The Pharma Innovation Journal 2023; 12(12): 2264-2266

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(12): 2264-2266

www.thepharmajournal.com
Received: 14-10-2023
Accepted: 18-11-2023

Md. Jahed Rana
Faculty of Pharmacy, State University of Bangladesh, 77 Satmasjid Road, Dhaka-1205, Bangladesh

Corresponding Author:
Md. Jahed Rana
Faculty of Pharmacy, State University of Bangladesh, 77 Satmasjid Road, Dhaka-1205, Bangladesh

Semaglutide: A GLP-1 agonist for treating type 2 diabetes

Md. Jahed Rana

Abstract
Glucagon-like peptide 1 (GLP-1) is a hormone released from the intestinal L-cell that stimulates insulin secretion from the beta cell of the pancreas and reduces glucose production in the liver. But it is degraded by dipeptidyl peptidase-4 (DPP-4) and thus has a shorter half-life (2-3 minutes). To overcome this limitation various agonists have been developed, among them Semaglutide shows tremendous efficacy against both type-2 diabetes mellitus. Semaglutide has higher albumin affinity due to the attachment of hydrophobic linker "γGlu-2xOEG" at the 26th position of lysine residue which enhances plasma half-life to 160 hours. Another modification happens in the 8th and 34th positions. It was developed by Novo Nordisk and is available in both injection and oral dosage forms in the market. Both were approved by the U.S. Food and Drug Administration (FDA) and have high demand in the market for high efficacy and few side effects.

Keywords: GLP-1, DPP-4, Semaglutide, T2DM, FDA

Introduction
Type 2 diabetes mellitus (T2DM) is one of the most critical health disorders across the world. It occurs when the glucose levels in the blood rise high due to a lack of insulin or the development of insulin resistance in an individual. It causes serious damage to the heart, kidneys, eyes, liver, and nerves. As per the World Health Organization (WHO), about 422 million people are suffering from diabetes, and 4.2 million deaths are directly caused by diabetes each year [1]. They are predicting the number of having diabetes will increase to 592 million by 2035 [2]. Depending on the sales in the pharma industry antidiabetic drugs belong in the second largest position globally. Various drugs have developed considering different approaches to control glycemia and to minimize adverse effects. Human insulin was approved in 1982 and since then 59 unique antidiabetic drugs have been approved by FDA [3]. Among them, semaglutide a recently approved GLP-1 agonist developed by Novo Nordisk has great demand in the market. It is available in subcutaneous injection form as Ozempic and oral form as Rybelsus. The vital feature of this molecule is the longest half-life and thus the dose is only 0.5 mg or 1 mg once a week for injection. In the case of oral tablets, the dose is 3, 7, or 14 mg once a day. It has minimal side effects and does not require any dose adjustment, especially for cardiac patients. Semaglutide is also used to reduce body weight, which is another vital role for popularity [4-6].

Materials and Methods
Requirement of GLP-1 agonist to treat T2DM: Glucagone-like peptide-1 (GLP-1) is an incretin hormone released from the intestinal L-cell. This hormone plays a vital role in controlling diabetes. It stimulates insulin secretion from the beta cell and reduces glucagon synthesis in the liver. The major limitation of this hormone is the shortest half-life (2-4 minutes) and degradation by the Dipeptidyl Peptidase-4 (DPP-4). Thus, the focus of developing GLP-1 agonists was to enhance the half-life and inhibit the DPP-4 enzyme [7-8]. The first GLP-1 agonist was Exenatide, developed by AstraZeneca and approved by FDA in 2005. It has around a 2.5-hour half-life. Since then, several molecules have been developed like liraglutide, albiglutide, dulaglutide, and so on. Finally, semaglutide came into the market with a half-life of approximately 160 hours by Novo Nordisk. FDA approved the injection form in 2017 and then the oral form in 2019 [4, 9].

Table 1: Overview of GLP-1 analogues

Drug Name	Brand Name	Company	FDA approval	Half-life (hours)
Exenatide	Byetta	AstraZeneca	2005	~ 2.5
Liraglutide	Victoza/Saxenda	Novo Nordisk	2010	~ 12.0
Exenatide extended release	Bydureon	AstraZeneca	2012	N/A
Dulaglutide	Trulicity	Eli Lilly	2014	~ 90.0
Lixisenatide	Lyxumia	Sanofi-Aventis	2016	~ 3.0-4.0
Semaglutide	Ozempic	Novo Nordisk	2017	~ 160

*N/A: Not Applicable

Structural modification and formulation development: To improve a new drug to administer once a week, the molecule needs to bind with albumin with high affinity to improve the half-life. Also, modification at the N-terminal is required to inhibit the DPP-4 degradation. Novo Nordisk developed the semaglutide in such a way that is 94.0% homologous to the natural GLP-1. Several analogues have been designed and *in vitro* potency and binding affinity were compared to finalize the drug.

The chemical formula and molecular weight of Semaglutide are C187H291N45O59 and 4113.58 g/mol respectively. The alanine residue is substituted with the Aib (2-aminoisobutyric acid) at the 8th position. This modification gives protection from enzymatic degradation. The lysine residue was replaced by the arginine at the 34th position which favors the production of the GLP-1 analogue. The vital modification happens on the 26th position. Here the lysine residue was attached with a C18 fatty diacid through a hydrophobic linker "$_{\gamma}$Glu-2xOEG". This has a greater impact on the albumin binding affinity and improves the plasma half-life [5, 10].

After the development of injection, the focus was on using it in an oral form. The main challenge was to protect drugs from proteolytic degradation at the acidic pH of the stomach. Thus, SNAC (Sodium-N-[8-(2-hydroxybenzoyl)amino]caprylate) has been used as a permeation enhancer. It enhances the solubility of semaglutide to cross the cell membrane by increasing the pH of the local environment [11-12].

Benefits and adverse effects: The biggest advantage of semaglutide is the no risk of weight gain and hypoglycemia. Also reduces cardiovascular risks and no need for dose adjustment. It has some mild adverse effects like diarrhea, vomiting, nausea, headache, and dyspepsia. Another worst-case for semaglutide is the high cost [10].

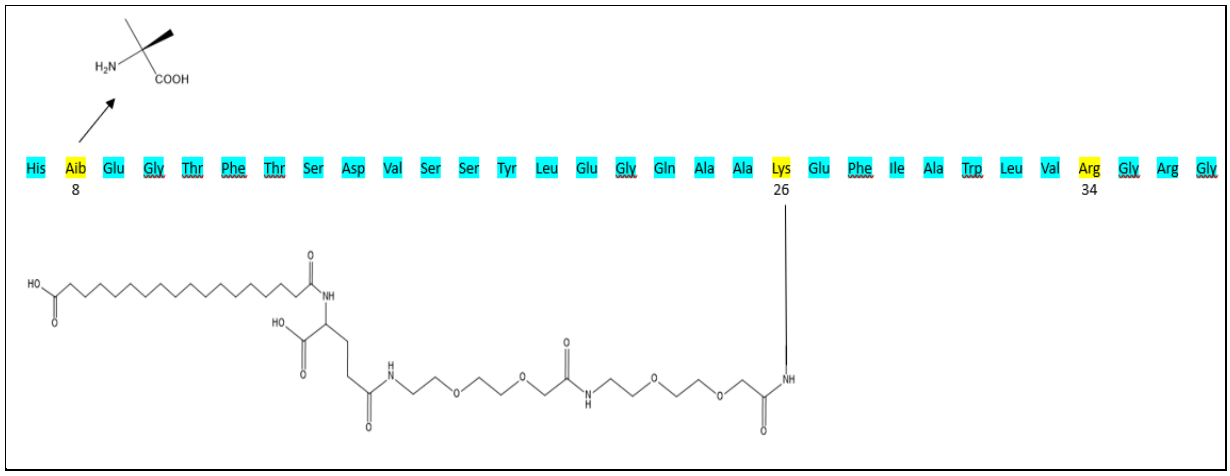

Fig 1: Structure of Semaglutide

Conclusion

Semaglutide has been proven as a wonderful therapeutic drug to control blood glucose levels. The development of subcutaneous injection has reduced the frequency of intake of dose. Oral formulation is a milestone in the development of peptide-based drug therapy. Several studies are required to develop safe drugs like semaglutide.

Acknowledgements

The author is grateful to the faculty of pharmacy, State University of Bangladesh for guidance in conducting database searches.

References

1. PAHO/WHO. Diabetes: Overview, Symptom, Treatment. https://www.paho.org/en/topics/diabetes.10 December 2023.
2. Tiwari N, Thakur AK, Kumar V, Dey A, Kumar V. Therapeutic Targets for Diabetes Mellitus: An Update. Clinical Pharmacology & Biopharmaceutics. 2014;3:117.
3. Dahlén AD, Dashi G, Maslov I, Attwood MM, Jonsson J, Trukhan V, *et al*. Trends in Antidiabetic Drug Discovery: FDA Approved Drugs, New Drugs in Clinical Trials and Global Sales. Frontiers in Pharmacology. 2022;12:807548.
4. Suzuki R, Brown GA, Christopher JA, Scully CCG, Congreve M. Recent Developments in Therapeutic Peptides for the Glucagon-like Peptide 1 and 2 Receptors. Journal of Medicinal Chemistry. 2020;63(3):905-927.
5. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, *et al*. Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. J Med. Chem. 2015;58(18):7370-7380.
6. Ahrén B. Creative use of novel glucose-lowering drugs

for type 2 diabetes: where will we head in the next 50 years? Diabetologia. 2015;58:1740-1744.
7. Laurie L. Baggio, Daniel J. Drucker. Biology of Incretins: GLP-1 and GIP. Gastroenterology. 2007;132:2131-2157.
8. Holst JJ. The Physiology of Glucagon-like Peptide 1. Physiological Reviews. 2007;87(4):1409-1439.
9. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, *et al*. Glucagon- like peptide 1 (GLP-1). Molecular Metabolism. 2019;30:72-130.
10. Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Reviews in Endocrine and Metabolic Disorders. 2022;23:521-539.
11. Kalra S, Sahay R. A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther. 2020;11:1965-1982.
12. Kommineni N, Jyothi VSGS, Butreddy A, Raju S, Shapira T, Khan W, *et al*. SNAC for Enhanced Oral Bioavailability: An Updated Review. Pharmaceutical Research. 2023;40:633-650.