagon release. The unique structure of these biologics allows for glucose homeostasis control, acting as basis of the most significant peptide therapeutics for metabolic diseases [2].

Delivery method and system are also essential to GLP-1 agonist therapeutic success. Recent innovations in drug delivery systems aim to improve the stability and bioavailability of these biologics. Long-acting formulations of GLP-1 receptor agonists are defined to have a minimum of 24-hour duration of clinically relevant effects after administration [3]. These formulations use various techniques, including microspheres or liposomes, to encapsulate the peptides, thus leading to sustained release over time. This innovation reduces the need for frequent injections and improving patient adherence to treatment regimens. The use of nanoparticles in drug delivery systems are also advantageous, as nanoparticles can enhance the stability of GLP-1 agonists by protecting them from premature interaction and degradation in the biological environment such as gastrointestinal tract, thereby enhancing permeation and retention effect and improving oral bioavailability [4]. Innovations in oral delivery methods for peptide-based drugs are also being studied. Enteric coating is a common procedure and it helps prevent the drug from acidic environment and enzymatic degradation [5]. Applying absorption enhancers such as 1-phenylpiperazine (PPZ) and sodium deoxycholate (SDC) have also been proved to be able to increase oral delivery of macromolecules up to 70 kDa in size [6]. Successful application of these techniques could improve patient experience.

3. Drug Engineering and Optimization

Protein engineering has been employed to enhance GLP-1 agonists. Previous experiments have focused on various improvements, such as augmenting efficacy, prolonging half-life and duration of action, as well as increasing stability against degradation. Picha et al. engineered a protein called

CNTO736 based on their proprietary MIMETIBODY platform [7]. By fusing the GLP-1 receptor with an antibody Fc domain, this new protein demonstrates an improved pharmacokinetic profile, offering a longer duration and sustained efficacy in reducing blood glucose levels. Additionally, the protein retains the characteristics of native GLP-1 agonists. Lei Sun et al. explored potential improvements through protein engineering to resist dipeptidyl peptidase-4 (DPP-4) degradation [8]. A cysteine mutation introduces an intra-chain disulfide bond, resulting in a spatial change between the antiparallel β-folded domain and the GLP-1 molecule [8]. This modification enhances the action of GLP-1RAs by making them less susceptible to DPP-4 degradation, thereby strengthening their resistance to breakdown. Matthieu Chodorge et al. fused the GLP-1 receptor with proprotein convertase subtilisin/kexin type 9 (PCSK9) [9]. This dual-action molecule not only lowers LDL cholesterol and improves glycemic control but also shows enhanced therapeutic efficacy for Type 2 Diabetes and favorable manufacturability.

Few comprehensive structure-activity analyses have been performed on GLP-1. A more thorough examination was conducted in 1994 by Kim Adelhorst et al., focusing on identifying important residues for receptor affinity [10]. His, Gly, Phe, Thr, and Asp all contain side chains that are crucial for receptor interaction, and substitution of these residues reduces both receptor affinity and the capacity to activate adenylyl cyclase [10]. They also revealed that substitution of Phe and Ile could potentially affect the secondary structure of the peptide and induce conformational changes [10]. This was further studied by Bikash Manandhar et al. in recent years, who hypothesized that the C-terminal appears essential for receptor binding, while the N-terminal plays a more critical role in receptor activation [11]. When designing Semaglutide, one of the most prominent GLP-1 drugs, Novo Nordisk aimed to prevent the binding of GLP-1 analogs to albumin, which would negatively impact drug affinity due to competition with receptor binding [12]. One solution, based on structure-activity analysis, was to substitute Ala with Aib at position 8 of the peptide backbone [12]. This substitution was found to improve binding affinity and resistance to degradation [12].

Abundant studies have been conducted on the efficacy and safety of GLP-1 agonists. En-Hao Hu et al. compared the efficacy of various GLP-1 drug products and summarized the effectiveness order for both glycemic control and weight loss as follows: 1 mg of semaglutide, 1.8 mg of liraglutide, 1.5 mg of dulaglutide, 50 mg of albiglutide, 2 mg weekly of exenatide, and 10 μg twice daily of exenatide [13]. Due to the presence of a bypass effect, oral dosage and subcutaneous injection demonstrate different levels of efficacy.

Numerous safety concerns have been associated with GLP-1 agonist drugs. Diarrhea, nausea, vomiting, and injection-site reactions or nodules are among the most common adverse effects. Different analogs also exhibit varying adverse reactions. Based on previous studies, diarrhea is the most prevalent adverse effect for albiglutide, while nausea is most common for dulaglutide (regardless of dose), liraglutide, and exenatide [14]. No evidence of a correlation between GLP-1 agonist use and symptoms such as hypoglycemia and cardiovascular risk has been found, though a potential association with acute kidney injury remains possible [15].

Protein engineering offers effective ways to mitigate the side effects associated with GLP-1. Michael Garton et al. utilized a mirror image version of the protein data bank and converted (L)-peptides to more stable (D)-analogs [16]. This engineered version of GLP-1 agonists successfully activates GLP-1 receptors, offering stronger stability and potentially reducing adverse effects caused by DPP-4 degradation.

4. Manufacturing Process

During the manufacturing of GLP-1 agonists, one of the most commonly used technologies is recombinant technology. Due to E. coli's rapid growth rate and its capability to produce high yields of recombinant proteins, it is the most frequently used bacterial expression system in GLP-1 agonist manufacturing. Fangfang Xu et al. recently created a GLP-1 variant called 6xmGLP-1 using E. coli, achieving a yield of around 20 mg/L [17]. The expression system included codon optimization and a

His-tag on the C-terminus, facilitating isolation through chromatography. Through recombinant technology, 6xmGLP-1 has enhanced resistance to DPP-4 degradation, thus offering better therapeutic potential [17].

In addition to E. coli, other cell lines, such as yeast and mammalian cells, can also be used. Yeast systems can provide post-translational modifications, which may be advantageous for GLP-1. Qing Wang et al. successfully expressed a GLP-1 analog in Pichia pastoris, achieving high yields and functional success [18]. Beyond yeast, mammalian cell systems, such as Chinese hamster ovary (CHO) cells, are also viable options. Zhikai Zheng et al. demonstrated that GLP-1 agonists produced in CHO cells exhibit improved half-life and stronger bioactivity compared to those produced in bacterial systems, resulting in better therapeutic outcomes [19]. A key difference is that mammalian cell lines enable precise editing, such as fine-tuning glycosylation patterns, which enhances overall efficacy [20].

In the manufacturing of GLP-1 agonists, the purification process is also crucial. Contaminants in the products can easily impair bioactivity and safety, rendering the entire product unusable. Purification involves several stages. The first step is affinity chromatography, followed by further refinement. Additional techniques, such as reversed-phase high-performance liquid chromatography (RP-HPLC), can improve purity levels to meet clinical application standards [20]. Often, more advanced purification steps are required to achieve higher levels of quality. These processes ensure that the final products maintain structural integrity and exhibit the desired biological activity.

Advanced technologies have also focused on enhancing the pharmacokinetic properties of GLP-1 agonists. A protein developed by Sam Lear et al. demonstrated greater stability and half-life through polyethylene glycol (PEG) stapling technology [20]. By attaching PEG moieties to peptides through covalent bonding, solubility, half-life, and resistance to proteolytic degradation are significantly improved. PEGylation also reduces the immunogenic potential of therapeutic peptides, allowing for greater tolerability in patients, which is essential for drug development.

The overall manufacturing process can be divided into four steps: raw material verification, in-process quality control, final product testing, and compliance check. This system is designed to ensure the safety, efficacy, and consistency of the product. For raw material verification, all raw materials must meet predefined specifications. Tests in this stage include high-performance liquid chromatography (HPLC) and mass spectrometry to assess the purity of the materials. In-process quality control focuses on monitoring conditions (temperature, humidity, pH, time, etc.) to ensure that manufacturing proceeds according to design. Intermediate products are often analyzed for potency and purity to confirm they meet quality standards before advancing to the next stage of production, thereby increasing the overall qualifying rate. Potency assays measure the biological activity of these intermediate products and are key to ensuring that any modifications during synthesis have not adversely affected efficacy.

Final products are tested against stringent standards to confirm their qualification. Potency, purity, and stability are all examined at this stage. Potency tests are often conducted in vitro, primarily to verify that GLP-1 agonists can successfully activate GLP-1 receptors. Stability tests include accelerated stability studies in which products are tested under various conditions. Purity tests assess the purity of the products, using techniques such as HPLC and capillary electrophoresis to detect contaminants or degraded products. These tests complement each other to ensure product quality. Finally, manufacturers must ensure compliance with regulations and adherence to GMP standards, as all processes are subject to inspection and regulation.

Mass manufacturing presents additional challenges. The first is ensuring bioactivity across all batches and materials used during the process. Controlled environmental conditions are crucial in this case, as peptides are sensitive to slight environmental changes. Another consideration is to apply regular bioassays on the products to ensure consistent pharmacological activity of GLP-1 products. The second challenge is achieving consistency across batches. Implementing SOPs for purification, formulation, and synthesis can help maintain controlled production conditions. Batch record documentation is also essential as a reliable method to track products. Regulations for mass

production are stringent, so consistent employee training and quality management systems (QMS) are necessary to rigorously oversee manufacturing processes.

5. Market and Regulation

The GLP-1 agonist market has seen significant growth over the past several years, driven by blockbuster drugs entering the market and strong demand. The growing population of type 2 diabetes patients, along with individuals pursuing weight loss management, are increasingly seeking GLP-1 agonist drugs for treatment. The global GLP-1 agonist market was valued at approximately USD 36.79 billion in 2023 and is expected to reach USD 138 billion by 2031, with a CAGR of 18.0% [21].

The number of diabetes patients is projected to reach 700 million by 2045. The weight loss market is also expanding, with a target market size of USD 405 billion by 2030 [22]. This growth is driven by an increasing awareness of healthy lifestyles, obesity as a key contributor to various issues like cardiovascular disease, and the need for weight control. Both the diabetes and weight loss markets are substantial, with vast growth prospects.

The competitive landscape for GLP-1 receptor agonists is dynamic and rapidly evolving. Large pharmaceutical companies such as Novo Nordisk, Eli Lilly, and Sanofi dominate the market with their blockbuster products, including semaglutide (Ozempic/Wegovy) from Novo Nordisk, tirzepatide (Mounjaro/Zepbound) from Eli Lilly, and dulaglutide (Trulicity), also from Eli Lilly. Each medication offers distinct advantages, intensifying competition in terms of efficacy, safety profiles, and patient adherence. Novo Nordisk's semaglutide is known for its impressive weight-loss results and convenient mode of administration. The launch of Wegovy, specifically approved for weight loss management, has further strengthened Novo’s leading position in the market. Meanwhile, Eli Lilly's tirzepatide, also approved for obesity management, has shown promising results in clinical trials. In addition to competition within the GLP-1 agonists category, these medications also face challenges from other treatment options for obesity and diabetes. Alternatives, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors, are also in use. While GLP-1 receptor agonists provide unique benefits that have made them highly desirable and advantageous, the presence of alternative therapies implies a need for continuous research and differentiation to defend and further capture market share.

Looking ahead, the future of the GLP-1 receptor agonist market is promising. The increasing prevalence of obesity and type 2 diabetes, coupled with growing awareness of the importance of weight management in chronic disease treatment, drives persistent demand for these medications. Simultaneously, ongoing research and development in GLP-1 agonist drug candidates will continue to strengthen the supply side, propelling the overall growth of the drug market. This may lead to longer-lasting formulations or improved efficacy. Protein engineering technology, as discussed in previous sections, could play an important role. Another area to explore is combination therapies that pair GLP-1 agonists with other molecules, such as SGLT-2 inhibitors. The introduction of oral formulations also marks a significant milestone, enabling patients to choose an alternative method to subcutaneous injection. A near-term focus could be on developing more oral formulations, which could enhance patient adherence. This shift aligns with consumer preferences for less invasive treatment options. Additionally, more personalized medicine could be explored. Tailored treatments may provide greater efficacy by being more specific to individual patients. As pharmaceutical companies continue to innovate and expand product offerings, the competitive landscape is likely to evolve, providing more options for patients and healthcare providers. The overall GLP-1 receptor agonist market is poised for sustainable growth, driven by the rising number of type 2 diabetes and obesity patients, intense competition among existing drugs, and the emergence of new treatment modalities.

The approval processes of regulatory bodies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are essential in ensuring the safety and efficacy of these medicines. The FDA and EMA have established rigorous frameworks for the evaluation of new drugs, including GLP-1 receptor agonists. The FDA's approval process involves several phases, beginning

with preclinical studies to assess the drug's safety and biological activity. After obtaining successful preclinical results, the pharmaceutical company submits an Investigational New Drug (IND) application, which must be approved before clinical trials can commence. Clinical trials are conducted in three phases, with each phase designed to gather specific data on the drug's safety, efficacy, and optimal dosing. Upon completion of the three clinical stages, the manufacturer submits a New Drug Application (NDA) to the FDA, including all data from previous preclinical and clinical trials. The FDA reviews this application, and if the drug meets the standards, it is granted approval for marketing. The EMA generally follows a similar process, requiring comprehensive preclinical and clinical studies for approval.

For GLP-1 agonists, the FDA typically requires a statistically significant reduction in HbA1c levels, often expecting a decrease of at least 0.5% to 1% from baseline in clinical trials. For weight loss indications, a mean weight loss of at least 5% of body weight is often targeted for approval, with statistical significance ($p < 0.05$) compared to placebo. Regarding adverse events, the FDA generally expects an incidence rate of less than 5% during clinical trials. For long-term safety, Phase 3 clinical trial data should demonstrate that serious adverse events remain low over extended periods (typically 6 months to 2 years). P-values are expected to be less than 0.05 for efficacy outcomes to establish a statistically significant difference from placebo or comparator treatments.

GLP-1 agonists are classified as biologics, which entails specific regulatory requirements. For instance, the FDA requires a Biologics License Application (BLA) for the approval of biologics, including detailed information about the manufacturing process, product characterization, and stability studies. The EMA has specific guidelines for the development and evaluation of biologics as well, emphasizing comprehensive data on trial results and the manufacturing process. Since biologics are generally more complex, post-marketing surveillance to monitor long-term safety and effectiveness is also required.

6. Conclusion

The development and production of GLP-1 receptor agonists represent a significant advancement in diabetes management, especially for type 2 diabetes. Recent biotechnological advancements such as protein engineering have led to the development of more effective GLP-1 agonists, targeting the vast type 2 diabetes market and weight loss population. Key improvements include modifications that enhance the pharmacokinetic properties, such as extended half-lives and improved stability. Moreover, bioengineering techniques have enabled the development of novel delivery systems, such as oral formulations and microneedle patches, which benefit patients in terms of convenience and comfort.

Looking ahead, there are still significant opportunities for further research and innovation in this field. Researches have already been on going in dual agonism—targeting both GLP-1 and other hormones like GIP (gastric inhibitory polypeptide) or glucagon, which could have stronger potency than only GLP-1 agonist. Currently Tirzepatide is the most advanced, but this area would benefit from further research. Another area of potential growth is the incorporation of personalized medicine into GLP-1 receptor agonist therapy, thus creating tailor made therapies that are unique to each individual.

One key challenge for GLP-1 agonists medicines is the high price. This could be attributed to the fact that this class of medication is still at early stage, and biosimilar would be available only in another several years. Mass production and ensuring consistency and quality is also key consideration factor for GLP-1 agonists, which would lead to rising cost and thus high prices. As the industry develops, it should be expected that the price might fall with the expanding scale and more mature technologies, as well as a more competitive market.

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