ISSN: 2754-6675

Journal of Chemistry & its Applications

SCIENTIFIC Research and Community

Research Article

Open Access

Semaglutide, an Anti-Diabetic and Anti-Obesity Drug: A Perspective

Narsimhaswamy Dubasi[1] and Ravi Varala[2*]

[1]Independent Researcher, Belcher Road S, Apt N226, Largo, Florida, 33773, USA

[2]Research Fellow, Health and Life Sciences, INTI International University, Nilai, 71800, Malaysia; Shinawatra University, Pathum Thani 12160, Thailand

ABSTRACT

Glucagon-Like Peptide-1 (GLP-1) receptor agonist often used in treatment of type 2 diabetes mellitus and obesity: Semaglutide It improves glycemic control by increasing insulin secretion, inhibiting glucagon release, slowing stomach emptying and lowering appetite. Due to its lengthy half-life, semaglutide can be given once weekly, leading to better patient compliance than daily therapy. Clinical trials have shown considerable declines in glycated hemoglobin (HbA1c), body weight, and cardiovascular risk in people receiving semaglutide. Semaglutide has demonstrated significant effectiveness in achieving durable weight loss in conjunction with lifestyle changes for the management of obesity. Emerging data also suggest possible benefits in lowering inflammation, enhancing metabolic health, and preventing cardiovascular problems. This drug has therapeutic benefits but commonly causes nausea, vomiting, diarrhea and gastrointestinal upset, particularly when the dose is being increased. Rare but serious issues, like pancreatitis and thyroid-related consequences, require close monitoring. Overall, semaglutide represents an important step forward in the management of metabolic disorder, providing good glycemic control, significant weight loss, and an attractive clinical profile.

***Corresponding author**

Ravi Varala, Research Fellow, Health and Life Sciences, INTI International University, Nilai, 71800, Malaysia; Shinawatra University, Pathum Thani 12160, Thailand.

Received: May 10, 2026; **Accepted:** May 18, 2026; **Published:** May 24, 2026

Keywords: Semaglutide, Glucagon-Like Peptide-1 (GLP-1) receptor, T2D (Type 2 Diabetes), Anti-Obese

Introduction

Diabetes is a long-term condition that happens when either the pancreas doesn't generate enough insulin, or the body can't effectively use the insulin it produces [1]. Insulin is a hormone that controls blood glucose. Hyperglycaemia, or elevated blood glucose or raised blood sugar is a common result of untreated diabetes that over time causes catastrophic damage to many of the body's systems, especially the neurons and blood vessels [2]. In 2021, diabetes directly caused 1.6 million fatalities, with 47% of all diabetes-related deaths occurring before the age of 70. Diabetes caused another 530 000 deaths from kidney disease and high blood glucose is responsible for about 11% of fatalities from cardiovascular disease [3]. The present treatment for Diabetes is provided by metformin, sulfonylureas and sodium-glucose co-transporters type 2 (SGLT-2) inhibitors. Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin) are a type of diabetes drug that work by blocking the reabsorption of glucose in the kidneys, resulting in excess sugar being excreted in the urine, which lowers blood sugar, blood pressure, and weight, and provides significant cardiovascular and kidney protection even in non-diabetics with heart failure or kidney disease [4]. We recently evaluated the relevance of SGLT-2 inhibitors (Gliflozins) [5].

Likewise, overweight and obesity are characterized by abnormal or excessive fat buildup that may impair health [6]. Overweight is a body mass index (BMI) of over 25 and obesity is a BMI of over 30. In 2019, almost 5 million fatalities from non-communicable diseases (NCDs) were attributable to higher-than-optimal BMI. Overweight and obesity are the consequences of an imbalance between energy intake (diet) and energy expenditure (physical activity). In the world, 1 in 8 individuals had obesity in 2022. In December 2025, WHO released the recommendation on the use of glucagon-like peptide-1 (GLP-1) treatments for the treatment of obesity in adults [7]. GLP-1 receptor agonists are a class of drugs that can help reduce blood sugar, aid in weight loss, lower the risk of heart and renal issues, and even reduce the chance of early mortality in persons with type 2 diabetes. This guideline makes recommendations specifically for three medicines used in the long-term treatment of obesity in adults: liraglutide, semaglutide and tirzepatide [8-10]. From this point of view, we intend to highlight the background and actual utility of these three well-known innovative medications efficiently employed in obesity and chronic diabetes conditions. Furthermore, specific emphasis will be placed on Semaglutide in particular.

Results and Discussion

Liraglutide (trade name Vitoza and others) is an anti-diabetic drug used for type 2 diabetes and chronic obesity [8]. It is a second line medication for diabetes after first line therapy with metformin. It is delivered by subcutaneous injection. It is a glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist) also called 'incretin mimetics'. It enhances insulin release from the pancreas and reduces excessive glucagon secretion. It was licensed for medical use in the European Union in 2009 and the United States

in 2010. It is accessible as a generic drug. In 2023 it was the 209th most prescribed medicine in the United States with more than 2 million prescriptions. Tirzepatide is an anti diabetic drug for the treatment of type 2 diabetes and weight loss [9]. Tirzepatide is delivered by subcutaneous (under the skin) injections. In the United States it is marketed under the brand name Mounjaro for diabetes management and Zepbound for weight loss and treatment of obstructive sleep apnea. Tirzepatide is a product of Eli Lilly and Company. It was approved in the United States for the treatment of diabetes in May 2022, in the European Union in September 2022, in Canada in November 2022 and in Australia in December 2022. It's a first-in-class drug, according to the U.S. Food and Drug Administration (FDA). The FDA authorized it for weight loss in November 2023.

The CAS number of Semaglutide is 910463-68-2, the molecular formula is $C_{187}H_{291}N_{45}O_{59}$, the molecular weight is 4113.64 g/mol, and the peptide sequence is: H-His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys(AEEA-AEEA-γ-Glu-Octadecanedioic)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH (Figure 1). Semaglutide is also a glucagon-like peptide-1 (GLP-1) receptor agonist like other glutides. 94% structural homology to native human GLP-1 is exhibited by semaglutide, and is characterized by three modifications: 1) amino-acid substitutions at position 8 (alanine to α-aminoisobutyric acid or Aib) and position 34 (lysine to arginine), and acylation of the lysine in position 26 with a spacer of two 8-amino-3,6-dioxaoctanoic acid (ADO) moieties, a glutamic acid moiety, and a C-18 fatty di-acid side chain.

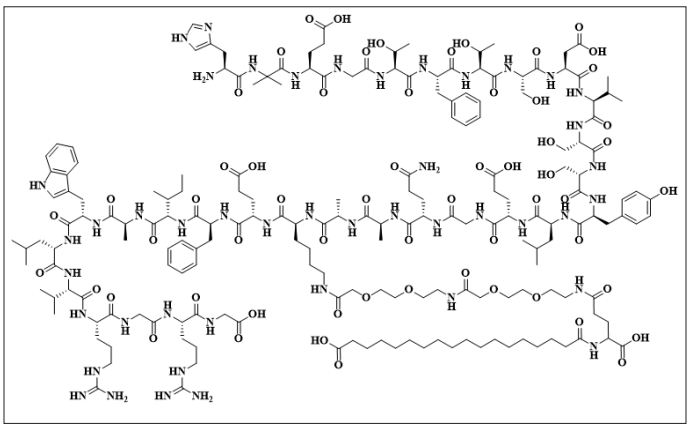

Figure 1: Structure of Semaglutide

Semaglutide is a semi-synthetic substance, not a natural product. It is manufactured by recombinant DNA technology,[28] where a basic peptide is synthesized in yeast and then modified synthetically with an attached fatty acid and other alterations to increase its stability and duration of activity in the body. It is an anti-diabetic drug for the treatment of type 2 diabetes (T2D) and an anti-obesity drug for long-term weight management [10]. It is a peptide that is comparable to the hormone glucagon-like peptide-1 (GLP-1) with a side chain modification. It may be given by subcutaneous injection or orally. Semaglutide has a long half-life of around a week, which means the injectable version can be dosed once a week. Novo Nordisk sells it under the brand names Ozempic and Rybelsus for diabetes and under the brand name Wegovy for weight management, weight loss.

Semaglutide had been approved for the treatment of T2D by the US FDA in 2017;[11] in 2021 it was the 90th most prescribed medicine in the US with 8 million prescriptions. Cardiovascular disease (CVD) is a common and serious consequence of type 2 diabetes (T2D) [12-13]. In August 2025, the US Food and Drug Administration expanded the indication for semaglutide to include therapy of metabolic-associated steatohepatitis (MASH) in people with moderate-to-advanced fibrosis (excessive scar tissue in the liver) [14-15].

Synthetic Approaches

From the application standpoint, the problems of building semaglutide are not only in the chemical construction but also in how to obtain the pharmacokinetic advantages through structure design [16]. A common strategy is to add a fatty acid chain to improve albumin binding and hence provide a prolonged release in vivo. This design philosophy allows semaglutide to achieve long-lasting receptor activation and metabolic stability, making it a leading long-acting GLP-1 receptor agonist [17-29].

Semaglutide synthesis utilizes SPPS, which permits sequential addition of amino acids from C-terminus to the N-terminus of the peptide chain [25,30]. Compared to natural GLP-1, semaglutide has particular changes to enhance its enzymatic resistance and half-life. One major change is swapping alanine at position 2 with α-aminoisobutyric acid (Aib) to boost resistance to degradation by DPP-4. Furthermore, a long-chain fatty acid (C18) is attached to the residue lysine 26 via a hydrophilic spacer, which considerably increases the affinity for albumin and extends the therapeutic window. These structural modifications result in a once-weekly dose profile for semaglutide,18 which represents a significant improvement over older GLP-1 analogs that needed more regular administration.

Fatty acid conjugation is a key post-assembly side-chain modification step in the semaglutide production. This step requires the use of very selective coupling procedures to avoid unwanted side reactions with other functional groups. Site specificity is often achieved by protecting group chemistry, and effective coupling agents such as HATU or DIC/HOAt allow the efficient coupling of the fatty acid to the peptide scaffold in high yields. Following the synthesis of semaglutide, extensive purification steps are performed, including reverse-phase high-performance liquid chromatography (RP-HPLC) and mass spectrometry validation to guarantee product purity and precise stereochemistry [19-29]. These methods are necessary to maintain the structural integrity and biological activity, and provide the basis of quality control for the manufacture of peptide drugs.

The manufacturing of semaglutide is now the most promising antidiabetic medicine especially for the treatment of type 2 diabetes mellitus, but it is expensive. Therefore, a new synthetic pathway of semaglutide production that possesses great yield and high purity is of crucial relevance. Ma and co-workers revealed a new synthetic approach of semaglutide which is easy and efficient. The synthetic route is based on a soluble hydrophobic-support-assisted liquid-phase synthetic method. The authors applied Alloc-chemistry to the synthesis of the main chain peptide and side chain peptide of semaglutide [15]. By careful adjustment of the reaction condition and unique method of post-synthetic treatments, the total yield and purity of the crude semaglutide was improved satisfactorily.

Semaglutide is a long-acting GLP-1 analog created by Novo Nordisk (4114 Da) and was authorized by the US FDA in 2017. Hybio Pharmaceutical Co. Ltd. has manufactured semaglutide in the technological field of polypeptides. At now, the published methods for the preparation of semaglutide can be loosely split into

two types [31-42]. One is to take the Lys-containing side chains as a fragment to directly link with the main chain of semaglutide to complete the synthesis. Patent CN104356224A offers a technique for producing semaglutide, which includes attaching a side chain to the ε-NH_2 of Lys by a liquid-phase process, and then sequentially condensing amino acids on a resin. The other is to complete the coupling of the main chain and side chain of semaglutide, respectively. Patent CN 201511027176 discloses stepwise synthesis of semaglutide linear peptide in solid phase, synthesis of side chain modifying group, removing protective group of Lys, coupling of side chain modifying group and lastly cleavage to produce polypeptide product.

Conclusion

Semaglutide has emerged as a very efficient therapeutic drug for the control of type 2 diabetes mellitus and obesity. Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that leads to improved glycaemic management, considerable weight loss, appetite suppression and a reduced risk of cardiovascular problems in people at high risk. Clinical trials have shown that it is more effective than several standard antidiabetic and anti-obesity medications, with better long term metabolic benefits. The weekly administration of the same also leads to better patient compliance and treatment adherence. However, some restrictions must be considered, such as gastrointestinal adverse effects, high cost of therapy, and lack of long-term safety data in some groups. In conclusion, semaglutide represents a substantial development in the treatment of metabolic disease and continues to revolutionize the therapeutic landscape of diabetes and obesity management.

Future Scope

The future of semaglutide is bright and far-reaching, given its growing therapeutic applications and further scientific progress. Future research could involve:

Long-Term Safety and Effectiveness Data

Extensive clinical trials are still needed to determine long-term safety, cardiovascular endpoints and sustainability of weight loss with semaglutide therapy.

Use in Other Disorders

Semaglutide is also being studied for the treatment of other diseases such as non-alcoholic fatty liver disease (NAFLD), polycystic ovarian syndrome (PCOS), cardiovascular diseases, and neurological diseases.

Personalised Medicine Approaches

Further research may find genetic or metabolic indicators that may help predict which patients would do well with semaglutide, leading to tailored therapy.

Oral & Combination Therapies Development

Further convenience of use and therapeutic improvements might be possible with advances in oral formulations and combination therapy with other metabolic drugs.

Cost Reduction and Accessibility

More patients could have access to semaglutide if its manufacturing costs were lowered and its availability increased globally.

Investigation in Pediatric and Elderly Populations

Additional studies are required to demonstrate the best dose, safety and efficacy in children, adolescent and elderly patients.

Research of Mechanisms

A deeper understanding of the molecular mechanisms of semaglutide may identify novel therapeutic targets and extend its medical use.

References

1. Tegegne BA, Adugna A, Yenet A, Yihunie Belay W, Yibeltal Y, et al. (2024) A critical review on diabetes mellitus type 1 and type 2 management approaches: from lifestyle modification to current and novel targets and therapeutic agents. Front. Endocrinol (Lausanne) 15: 1440456.
2. Goyal M, Choudhary D (2021) A Review on Hyperglycemia: Symptoms and Risk Factors. Journal of Pharmaceutical Research International 33: 756-762.
3. (2024) Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2021. Results. Institute for Health Metrics and Evaluation. (https://vizhub.healthdata.org/gbd-results/).
4. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-inhibitors.
5. Varala R, Dubasi N (2024) Update on the Chemistry of Jardiance (Empagliflozin). J. Pharmaceutics and Pharmacology Research 7.
6. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
7. https://www.who.int/news/item/01-12-2025-who-issues-global-guideline-on-the-use-of-glp-1-medicines-in-treating-obesity.
8. Mehta A, Marso SP, Neeland IJ (2017) Liraglutide for weight management: a critical review of the evidence. Obes. Sci. Pract 3: 3-14.
9. Sokary S, Bawadi H (2025) The promise of tirzepatide: A narrative review of metabolic benefits. Primary Care Diabetes 19: 229-237.
10. https://en.wikipedia.org/wiki/Semaglutide.
11. Dhillon S (2018) Semaglutide: First Global Approval. Drugs. 78: 275-284.
12. Mahapatra MK, Karuppasamy M, Sahoo BM (2022) Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev. Endocr. Metab. Disord 23: 521-539.
13. Tentolouris A, Siafarikas C, Ntanasis Stathopoulos I, Anastasiou IA, Kalara E, et al. (2026) Semaglutide and tirzepatide in prediabetes: Evidence for diabetes prevention and cardiovascular protection. Primary Care Diabetes 20: 178-184.
14. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-serious-liver-disease-known-mash.
15. Connolly DL, Bain SC, Collins E, Ren H, Ming SWY, et al. (2024) Real-world data analysis investigating the cardioprotective effects of glucagon-like peptide-1 receptor agonists among people with type 2 diabetes in England. European Heart Journal 45: 1.
16. Luna Ceron E, Reddy SD, Kattamuri L, Muvva DM, Chozet L, et al. (2025) Current Insights, Advantages and Challenges of Small Molecule Glucagon-like Peptide 1 Receptor Agonists: A Scoping Review. J Brown Hosp Med 4: 19-32.
17. Kapitza C, Nosek L, Jensen L, Hartvig H, Jensen CB, et al. (2015) Semaglutide, a Once-Weekly Human GLP-1 Analog, does not reduce the Bioavailability of the Combined Oral Contraceptive, Ethinylestradiol/Levonorgestrel. Journal of Clinical Pharmacology 55: 497-504.
18. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, et al.

(2015) Discovery of the Once-Weekly Glucagon-Like Peptide-1 (GLP-1) Analogue Semaglutide. Journal of Medicinal Chemistry 58: 7370-7380.

19. Jensen L, Helleberg H, Roffel A, van Lier JJ, Bjørnsdottir I, et al. (2017) Absorption, metabolism and excretion of the GLP-1 analogue semaglutide in humans and nonclinical species. Eur J Pharm Sci 104: 31-41.
20. Hausner H, Derving Karsbøl J, Holst AG, Jacobsen JB, Wagner FD, et al. (2017) Effect of Semaglutide on the Pharmacokinetics of Metformin, Warfarin, Atorvastatin and Digoxin in Healthy Subjects. Clin Pharmacokinet 56: 1391-1401.
21. Knudsen LB, Lau J (2019) The Discovery and Development of Liraglutide and Semaglutide. Front Endocrinol (Lausanne) 10: 155.
22. Kalra S, Sahay R (2020) A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Ther 11: 1965-1982.
23. I Guryanov, A Orlandin, ID Paola, A Viola, B Biondi, et al. (2021) Copper (II) Lysinate and Pseudoproline Assistance in the Convergent Synthesis of the GLP-1 Receptor Agonists Liraglutide and Semaglutide. Org. Process Res. Dev 25: 1598–1611.
24. Zhang X, Belousoff MJ, Liang YL, Danev R, Sexton PM, et al. (2021) Structure and dynamics of semaglutide- and taspoglutide-bound GLP-1R-Gs complexes. Cell Rep 36: 109374.
25. Peng D, Li Y, Si L, Zhu B, Wu P, et al. (2024) A two-step method preparation of semaglutide through solid-phase synthesis and inclusion body expression. Protein Expression and Purification 219: 106477.
26. Oleksak I, Maliszewska K, Szawłoga T, Welian Polus I, Wilanowska W, et al. (2024) Semaglutide – a long – awaited cure for obesity or an elusive treatment?. Eur. J. Clin. Exp. Med 22: 897-904.
27. Pawar SS, Rasal PB, Kulkarni KH, Pawar SB (2025) Semaglutide: A Comprehensive Review of its Pharmacology, Clinical Applications, and Future Therapeutic Potential. Journal of Drug Delivery and Therapeutics 15: 103-114.
28. Kim SH, Kim SS, Kim HJ, Park EJ, Na DH (2025) Peptide mapping analysis of synthetic semaglutide and liraglutide for generic development of drugs originating from recombinant DNA technology. Journal of Pharmaceutical and Biomedical Analysis 256: 116682.
29. Eisa N, Barood O (2026) Semaglutide and Non-Arteritic Anterior Ischemic Optic Neuropathy: A Systematic Review and Narrative Synthesis. AACE Endocrinology and Diabetes.
30. Liu X, Zhang N, Gu X, Qin Y, Song D, et al. (2020) Total Synthesis of Semaglutide Based on a Soluble Hydrophobic-Support-Assisted Liquid-Phase Synthetic Method. ACS Comb. Sci 22: 821-825.
31. Synthesis method of semaglutide. CN 112028986 A [Harbin Jixianglong Biological Technology Co ltd]
32. Synthesis method of semaglutide. [Nanjing Hanxin Pharmaceutical Technology Co ltd [CN]]
33. Method for synthesizing semaglutide. [Zhejiang Jiuzhou Pharmaceutical Co., Ltd. CN 115322250 A]
34. Lin Y, Lixiang Z, Minmin T, Xinyu L, Lifen W. A kind of synthetic method of semaglutide. CN-111944039-A
35. Chen X, Pengcheng, MI, Anjin T, Jiancheng Y Method for preparing semaglutide. EP 3 398 960 B1.
36. Ana Toplak, Peter Jan Leonard Mario Quaedflieg Timo Nuijens Chemo-enzymatic synthesis of semaglutide, liraglutide and GLP-1. US 10,920,258 B2.
37. Pranav K, Sindhuamuthan K, Vijaykumar V, Gaurav T. A Process for the Preparation of Semaglutide. WO-2025172908-A1.
38. Improved processes for the preparation of semaglutide. WO 2020/190757 A1 (2020) Teva Pharmaceuticals USA, Inc.
39. Thirumalai Rajan Srinivasan, Eswaraiah Sajja, Venkat Reddy Ghojala, Venkat Reddy Mallepally. Process for the preparation of semaglutide. MSN Laboratories Pvt Ltd. WO 2023/012829 A1.
40. Dipeptide fragment derivative for synthesizing semaglutide and preparation method thereof. Jinan Kanghe Medical Technology Co Ltd. CN 112625087 A.
41. Kunta KS, Godumala M (2026) Fmoc-His-Aib-OH as a Semaglutide Precursor: Efficient One-Pot Synthesis and Computational Insights. Polycyclic Aromatic Compounds 1-14.
42. Xu, OP Kuipers (2025) Design and Biosynthesis of Ornithine 8 Containing Semaglutide Variants with a Click Chemistry-Modifiable Position 26. ACS Synth. Biol 14: 1790-1801.