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Commentary

Stimuli-Responsive Nanogels for On-Demand Insulin Release with Glucose Sensing Capabilities

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DESCRIPTION

The management of diabetes mellitus remains challenging despite advances in insulin formulations and delivery technologies. Current approaches require frequent blood glucose monitoring and manual insulin administration, creating significant burden on patients and often resulting in suboptimal glycemic control. We have developed stimuli-responsive nanogels that combine glucose sensing with automated insulin release, potentially enabling physiologically responsive insulin delivery without external intervention. These nanogels, approximately 200 nm in diameter, were synthesized through polymerization of acrylamide derivatives containing phenylboronic acid moieties, which serve as both glucose-sensing elements and reversible crosslinking sites.

The nanogel architecture was engineered to exhibit a volume phase transition in response to physiologically relevant glucose concentrations (4-20 mM). At normoglycemic levels, boronate ester crosslinks maintain the gel in a relatively collapsed state, physically entrapping insulin within the polymer network. Upon exposure to elevated glucose concentrations, competitive binding of glucose to the phenylboronic acid groups disrupts these crosslinks, causing network expansion and facilitating insulin release. Kinetic analysis demonstrated that release rates correlate directly with glucose concentration, with approximately 80% release occurring within 45 minutes at hyperglycemic conditions (20 mM) compared to less than 15% release over 24 hours at normoglycemic levels (5 mM). Importantly, this response demonstrated reversibility, with release rates decreasing upon return to normal glucose levels, thus creating a self-regulating system.

The insulin loading capacity was optimized through adjustment of polymer composition and crosslinking density, achieving approximately 35% w/w loading efficiency while maintaining responsiveness. Circular dichroism and enzyme-linked immunosorbent assays confirmed preservation of insulin's structural integrity and bioactivity following encapsulation and release processes. Stability studies demonstrated retention of both physical characteristics and glucose-responsive behavior for at least 3 months when stored at 4°C in lyophilized form. Importantly, the nanogels exhibited minimal interaction with plasma proteins as assessed by protein corona analysis, suggesting good biocompatibility and potential for extended circulation following subcutaneous administration.

In vitro evaluation using a microfluidic device simulating subcutaneous conditions with programmable glucose fluctuations demonstrated proportional insulin release profiles closely matching physiological requirements. When tested in streptozotocin-induced diabetic rats, subcutaneous injection of insulin-loaded nanogels maintained normoglycemia for approximately 5 days, with blood glucose levels fluctuating within the normal range despite glucose challenges through oral administration. Continuous glucose monitoring revealed that postprandial glucose excursions were significantly blunted compared to control animals receiving standard insulin injections, with no evidence of hypoglycemic events during the study period. Pharmacokinetic analysis demonstrated that plasma insulin levels correlated directly with blood glucose concentrations, confirming functionality of the glucose-responsive mechanism *in vivo*.

Histological examination of injection sites showed minimal inflammatory response and no evidence of fibrosis following repeated administration over a 4-week period. Comprehensive toxicological assessment revealed no significant alterations in hematological parameters, liver and kidney function tests, or histopathological findings in major organs. Furthermore, immunogenicity studies demonstrated no significant antibody production against either the nanogel components or the encapsulated insulin. These glucose-responsive nanogels represent a promising approach for "closed-loop" insulin delivery without requiring external devices or power sources, potentially addressing a critical need for simplified yet effective diabetes management systems that could improve patient compliance and clinical outcomes while reducing the burden of disease management.

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