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Hypoglycemic Peptides: Impurity Profile in Solid-Phase Synthesis and Quality Control

With the rising prevalence of diabetes, hypoglycemic peptide drugs have emerged as a fast-growing class of therapeutics, valued for high specificity, low toxicity, and good efficacy. Solid-phase peptide synthesis (SPPS) is the mainstream industrial method for their production, offering automation and scalability. However, SPPS readily generates various related substances (impurities) during synthesis and storage, which affect drug purity, safety, and efficacy. This article systematically reviews the sources, types, and causes of impurities in SPPS of hypoglycemic peptides, providing insights for process optimization and quality improvement.

1.Research Background

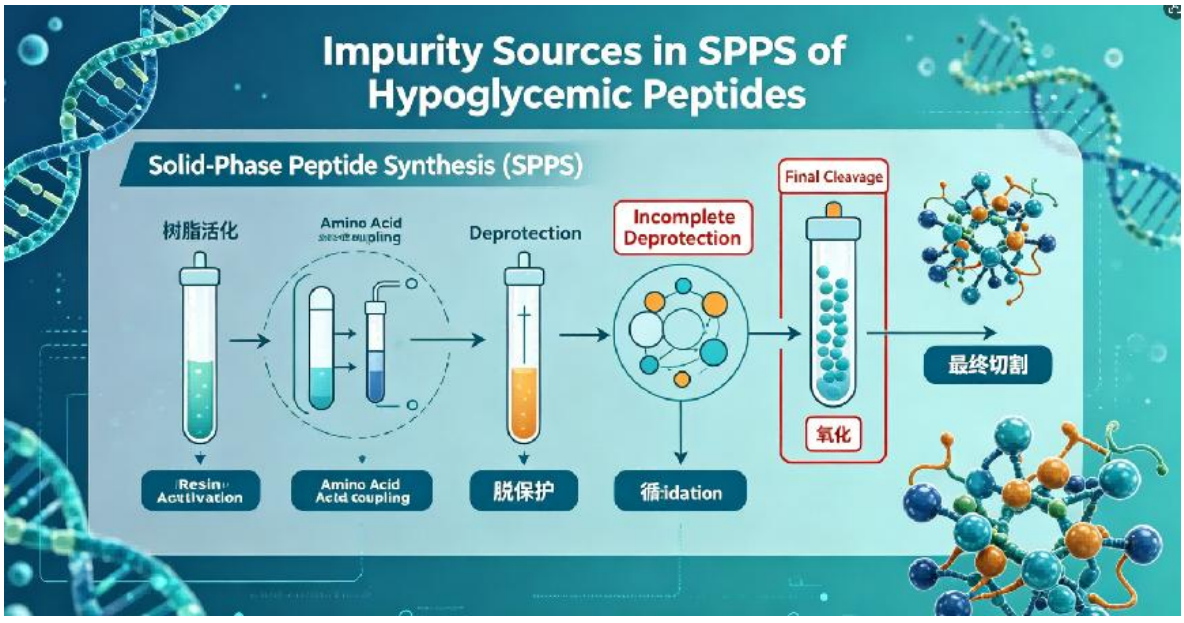
Diabetes prevalence continues to increase globally, driving demand for safe and effective hypoglycemic drugs. Peptide drugs, such as GLP-1 analogs, have become research hotspots due to their advantages. SPPS is widely used for industrial peptide production, with simple reaction setup and easy automation. Nevertheless, SPPS has inherent limitations: byproducts cannot be removed in situ, and harsh reaction conditions lead

to structural impurities. Impurities like amino acid deletion/insertion, racemization, oxidation, and protecting group residues may trigger immunogenicity and reduce drug safety, making impurity control critical.

2.Research Purpose and Significance

This review aims to systematically analyze the types, formation mechanisms, and influencing factors of impurities in SPPS of hypoglycemic peptides, summarize research progress, and provide theoretical guidance for impurity control and process optimization. Clarifying impurity origins and risks helps reduce byproduct formation, improve product purity and stability, lower immunogenicity, and ensure clinical safety. The findings support industrial scale-up and quality standard establishment, promoting the high-quality development of hypoglycemic peptide drugs.

3. Research Content



SPPS impurities mainly arise from amino acid characteristics and reaction conditions. Amino acids such as Ser, Thr, Asp, Asn are prone to β-elimination, racemization, or cyclization under alkaline/acidic conditions. Common impurities include deletion/insertion peptides, racemized peptides, oxidized/reduced derivatives, protecting group residues, and high-molecular-weight aggregates. These impurities stem from incomplete deprotection, insufficient activation, side reactions, and storage degradation. Strategies like optimizing coupling reagents (DIC/HOBt), controlling pH/temperature, and using orthogonal protecting groups can mitigate impurity formation.

4.Conclusion and Outlook

Impurity formation in SPPS of hypoglycemic peptides is closely linked to amino acid properties and process parameters, directly impacting drug quality and safety. Current impurity control relies on reagent selection and condition optimization, but challenges remain in trace impurity removal and stability improvement. Future research will focus on in-depth impurity mechanism studies, development of green and efficient synthesis strategies, and establishment of precise detection methods. Continuous process innovation will further enhance purity, reduce costs, and drive the industrialization and clinical application of high-quality hypoglycemic peptide drugs.