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A stimuli-responsive insulin delivery system based on reversible phenylboronate modified cyclodextrin with glucose triggered host-guest interaction

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10 **Abstract**

11 Injection of insulin is an effective therapy to treat most patients with the type I diabetes and some with
12 type II diabetes. Additionally, the release of insulin under specific conditions has attracted widespread
13 interest. In this study, a smart drug carrier that can release insulin depending on the changes in blood
14 glucose levels was designed. Combining two popular molecules through facile synthetic processes, a drug
15 carrier of reversible phenylboronate group modified cyclodextrin (β -CD-EPDME) was fabricated. The
16 drug carrier is composed of cyclodextrin, which can encapsulate insulin, and phenylboronate, which is
17 sensitive to the *cis*-diols in some saccharides. Moreover, β -CD-EPDME can successfully encapsulate
18 insulin and almost completely release insulin in the presence of glucose. The detached phenylboronic acid
19 moiety triggered by glucose can attack the β -CD cavity and form a host-guest complex, which can force
20 out the encapsulated insulin within the cavity. In addition, the insulin released from the β -CD-
21 EPDME@Insulin complex retains its secondary structure, and the drug carrier has been proven to have
22 low cytotoxicity. Thus, this safe and glucose-responsive drug carrier shows the potential for use in the
23 therapy of diabetes.

24 **Keywords:** insulin, diabetes mellitus, glucose-sensitive, cyclodextrin, phenylboronic acid.

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