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# Battle of GLP-1 delivery technologies☆

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) belong to an important therapeutic class for treatment of type 2 diabetes. Six GLP-1 RAs, each utilizing a unique drug delivery strategy, are now approved by the Food and Drug Administration (FDA) and additional, novel GLP-1 RAs are still under development, making for a crowded marketplace and fierce competition among the manufacturers of these products. As rapid elimination is a major challenge for clinical application of GLP-1 RAs, various half-life extension strategies have been successfully employed including sequential modification, attachment of fatty-acid to peptide, fusion with human serum albumin, fusion with the fragment crystallizable (Fc) region of a monoclonal antibody, sustained drug delivery systems, and PEGylation. In this review, we discuss the scientific rationale of the various half-life extension strategies used for GLP-1 RA development. By analyzing and comparing different approved GLP-1 RAs and those in development, we focus on assessing how half-life extending strategies impact the pharmacokinetics, pharmacodynamics, safety, patient usability and ultimately, the commercial success of GLP-1 RA products. We also anticipate future GLP-1 RA development trends. Since similar drug delivery strategies are also applied for developing other therapeutic peptides, we expect this case study of GLP-1 RAs will provide generalizable concepts for the rational design of therapeutic peptides products with extended duration of action.



**Contents**



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## 1. Introduction

Type-2 diabetes is a chronic metabolic disease characterized by hyperglycemia, reduced insulin secretion, and insulin resistance. If not properly treated, type 2 diabetes can result in serious or even fatal complications including blindness, limb amputation, kidney failure, and cardiovascular diseases. In 2017, the International Diabetes Federation estimated that, globally, 425 million people between the ages of 20 and 79 had diabetes, and that type 2 diabetes comprised about 90% of these cases [1, 2]. That same year, the global economy spent an estimated 727 billion USD for diabetes treatment [1]. As both diabetes diagnoses and the life expectancy of individuals with diabetes continue to rise, the total number of diabetic patients is expected to reach 629 million by 2045 [1], resulting in an increasing demand for anti-diabetes therapies.

Historically, metformin has remained the first-line treatment for type 2 diabetes. Other long-used therapeutic options to help manage glucose levels include insulin, sulphonylureas, and thiazolidinediones [3]. However, maintaining glucose homeostasis with these agents remains challenging for many patients [4]. Furthermore, some of these drugs—particularly insulin and sulfonylurea—lead to undesired risks including hypoglycemia and weight gain [5]. Thus, identifying new drug targets and developing more effective and safer treatments is necessary to achieve optimal management of type 2 diabetes.

Glucagon-like peptide-1 (GLP-1) emerged as a target for type-2 diabetes treatment due to its unique mechanism of action. GLP-1 is an endogenous incretin hormone produced by intestinal enteroendocrine L-cells following nutrient ingestion [6]. The initial product, GLP-1 (1-37), is quickly cleaved by enzymes, resulting two active truncated forms GLP-1 (7-36) and GLP-1 (7-37) [7]. GLP-1 exerts multiple physiological effects by activating GLP-1 receptors distributed in various organs, including the pancreas, gastrointestinal (GI) tract, brain, heart and the kidneys [7, 8]. When glucose levels are elevated, GLP-1 promotes insulin secretion in the pancreas but has minimal effect when glucose levels are normal [9]. This glucose-dependent insulinotropic effect is particularly favorable for diabetes treatment because it avoids the risks of hypoglycemia, a common side effect of some anti-diabetes drugs, including insulin [9]. GLP-1 also decreases glucagon secretion, further contributing to reduction of glucose levels [6, 10]. Studies have also suggested that GLP-1 can improve β-cell function and inhibit β-cell apoptosis, both of which could prevent or slow the progression of β-cell failure in type 2 diabetes [6, 11, 12]. GLP-1 also displays positive effects on other tissues and organs. In the GI tract, GLP-1 slows gastric emptying, leading to lower postprandial glucose levels [13, 14]. By activating GLP-1 receptors in the nervous system, GLP-1 could enhance satiety and inhibit energy intake, which may help reduce bodyweight [15, 16].

Despite its potent anti-diabetes effects, the clinical application of native GLP-1 is hindered by its rapid clearance by the dipeptidyl peptidase-4 (DPP-4) enzyme *in vivo*, resulting in a half-life of only 2 min [17, 18]. GLP-RA developers have applied various half-life extending strategies and some of them have successfully resulted in FDA-approved diabetes products (Table 1). Simple sequential modification enhances DPP-4 resistance and improves GLP-1 receptor activation potency. This strategy led to the twice-daily and once-daily products, Byetta® and Adlyxin®, respectively. Sequence modification to enhance DPP-4 resistance combined with covalent attachment of a fatty acid leads to slower absorption and mediates albumin binding in plasma, a strategy employed in the development of the once-daily and once-weekly agents, Victoza® and Ozempic®, respectively. More complicated molecular modifications that led to the approval of once-weekly products include fusing either recombinant human serum albumin (Tanzeum®) or an antibody fragment crystallizable (Fc) moiety (Trulicity®) to a GLP-1 analog. Other GLP-1 modifications have also been tested, including GLP-1 RA modified either with a recombinant peptide polymer XTEN® (VRS-859) or polyethylene glycol (LY2428757). Both molecules progressed into clinic trials, leading to the possibility of once-monthly and once-weekly products, but the development of these molecules appears to have been halted. Controlled release GLP-RA products have also been developed including the FDA-approved once-weekly poly(lactide-*co*-glycolide) microspheres (Bydureon®) and a once-yearly titanium implant (ITCA 650) which is currently under review by the FDA.

The employment of different half-life extension strategies, thus, results in significant differences in the pharmacokinetic profiles, efficacy, safety, and usability of these products, which in turn largely impacts the use and market penetration of GLP-1 RA products. In this review, we discuss the structure-activity relationship, pharmacokinetics, efficacy and market dominance of approved GLP-1 RA products, GLP-1 RA molecules in development and combination therapy strategies. The implementation of various creative delivery technologies for improving circulation half-life of molecules will likely be repeated for other peptide or protein products, making this review relevant for scientists working within the drug delivery field.

## 2. Strategies to increase half-life

To design GLP-RAs with an increased circulation time, a broad array of half-life extension strategies has been utilized including sequential modification (Byetta® and Adlyxin®), attachment of a fatty-acid (Victoza® and Ozempic®), development of a polymer-based sustained release formulation (Bydureon®), fusion with human serum albumin (Tanzeum®), and fusion with the fragment crystallizable (Fc) region of a monoclonal antibody (Trulicity®) (Fig. 1). In this section we review the structure-activity relationship behind the various half-life extending strategies in the context of GLP-1 RA development and, in turn, how these modifications impact pharmacokinetic parameters and dosing scheduling of the resulting GLP-1 RA products.

### 2.1. Critical structural elements of GLP-1 sequence

Early structure-activity studies of endogenous GLP-1 revealed the key sequence domains that correlate with potency and enzymatic degradation. Studies have suggested that the N-terminal residues His7, Gly10, Phe12, Thr13 and Asp15 are essential for interaction with the GLP-1 receptor, as substituting these residues with L-Ala leads to a severe loss of affinity for its receptor [43]. Similarly, C-terminal positions Phe28 and Ile29 are also important for receptor binding due to their role in maintaining the peptide's secondary structure [43]. Endogenous GLP-1 has a short plasma half-life because of its rapid degradation by DPP-4, which cleaves GLP-1 between the Ala8 and Glu9 amino acids [44]. In addition, neutral endopeptidase (NEP) plays a minor role in GLP-1 degradation by cleaving at six sites, Asp15-Val16, Ser18-Tyr19, Tyr19-Leu20, Glu27-Phe28, Phe28-Ile29 and Trp31-Leu32, within the central and C-terminal peptide domains [44].

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