Beijing Dilun Biotechnology Co., Ltd.
Specializes in R&D and manufacturing of peptide synthesis equipment, providing comprehensive technical solutions and services.
Web: www.peptidescientific.com. Email: chengchao.wei@dilunbio.com

Solid-Phase Synthesis of Antidiabetic Peptide Drugs: Recent Advances in Related Substances Research

With the number of people with diabetes continuing to rise, antidiabetic peptide drugs have become a global focus of new drug R&D due to their advantages, including high efficacy, strong specificity, and low incidence of side effects. Solid-phase peptide synthesis (SPPS) is the mainstream technology for the industrial production of these drugs; it is highly automated and well-established. However, various structural impurities (substances of concern) are prone to form during synthesis and storage, directly affecting drug purity, safety, and efficacy. Recently, researchers conducted a systematic review of the sources, types, and key control points of impurities in the solid-phase synthesis of antidiabetic peptide drugs, providing important guidance for improving product quality and optimizing manufacturing processes.

I. Research Background

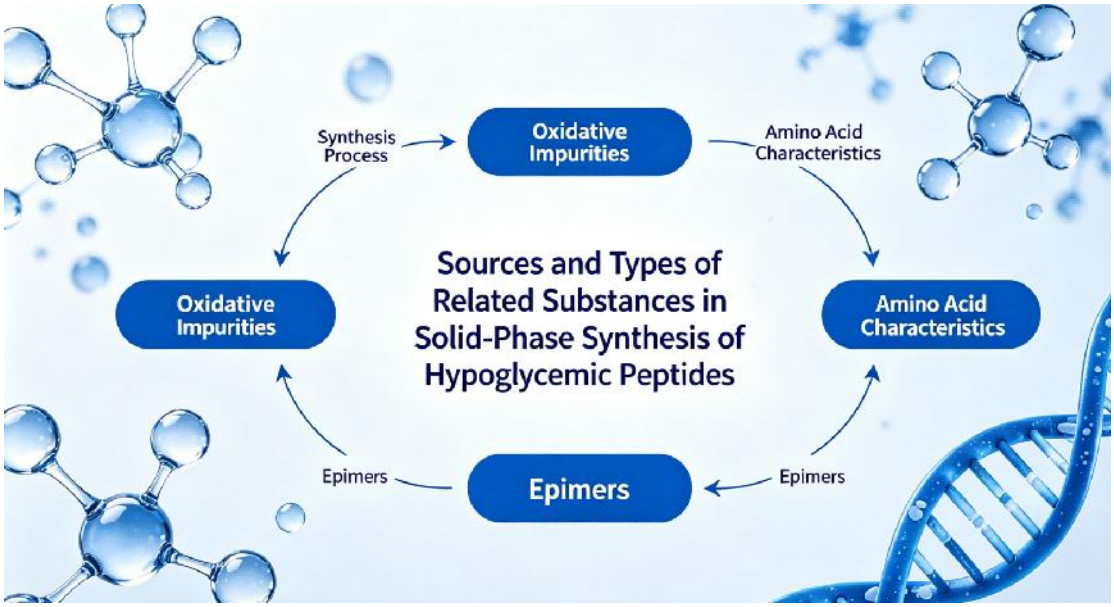
With the rising incidence of diabetes, there is an increasingly urgent need for long-acting, safe antidiabetic peptide drugs. The preparation of peptide drugs primarily involves natural extraction, chemical synthesis, and genetic recombination; among these, solid-phase synthesis has become the preferred method for industrial production due to its controllable reactions and ease of automation. However, solid-phase synthesis cannot remove byproducts in real time, and factors such as amino acid structure, reaction conditions, and protecting group strategies can all lead to the formation of impurities. Additionally, peptides may undergo degradation, oxidation, or aggregation during storage. These related substances not only reduce therapeutic efficacy but may

also pose immunogenicity risks, seriously compromising clinical safety; therefore, systematic research on these substances is of critical importance.

II. Research Objectives and Significance

This study aims to identify the causes, main types, and key influencing factors of impurities generated during the solid-phase synthesis of hypoglycemic peptide drugs, and to summarize the current state of research and control strategies both domestically and internationally. The findings will assist researchers in accurately identifying process impurities, optimizing synthesis conditions, and reducing the risk of side reactions. They will provide a scientific basis for the quality control, process improvement, and stable industrial production of hypoglycemic peptide drugs, thereby helping to elevate the purity standards and international competitiveness of domestically produced peptide drugs and ensuring the safety and efficacy of clinical medications.

III. Research Content

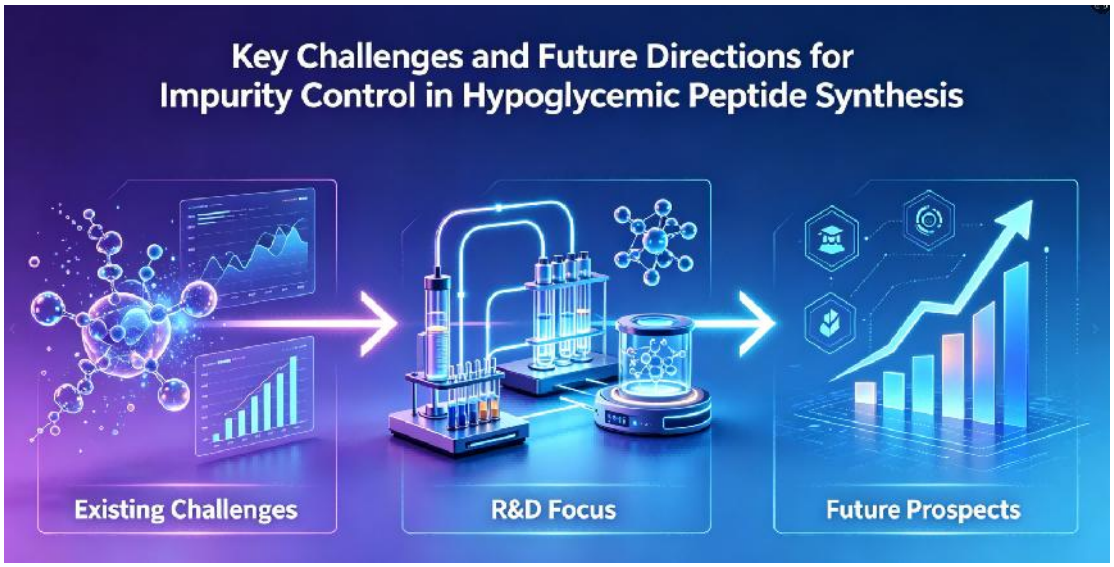


The research team focused on analyzing the sources and types of relevant substances in solid-phase synthesis, as well as the characteristics of amino acids prone to triggering side reactions. Sources of impurities include defects in the synthetic process (e.g., incomplete coupling, incomplete deprotection, amino acid deletions/insertions), inherent properties of amino acids (e.g., Ser/Thr/Tyr are prone to β-elimination,

Asp/Asn are prone to imide formation, and Cys is prone to oxidative dimerization), environmental factors (pH, temperature, metal ions), and degradation during storage. Major impurity types include: diastereopeptides (chiral racemization), deletion/insertion peptides, oxidation/reduction impurities, side-chain modification impurities, polymers/aggregates, protecting group residues, and degradation fragments; among these, high-molecular-weight aggregates (HMWP) may enhance immunogenicity and are a key focus of quality control. The study also noted that the use of condensing agents such as DIC/HOBt and PyBOP can effectively reduce the risk of racemization, while optimizing protection strategies and controlling reaction pH and temperature can minimize side reactions.

IV. Conclusions and Outlook

Research indicates that the substances involved in the solid-phase synthesis of glucose-lowering peptide drugs are complex and diverse; their formation is closely related to amino acid structure, process parameters, reagent selection, and storage conditions, and directly affects drug purity, stability, and safety. Currently, optimizing condensing agents, protecting group strategies, and reaction conditions can effectively reduce impurity levels, but completely eliminating them remains a challenge. In the future, the development of antidiabetic peptide drugs will continue to focus on the precise control of impurities and the greening of processes. On the one hand, this will involve a thorough analysis of the mechanisms underlying impurity formation and the establishment of highly efficient and sensitive methods for impurity detection and characterization; on the other hand, by optimizing solid-phase synthesis processes, screening for highly selective condensing agents, and refining storage stability protocols.



Concurrently, research into the relationship between impurities and immunogenicity will be strengthened to drive the development of antidiabetic peptide drugs toward higher purity, lower impurity levels, and greater safety, thereby providing clinicians with superior therapeutic options for diabetes management.