# Glucose-responsive oral insulin: A leap toward high-efficiency and safe diabetes management

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Diabetes and its associated complications pose a serious threat to the health of over 536 million people globally. In recent years, the disease burden of diabetes has increased significantly and is expected to aggravate in the next 30 years.[1] Effective blood glucose (BG) management through medication significantly lowers the risk of diabetes-related complications, including cardiovascular complications and ophthalmic complications. Currently, the primary treatment for type 1 diabetes involves subcutaneous insulin injections. After injection, insulin is absorbed into the peripheral bloodstream, where it is distributed to adipose tissue, muscle, and the liver. However, this method faces challenges such as low patient adherence, hypoglycemia risk, and unstable absorption of subcutaneous insulin. Patients often experience fear and aversion to subcutaneous insulin injections, resulting in poor compliance and inadequate BG control. Thus, mimicking the body's insulin secretion mechanism and optimizing insulin delivery methods are crucial for effective insulin therapy.

Gu et al. have developed an oral glucose-responsive micelle formulation capable of delivering insulin through the gastrointestinal tract.[2] The research team synthesized an amphiphilic diblock copolymer of $PCB_{0.5}$-$PEA_{0.2}$-$FPBA_{0.3}$ (named PPF), comprising a hydrophilic zwitterionic polycarboxybetaine (PCB) segment and hydrophobic segment modified with 4-carboxy-3-fluorophenyl-

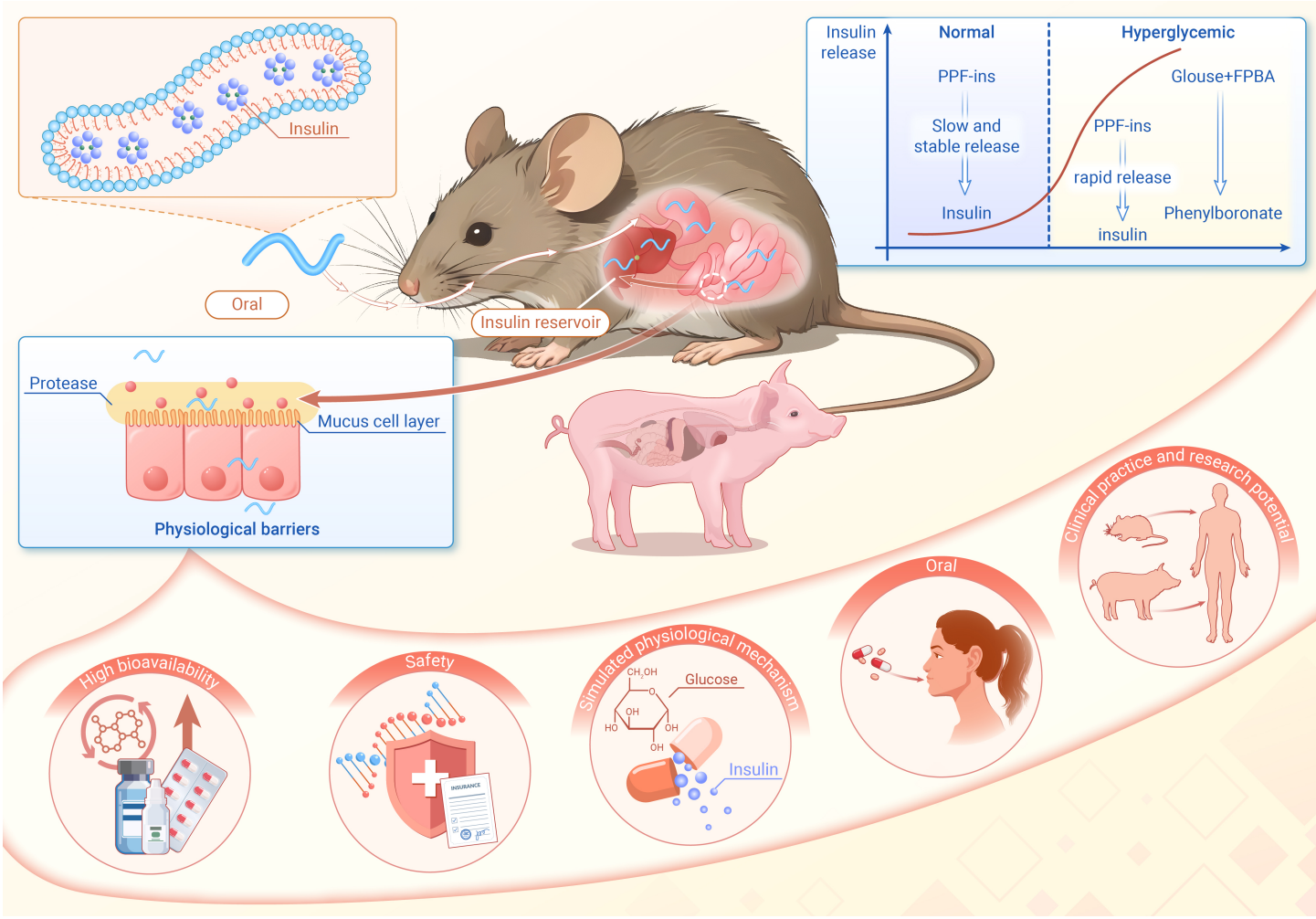


**Figure 1. The mechanism of action of PPF-ins in mice.**

boronic acid (FPBA) on poly (2-aminoethyl methacrylate). The micelle formulation self-assembles from PPF and hydrophobic insulin/$Zn^{2+}$ through electrostatic and hydrophobic interactions, with a hydrodynamic size of approximately 50 nm. This micelle significantly mitigates the burst release of insulin in the gastrointestinal tract and reduces enzymatic degradation. Its unique worm-like structure, small particle size, and zwitterionic surface enhance the efficient absorption of insulin in the intestine, facilitating its entry into the liver via the portal vein and forming a glucose-responsive insulin reservoir. The

reservoir adjusts the insulin release rate in real-time based on BG levels, releasing an appropriate amount of insulin into the liver before entering peripheral circulation. Under normal BG conditions, the polymer forms strong interactions with the insulin/$Zn^{2+}$, promoting a slow and stable release of insulin, effectively maintaining stable baseline BG levels. In hyperglycemic states, glucose quickly binds to FPBA to form phenylboronate esters, which decreases the positive charge density and hydrophobicity of the polymer's hydrophobic end, ultimately triggering a rapid release of insulin to help restore normal BG levels (Figure 1). This formulation achieved effective BG control for a full day without symptoms of hypoglycemia in type 1 diabetes mouse and pig models. The research results also indicate that PPF-ins has a good clearance rate and biocompatibility. After administering Cy5-labeled micelles to mice, fluorescence was observed in the abdomen, primarily concentrated in the liver, and disappeared after 36 hours. HE staining and Masson staining of major organs revealed no significant toxicity, and immunofluorescence staining showed no acute or chronic inflammatory reactions. And Biochemical analysis indicated normal blood parameters.

The results of the intraperitoneal glucose tolerance test showed that the glucose clearance efficiency of streptozotocin (STZ) -induced type 1 diabetic mice was comparable to that of healthy mice. In the isoglycaemic clamp experiments, the relative glucose infusion rate in the PPF-ins group was ten times higher under hyperglycemic conditions than under normoglycemic conditions. These results suggest that the PPF-ins significantly enhances glucose control under hyperglycemic conditions and holds potential for glucose-responsive drug release in vivo. Besides demonstrating therapeutic effectiveness, the experiment also contributed to enhancing the bioavailability of oral insulin formulations. Physiological barriers, such as the hydrolytic degradation of proteins within the gastrointestinal tract, the presence of a dense mucus cell layer in the stomach and intestines, and the substantial molecular size of peptides, contribute to the low bioavailability of orally administered insulin and other peptides. Currently, various strategies are employed to address these barriers, such as permeation enhancers, enzyme inhibitors, carrier systems, adhesion or mucus-penetration strategies, and microdevices. However, these approaches have achieved only limited success in enhancing bioavailability. For example, studies on various nanocarriers, encompassing natural and synthetic polymers for oral insulin delivery, demonstrated bioavailabilities not exceeding 15%.[3] In contrast, the bioavailability of the PPF-ins formulation was notably higher at 18.9% in type 1 diabetes mouse models induced by STZ.

The principal innovation of this study is the development of an orally administered insulin formulation that effectively regulates BG levels by mimicking physiological processes, with high bioavailability and safety. In recent years, insulin delivery has entered a new era due to the approvement of several sustained-released insulin formula. The world's first weekly insulin preparation, insulin icodec, was approved in the European Union for the treatment of type 2 diabetes mellitus, marking the beginning of the "weekly preparation" era in insulin therapy.[4] The FDA has also approved an integrated insulin pump, software, and continuous glucose monitor to create an "automated insulin delivery system" called the iLet Bionic Pancreas.[5] These innovations aim to reduce patient discomfort while enabling a more rational and scientifically based approach to insulin administration. Oral insulin offers a more comfortable and convenient alternative to subcutaneous injections, thereby reducing treatment discomfort and improving patient adherence. This formulation enables continuous and sustained insulin release via oral administration, ultimately reducing dosing frequency. This approach aids in maintaining stable BG levels while minimizing the challenges associated with frequent dosing. Furthermore, it enhances the potential for clinical translation of research findings by mimicking physiological mechanisms.

Despite the significant progress made in the field of oral insulin through this study, challenges remain in practical applications. For instance, the insulin dosage used in the oral PPF-ins formulation is still considerably higher than conventional subcutaneous doses. Therefore, further research is needed to enhance bioavailability and reduce therapeutic dosages. Although this preparation demonstrates good short-term safety, insulin treatment for diabetes requires the long-term biosafety management. Such studies could include identifying the metabolic pathway of PPF-ins in mice using fluorescent labeling and analyzing the composition and levels of PPF-ins metabolites. The formulation has demonstrated effective results in treating type 1 diabetes, further research could explore its therapeutic potential in type 2 diabetes as well. Moreover, this insulin delivery method, which simulates physiological mechanisms, offers valuable insights for the treatment of other endocrine-related diseases. The drug design employed in this study also provides valuable ideas for the research on oral administration of peptide drugs.

In summary, this study successfully synthesized a novel glucose-responsive insulin delivery system that effectively controls BG levels in both mice and pigs while significantly reducing the risk of hypoglycemia. This represents a substantial advancement in enhancing the bioavailability and safety of oral insulin, paving a new way for the further research and development in oral insulin delivery and diabetes treatment.

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## DECLARATION OF INTERESTS

The authors declare no competing interests.