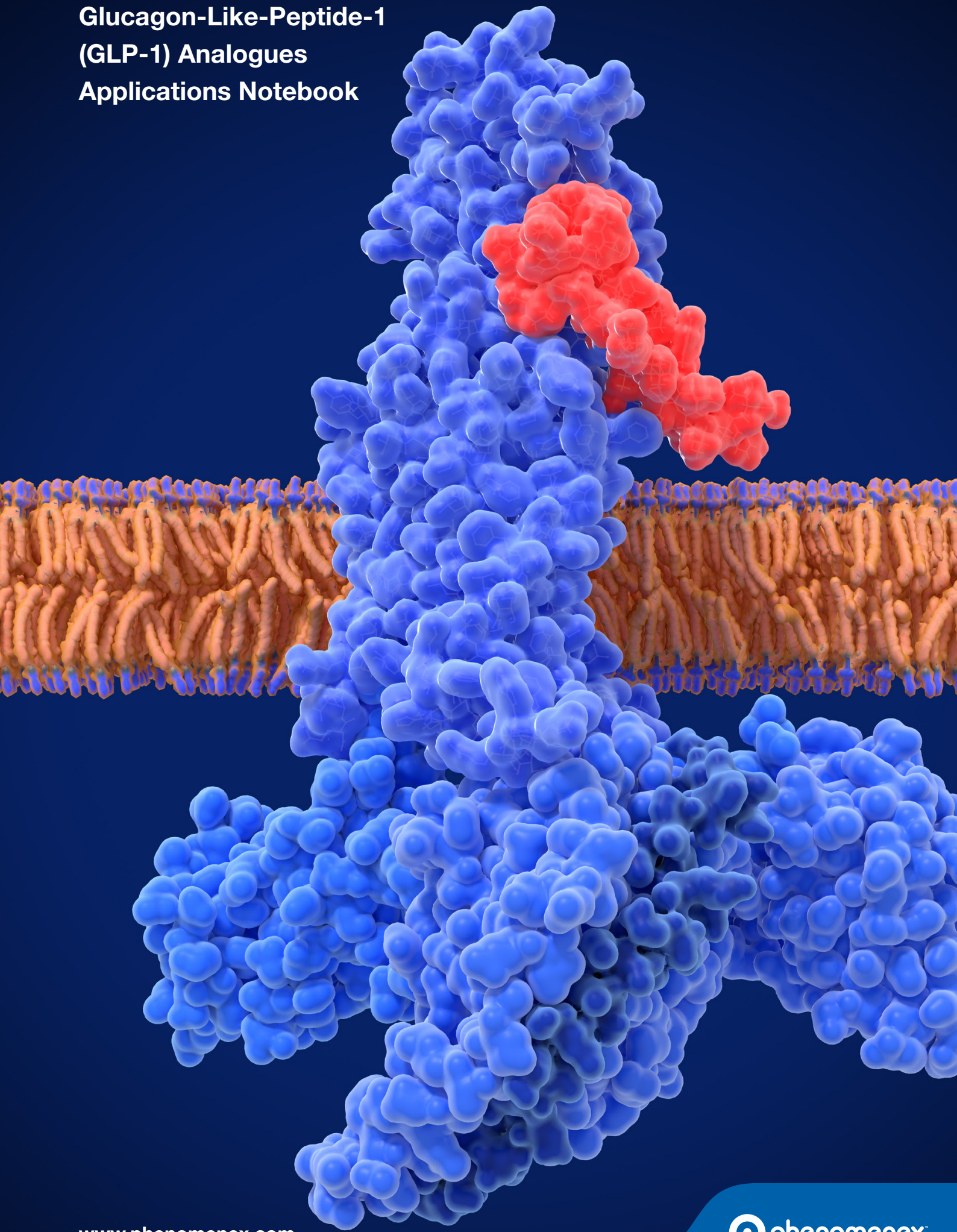
Glucagon-Like-Peptide-1 (GLP-1) Analogues Applications Notebook



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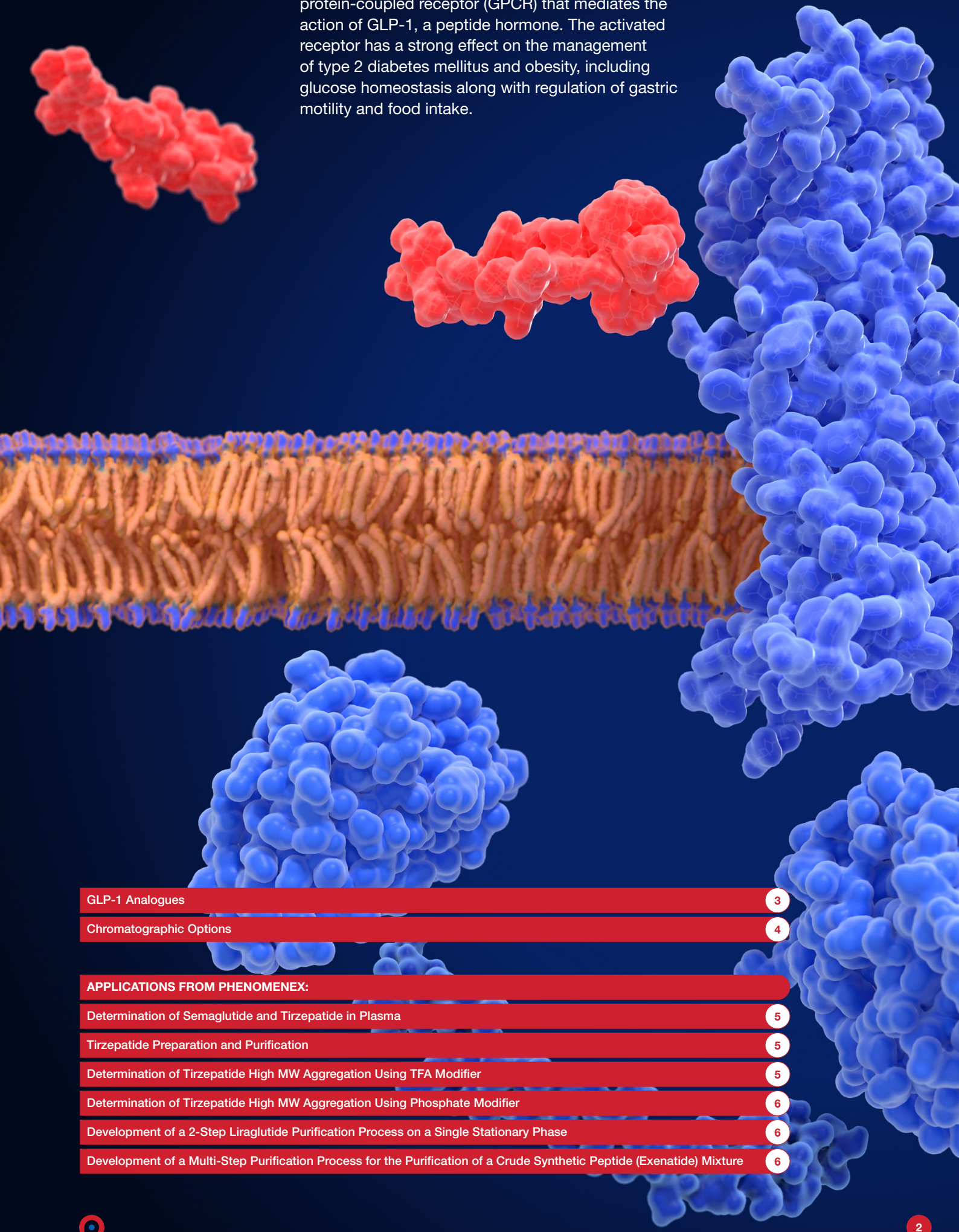
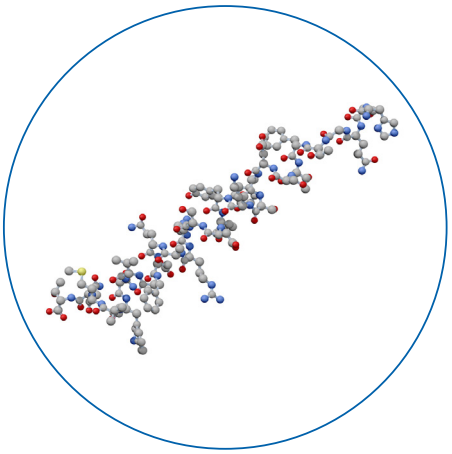
GLP-1 Contents

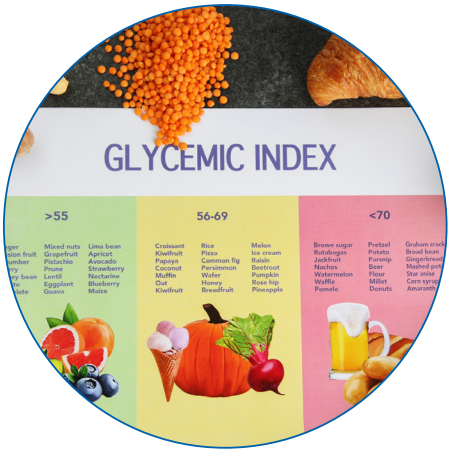
The glucagon-like-peptide-1 receptor (GLPr) is a G protein-coupled receptor (GPCR) that mediates the action of GLP-1, a peptide hormone. The activated receptor has a strong effect on the management of type 2 diabetes mellitus and obesity, including glucose homeostasis along with regulation of gastric motility and food intake.



GLP-1 Analogues



GLP-1 analogues, also known as glucagon-like peptide-1 analogues, are a class of medications used in the treatment of type 2 diabetes. They mimic the effects of the naturally occurring hormone called GLP-1, which helps regulate blood sugar levels.



Glucagon-like peptide agonists: A prospective review

GLP-1 analogues work by stimulating insulin secretion from the pancreas, reducing glucagon production, slowing down gastric emptying, and promoting a feeling of fullness. These actions help to control blood sugar levels, improve glycemic control, and may also lead to weight loss.[1]

Some commonly prescribed GLP-1 analogues include exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide. They are typically administered by injection, either once or twice daily, depending on the specific medication and dose. Newer analogues can be administered weekly.

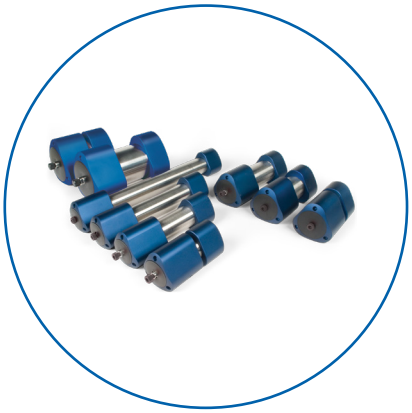
GLP-1 analogues are often used as an add-on therapy to other diabetes medications, such as metformin, when blood sugar levels are not well controlled. They have shown to be effective in lowering HbA1c levels, promoting weight loss, and reducing the risk of cardiovascular events.

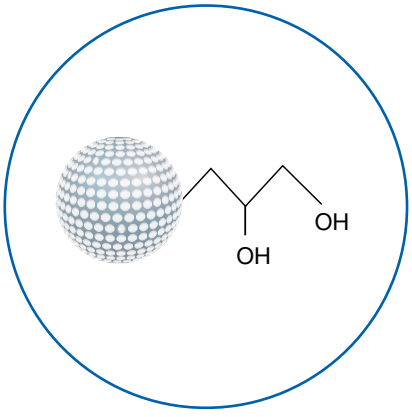
[1]Glucagon-like peptide agonists:
A prospective review Endocrinology, Diabetes & Metabolism

Zamara Mariam, Sarfaraz K. Niazi https://doi.org/10.1002/edm2.462

Selecting a Chromatographic Column to Fit Your Needs

Regardless of whether the peptides are produced through fermentation or synthetic methods, the resulting mixture is typically complex and includes closely related peptides, such as failed sequences, which necessitate chromatographic separation. Therefore, high-resolution solutions are essential to ensure the purity of the final product. Phenomenex provides a wide range of solutions to meet these needs.





Reversed Phase Separations

- Gradient conditions utilizing pH modifiers such as TFA, ammonium acetate, etc together with tailored organic ramp conditions provide high resolution separations.
- Column options with a range of particle sizes are available, allowing for selection of a high efficiency column compatible with the HPLC/UHPLC instrument available.

Recommended Columns

- Aeris Peptide
  A C18 core-shell option for peptides with di-isobutyl side chains, differentiating this C18 column. Superior peak shape is provided due to the shielding effect of the side chains, aiding in the prevention of unwanted secondary interactions.
- Biozen Peptide XB-C18
  A C18 stationary phase and di-isobutyl side chains on a core-shell particle offering inert BioTI hardware for enhanced peptide and peak shape.
- Kinetex Biphenyl
  Core-shell particle bonded with biphenyl as an alternative selectivity to C18, providing polar retention and aromatic selectivity.
- Kinetex EVO
  An organo-silica, inert core-shell C18 providing excellent robustness and peak shape, resistant to extreme pHs.
- Luna C18(2)
  Fully porous, good general C18 with the potential to scale directly to prep and bulk

Preparative Scale Separations

Flash cartridges, AXIA prepacked preparative columns and bulk material for self-packing are options for consideration.

Recommended prep columns/bulk materials

- Luna C8(3)
- Luna C18(3)
- Gemini C8(3)

Size Exclusion for Aggregate Analysis

When considering aggregation, size exclusion separations utilizing robust, durable columns are advised.

Recommended Column

- Biozen dSEC-2

Applications

Determination of Semaglutide and Tirzepatide in Plasma

Glucagon-like-peptide-1 (GLP-1) agonists are considered one of the most promising classes of diabetes drugs on the market. Semaglutide and Tirzepatide, as next-generation GLP-1 drugs, not only stimulate insulin release in the body effectively controlling blood sugar levels, but also inhibit gastrointestinal motility and increase satiety. This technical note establishes a method for determining Semaglutide and Tirzepatide drugs in plasma, providing a scientific basis for further research on drug safety and therapeutic efficacy.

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Tirzepatide Preparation and Purification

Tirzepatide is a Glucagon-like-peptide-1 (GLP-1) agonist and is considered one of the most promising diabetes drugs on the market. As a next generation GLP-1 drug, it not only stimulates insulin release in the body effectively controlling blood sugar levels, but also demonstrates advantages for decreasing appetite, inducing weight loss, and decreasing chances for other diabetes-related complications. This application note establishes a method for the HPLC purification of crude Tirzepatide using a Luna 10 µm-PREP C18(3) HPLC column. The purity of the Tirzepatide was tested using the Agilent 1100 HPLC system and a high-pressure preparation system coupled with a Luna 5 µm C18(2) HPLC column.

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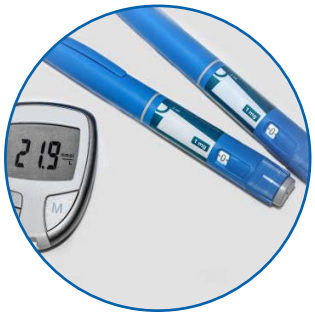

Determination of Tirzepatide High MW Aggregation Using TFA Modifier

Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP)/Glucagon-like peptide-1 (GLP-1) dual receptor agonist and a new drug for the treatment of Type 2 Diabetes. Compared to traditional GLP-1 receptor agonists, Tirzepatide has more significant hypoglycemic and weight loss effects.

This application note attempts to establish chromatographic conditions for the detection of Tirzepatide aggregates using a biologically inert size exclusion chromatographic (SEC) column. The Biozen dSEC-2 column contains highly hydrophilic particles packed into titanium alloy column hardware, thereby reducing any potential interaction between protein or peptide molecules and the column packing and column hardware. Due to the high inertness and sharp peak shape provided by the dSEC-2 column, the sensitivity for detecting trace amounts of aggregates in preparations can be improved. In this study a TFA based mobile phase system was utilized.

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Applications

Determination of Tirzepatide High MW Aggregation Using Phosphate Buffer

This application note attempts to establish chromatographic conditions for the detection of Tirzepatide aggregates using a biologically inert size exclusion chromatographic (SEC) column utilizing a phosphate buffer based mobile phase system. The Biozen dSEC-2 column contains highly hydrophilic particles packed into titanium alloy column hardware, thereby reducing any potential interaction between protein or peptide molecules and the column packing and column hardware. Due to the high inertness and sharp peak shape provided by the dSEC-2 column, the sensitivity for detecting trace amounts of aggregates in preparations can be improved.

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Development of a 2-Step Liraglutide Purification Process on a Single Stationary Phase

Liraglutide is a human glucagon-like peptide-1 (GLP-1) analogue with a 31 amino acids sequence that is 97 % similar to endogenous human GLP-1 (Figure 1). Liraglutide was approved in the EU in 2009, followed closely by approval in the U.S. in 2010. Currently, Liraglutide is commercially available in more than 95 countries and has been approved for the treatment of type 2 diabetes and obesity in adults with related comorbidity. Generic versions of Liraglutide are in development, this technical note is a useful method development starting point for new generic versions of Liraglutide.

Manufacturing a commercially successful synthetic peptide API often requires a multistep purification process to achieve the necessary purity, yield and throughput. The first step will typically isolate the desired component from the crude mixture but not achieve the purity level required. A “polishing” step is needed to achieve the desired purity. In order to keep manufacturing costs down, the purification process needs to be optimized. In particular, the number of steps and chromatographic stationary phases used should be kept to a minimum.

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Development of a Multi-Step Purification Process for the Purification of a Crude Synthetic Peptide (Exenatide) Mixture

Purification of crude synthetic peptide mixtures often employs a multi-step chromatographic purification process. The first step removes most of the undesired components, followed by another step to “polish” the material to the desired purity level. If applicable, a single step process can produce significant time and cost savings provided the single step can achieve the necessary purity while maintaining a desirable yield and throughput. A multi-step process using the same stationary phase, can provide considerable savings of time and costs compared to a process utilizing multiple stationary phases.

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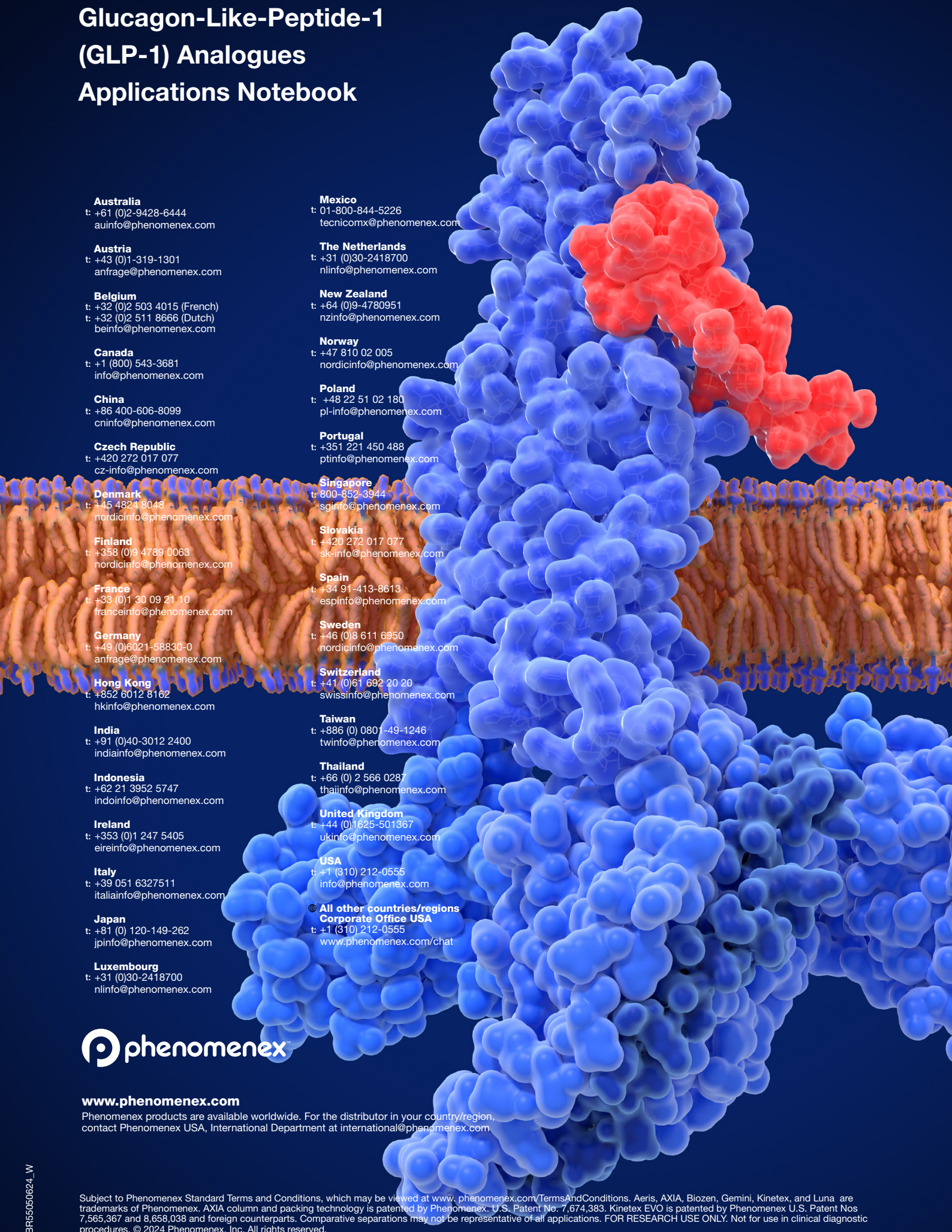

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