# Injectable *In Situ* Forming Glucose-Responsive Dextran-Based Hydrogels to Deliver Adipogenic Factor for Adipose Tissue Engineering

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**ABSTRACT:** An injectable and glucose-responsive hydrogel derived from dextran derivatives and lectin concanavalin A (ConA) was synthesized to deliver adipogenic factor for adipose tissue engineering. The gelation is attributed to the Schiff-base reaction cross-linking between aldehydic and aminated dextran. To enhance adipogenesis, the adipogenic factor of insulin was incorporated in the ConA immobilized hydrogels. The gelation time, compressive modulus, morphologies, weight loss, and swelling properties of the hydrogels were investigated. The ConA triggered a competitive displacement of dextran by glucose from the lectin receptor sites, and results in increasing swelling of the gel network. The swelling ratio (SR) of ConA immobilized hydrogel showed glucose dependent properties and linearly increased from 19.8 to 31.3 at 37°C in PBS at glucose concentrations between 0 and 1.0% (w/v). The *in vitro* release experiments showed that the insulin would be released from this dextran hydrogel into the local microenvironment in response to glucose, thus highlighting the potential of such a injectable and biodegradable hydrogel to be used as part of implantable scaffold to delivery adipogenic factor for adipose tissue engineering. © 2012 Wiley Periodicals, Inc. J Appl Polym Sci 000: 000–000, 2012

**Key words:** injectable hydrogels; drug delivery; adipogenic factor; tissue engineering

## INTRODUCTION

Among various tissue engineering scaffolds that have been investigated, biodegradable hydrogels remain the most appealing candidates due to their structural similarity to the natural extracellular matrix, inherent biocompatibility, high water content, and tunable viscoelasticity.[1–12] Biodegradable hydrogels, especially injectable hydrogels, carrying adipose-derived stem cells (ASCs) have been highlighted with promising potential for adipose tissue engineering.[13–18] The challenge is to deliver the necessary adipogenic factors such as insulin, insulin-like growth factor-1, cyclic adenosine monophosphate, ciglitazone, isobutylmethylxanthine, and dexamethasone to induce adipogenesis for practical adipose tissue engineering applications.[19–24]

Insulin is virtually a key adipogenic factor for adipogenesis as well as known as the only effective drug for the treatment of diabetes.[20–22] Because it could cause hypoglycemia in the patient when blood glucose level is decreased, unlike conventional drug delivery, steady release of insulin in a normal glucose environment is not desirable.[25–27] In this concept, there is a need for self-regulated delivery systems having the capability of adapting the rate of insulin release in response to changes in glucose concentration to keep the blood glucose levels within the normal range. Several approaches have been utilized for self-regulated insulin delivery designs as rate-control mechanisms including enzyme–substrate reactions, competitive binding and pH-sensitive polymers.[28,29]

Recently, a glucose-selective lectin of concanavalin A (ConA) have been immobilized into hydrogels to sense the change in the blood glucose concentration.[30–34] This glucose-sensitive biomaterial comprises of two parts: the branched glucose polymer and the lectin ConA, a protein with receptors that engage specifically with glucose moieties.[31] Insulin release occurred in the presence of glucose due to the binding competition between glucose and glucose moieties of

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dextran with ConA. This displacement causes a fall in viscosity within the gel network and allows a greater flux of insulin. Recently, several groups have developed reversible glucose-sensitive hydrogels based on ConA entrapment or covalently immobilization within the poly(ethylene glycol), polyacrylic acid, glycogen, dextran, and polysucrose gels.[32–37] These systems showed a differential delivery of insulin in response to glucose with *in vitro* diffusion experiments.

Despite extensive studies of pharmaceutical usage *in vitro*, the use of glucose-responsive hydrogel as an injectable cell scaffold for tissue engineering has received limited attention.[24] For example, the hydrogel resulting from the addition of methacrylic dextran to ConA has been documented,[31] but it is unsuitable for serving as cell scaffolds due to the poor injectability. Herein, we report on the use of an injectable and glucose-responsive dextran hydrogel to deliver insulin for adipose tissue engineering. The formation of glucose-sensitive gel is attributed to the Schiff-base reaction between amino and aldehyde groups of dextran derivatives, respectively. The Schiff-base coupling chemistry has the advantage that it introduces no potentially cytotoxic groups into the gels formed and can create a more biomimetic microenvironment for cell survival, rendering them more suitable for potential *in vivo* applications.

## EXPERIMENTAL

### Materials

Dextran (from Leuconostoc mesenteroides, average relative molecular weight 70 kDa), ConA (Type V), adipic dihydrazide (ADH), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole hydrate (HOBt), sodium periodate, ethylene glycol, *t*-butyl carbazate, human insulin, and trinitrobenzenesulfonic acid (TNBS) were purchased from Sigma-Aldrich, USA. Insulin Human Elisa Kit was purchased from Invitrogen, Eugene, Oregon. All chemicals and reagents were used as received.

### Synthesis of aldehydic dextran

Aldehydic dextran (Dex-CHO) was prepared in aqueous conditions following previously described procedures with slight modifications.[38,39] A 1.0 g dextran was dissolved in 100 mL nanopure $H_2O$ at a concentration of 10 mg/mL. An aqueous solution of sodium periodate (0.5 *M*, 5 mL) was added dropwise, and the reaction was stirred for 2 h at room temperature in the dark. A 0.3 mL ethylene glycol was then added to inactivate any unreacted periodate. The reaction was stirred for 1 h at ambient temperature, and the solution was purified by exhaustive dialysis against distilled $H_2O$ for 3 days, and the dry product was obtained by freeze-drying and kept at −20°C. Determination of the actual aldehyde content of Dex-CHO revealed an extent of oxidation of 36% by the *t*-butyl carbazate assay.[40]

### Synthesis of aminated dextran

Dextran were modified into aminated dextran (Dex-$NH_2$) as described previously.[39,40] In brief, 10 g of dextran were dissolved in 100 mL of distilled water overnight, to which 24 g of sodium hydroxide, and 30.2 g of chloroacetic acid were added. The solution was refluxed at 70°C for 145 min, quickly neutralized to pH 7.0 with 6*N* hydrochloric acid, dialyzed against distilled water for 3 days, and then lyophilized. A 0.5 g of lyophilized polymer was dissolved in 100 mL of distilled water, and reacted with 6.53 g of ADH in the presence of 0.78 g of EDC and 0. 77 g of HOBt at pH 6.8 overnight at room temperature. The product was purified by exhaustive dialysis for 3 days followed by ethanol precipitation, and then lyophilized and kept at −20°C. The percentage of hydrazide group substitution in the polymer was quantified as 41% using a TNBS assay.[16]

### Infrared spectroscopic measurement

Fourier transformed infrared (FTIR) spectra of dextran and derivatives were measured to confirm the expected pendant functionalities. Various samples were recorded with FTIR spectrometer (Nicolet Magna 550, Nicolet, USA) against a blank KBr pellet background. The dry samples were powered, mixed with KBr, and pressed into pellets manually.

### Hydrogel preparation

Dex-CHO and Dex-$NH_2$ solutions were prepared by dissolving modified dextran in PBS (pH 7.4) separately at a concentration of 6 wt % and cooled to 4°C, respectively. Human insulin were dissolved in PBS containing 3 vol % of HCl in an ice bath. ConA was added to the Dex-$NH_2$ solution and stirred to form a viscous mixture solution. For preparation of insulin-loaded gels, insulin solution, ConA, and Dex-$NH_2$ solution, were mixed with Dex-CHO solution, which resulted in formation of composite gels. The weight ratio of Dex-CHO and Dex-$NH_2$ was fixed as 1 : 1. Final concentrations of ConA and insulin were fixed with 2.5 and 3 mg/mL, respectively. The gelation time of composite hydrogels was monitored at 4°C. The gels were heated to 37°C for 15 min and resulted in composite gels.

### Morphologies

Morphologies of hydrogels were characterized by scanning electron microscopy (SEM) after gelation.

The hydrogels were lyophilized at −50°C for 24 h (Freezone 4.5, Labconco, MO, USA) and then gold-coated using a Cressington 108 Auto (Cressington, Watford, UK). The cross-sectional morphologies of gels were viewed using a JSM-6330F SEM (JEOL, Peabody, MA) operated at 10 kV accelerating.

### Weight loss and degradation

Weight loss of initial hydrogels ($W_0$, dried weight) was monitored as a function of incubation time in PBS at 37°C. At specified time intervals, hydrogels were removed from the PBS and lyophilized (−50°C) and weighed ($W_t$). The weight loss ratio was defined as $100\%(W_0 - W_t)/W_0$. The weight remaining ratio was defined as $1 - 100\%(W_0 - W_t)/W_0$.

### Compressive modulus

Mixtures of solutions described above were injected into a casting model to obtain columned hydrogels (10 mm in diameter and 5 mm in height). The compressive modulus of elasticity was measured in the elastic region of swollen discs using a dynamic mechanical analyzer (DMA-7, Perkin-Elmer) in unconfined compression at a constant stress rate of 40 mN $min^{-1}$ up to 20% strain at room temperature.

### Swelling properties

The known weights of hydrogels were immersed in PBS and kept at 37°C. For swelling experiment, the initially swollen hydrogel (0.5 mL) was immersed in 5 mL PBS with varying glucose concentrations (0.2, 0.4, 0.6, 0.8, and 1.0% w/v) and kept at 37°C. At predetermined intervals, the hydrogels were removed and immediately weighed with a microbalance after the excess of water lying on the surfaces was absorbed with a filter paper. The SR was calculated using the following equation of $SR = (W_s - W_d)/W_d$, where $W_s$ and $W_d$ are the weights of the hydrogels at the swelling state and at the dry state, respectively.

### Insulin release

A 0.5 mL of gels were continuously suspended in 5 mL of PBS without and with glucose at 37°C, provided a reservoir into which insulin could be released from the gel complex and subsequently measured. During diffusion experiments, the concentration of glucose was kept at 0.4 and 1.0% (w/v), respectively. At predetermined intervals, the insulin concentration of reservoir was monitored by Insulin Human Elisa Kit assay.

### Statistical analysis

The experimental data from all the studies were analyzed using Analysis of Variance. Statistical significance was set to $P$ value =0.05. Results are presented as mean ± standard deviation.

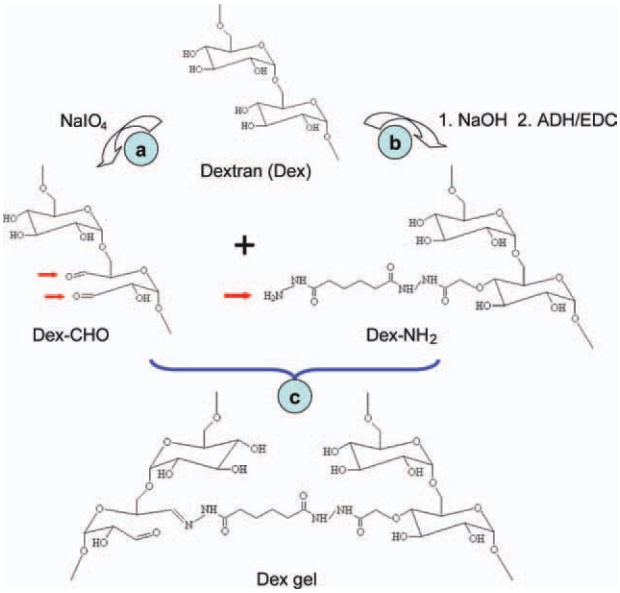


**Figure 1** Synthetic route of aldehydic dextran (a), aminated dextran (b), and dextran gel (c). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

## RESULTS AND DISCUSSION

### Synthesis of hydrogels

Aldehyde groups were introduced to dextran by reaction with sodium periodate, which oxidizes the vicinal hydroxyl groups to dialdehydes [Fig. 1(a)], thereby opening the sugar ring to form dialdehyde derivatives. Amino groups were introduced to dextran by coupling ADH onto carboxymethyl-dextran through amide bond linkages [Fig. 1(b)]. Dextran hydrogels based on Schiff-base cross-linking were generated by mixing Dex-CHO (6 wt % in PBS, pH 7.4) and Dex-$NH_2$ (6 wt % in PBS, pH 7.4) solutions [Fig. 1(c)]. Dextran and derivatives were then characterized by FTIR (Fig. 2). On FTIR, dextran showed an absorbance peak at 1650 $cm^{-1}$ [Fig. 2(a)]. By comparing with dextran, the spectrum of Dex-CHO showed new absorption peaks at around 1730 $cm^{-1}$ [Fig. 2(b)], which was corresponding to the stretching of the carbonyl from aldehyde groups. The spectrum of Dex-$NH_2$ was shown by emergence of the peak at around 1665 $cm^{-1}$ [Fig. 2(c)], reflecting stretching of the carbonyl of amide groups from hydrazide functionalities. ConA was simultaneously incorporated in the hydrogel network during Schiff-base cross-linking between its amino groups and aldehyde groups of Dex-CHO (Fig. 3). Insulin, a key adipogenic factor for ASCs, was trapped during the preparation of dextran-based composite hydrogel.

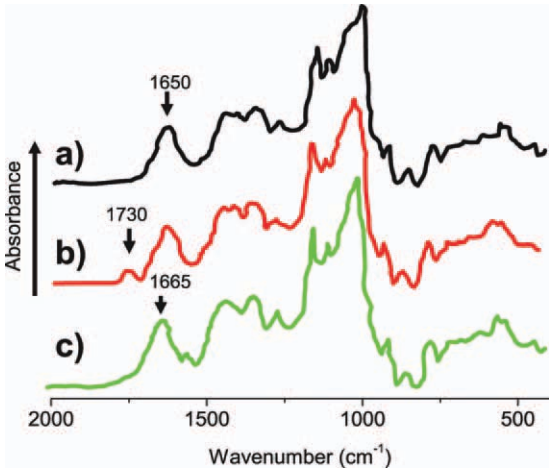


**Figure 2** FTIR spectra of dextran (a), aldehydic dextran (b), and aminated dextran (c). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The ConA in the hydrogel could form the specific carbohydrate complexation with the glucose moieties of dextran molecules.[31–34] The gelatinous three-dimensional complex would be partially dismantled by competitive displacement by free glucose.[32,33] As ConA was progressively dissociated from the gel on adding glucose, the cross-linking density decreased and the gel swelled. Competitive displacement results in temporarily lowering of the swelling of the hydrogel, which would trigger swelling in hydrogel and consequently facilitating the release of insulin by diffusion-mediated process.[34,35]

## Gelation time

The influence of ConA and insulin on gelation rate of composite hydrogels was studied (Fig. 4). All gelation occurred within 7 min with fixed weight ratios of Dex-CHO/Dex-$NH_2$ as 1 : 1. When 2.5 mg/mL of ConA was added, the gelation showed more quickly and occurred within 5 min.

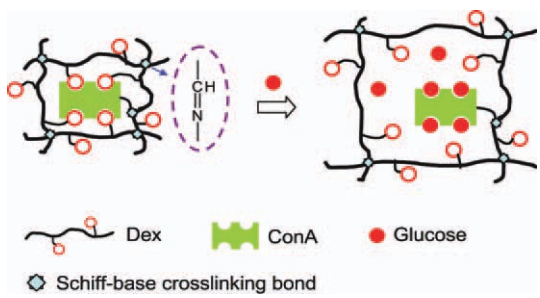


**Figure 3** Schematic illustration showing the strategy of biocompatible and glucose-responsive dextran hydrogel for self-regulating insulin delivery. Lectin ConA is covalently immobilized through Schiff-base reaction synchronously. Insulin would be released form gel by swelling of the hydrogel network. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

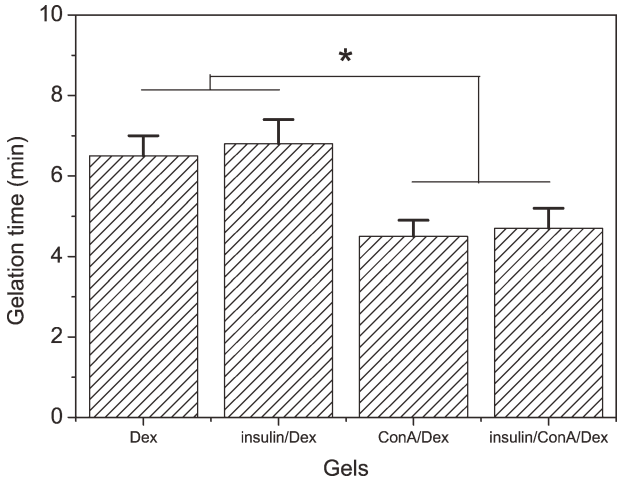


**Figure 4** Gelation time of hydrogels at 4°C. Insulin and ConA concentration were fixed with 3 mg/mL and 2.5 mg/mL, respectively. Values reported are an average $n = 5$, ±standard deviation.

The specific carbohydrate complexation between ConA and glucose moieties of dextran molecules resulted in a shorter gelation time. With addition of insulin in the hydrogels, the gelation time slightly increased, but no significant difference was found ($P > 0.05$). The results proved that the ConA played the role of an additional cross-linker in the formation of hydrogel.

## Compressive modulus

Compressive modulus of the hydrogels was determined by a dynamic mechanical analysis method (Fig. 5). With immobilization of ConA contents, the compressive modulus of the composite hydrogels was improved correspondingly. The ConA/Dex and

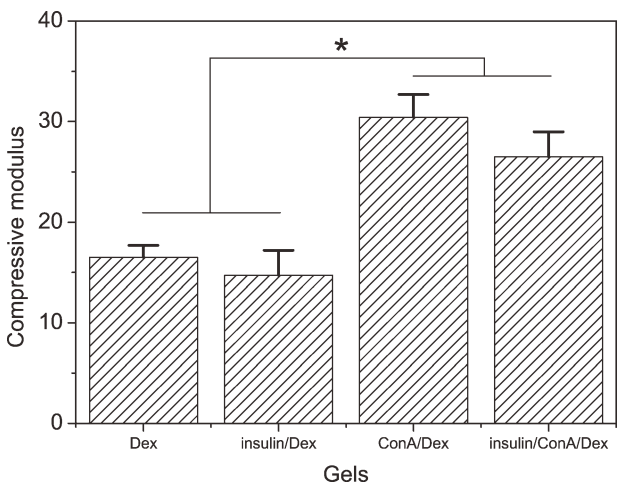


**Figure 5** Compressive modulus of hydrogels at room temperature. Insulin and ConA concentration were fixed with 3 mg/mL and 2.5 mg/mL, respectively. Values reported are an average $n = 5$, ±standard deviation.

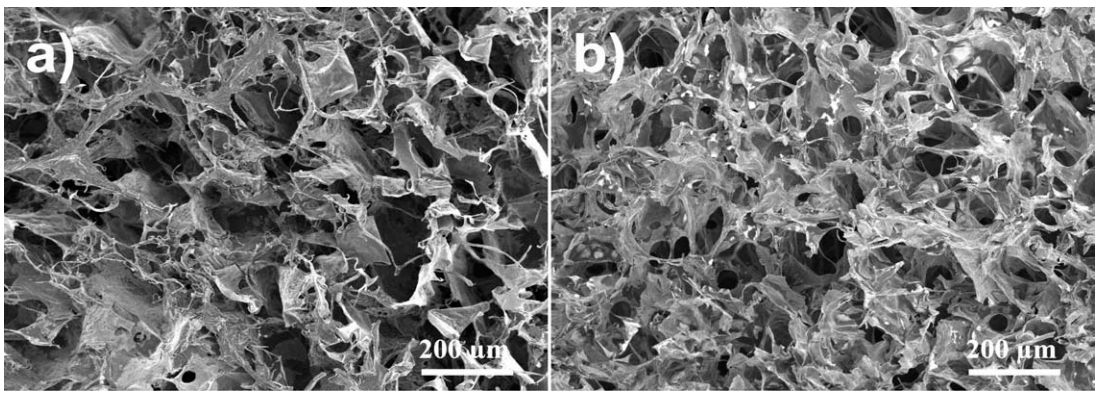


**Figure 6** SEM images of the lyophilized insulin/Dex (a) and insulin/ConA/Dex (b) hydrogels. Insulin and ConA concentration were fixed with 3 mg/mL and 2.5 mg/mL, respectively.

insulin/ConA/Dex hydrogels had a significantly larger compressive modulus than the control Dex and insulin/Dex hydrogels ($P < 0.05$), which were 30.4 and 26.3 kPa, respectively, whereas no difference was found between the ConA/Dex and insulin/ConA/Dex hydrogels. These observations would suggest a more solid and therefore stronger mixture for the immobilized ConA versions.

### Microstructure

SEM images characterized the microstructure of insulin/Dex and insulin/ConA/Dex hydrogels after freeze-drying (Fig. 6). According to cross-section morphologies, both of the hydrogels displayed a continuous and porous structure by virtue of the freeze-drying step resembling other polysaccharide hydrogel system structures. The pore diameter of the insulin/ConA hydrogel is in the range of 30–200 μm [Fig. 6(a)], which is larger than the 10–100 μm of insulin/ConA/Dex gel [Fig. 6(b)]. The morphologies of the freeze-dried hydrogels demonstrated that the incorporated ConA results in the formation of a tighter network structure in composite hydrogels due to the additionally carbohydrate complexation linkages. The ConA tended to tightly combine with dextran molecules with complexation bonds, which lead to a more compact appearance than the control Dex gel without ConA.

### Weight loss

The weight loss properties of insulin/Dex and insulin/ConA/Dex hydrogels were monitored as a function of incubation time in PBS at 37°C. As shown in Figure 7, the incorporation of ConA content has a significant influence on the weight loss behavior of hydrogels. The insulin/ConA/Dex hydrogel lost its weight steadily up to 14 days and showed a significantly slower weight losing rate than the insulin/Dex hydrogel during the incubation procession. At Day 14, the weight remaining of insulin/Dex and insulin/ConA/Dex hydrogels were 32% and 71%, respectively. This result suggested that the formulation of insulin/ConA/Dex gel is an appropriate candidate for insulin delivery and tissue engineering scaffold. Although Schiff-base cross-linking hydrogels hydrolyze quickly at acidic aqueous, this dextran hydrogel is relatively stable under physiological conditions.

### Swelling properties

Figure 8 indicates the equilibrium SRs of insulin/Dex and insulin/ConA/Dex hydrogels determined in PBS at 37°C. The immobilized ConA significantly influenced the equilibrium SR of hydrogels, i.e., the equilibrium SR of insulin/Dex in PBS was 23.5, which was significantly higher than 19.8 of insulin/ConA/Dex ($P < 0.05$). Both of the SR of insulin/Dex and

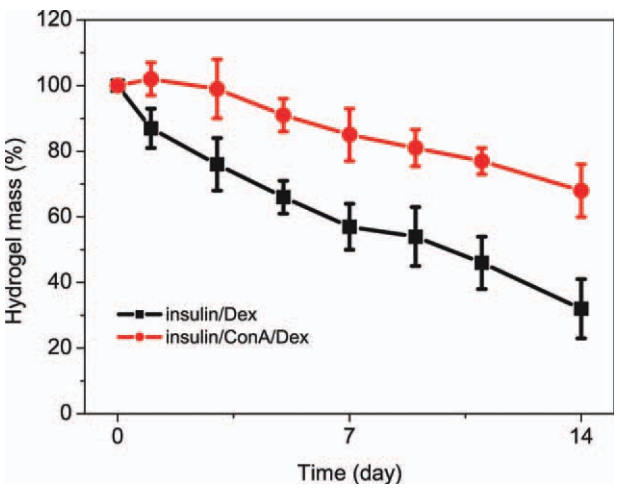


**Figure 7** Weight loss of insulin/Dex and insulin/ConA/Dex hydrogels in PBS at 37°C. Insulin and ConA concentration were fixed with 3 mg/mL and 2.5 mg/mL, respectively. Values reported are an average $n = 5$, ±standard deviation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

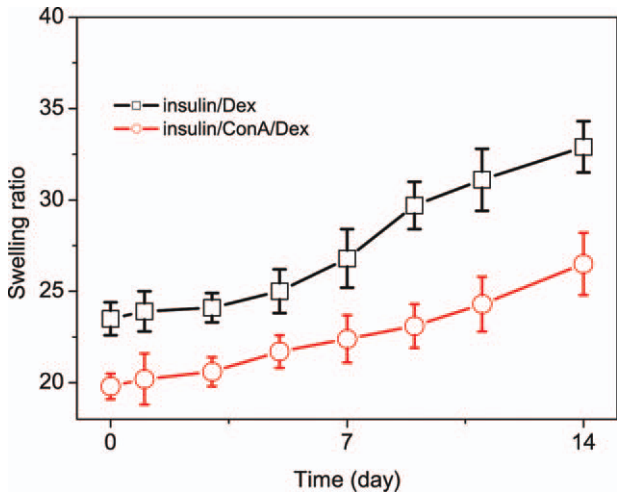


**Figure 8** Swelling ratio of insulin/Dex and insulin/ConA/Dex hydrogels incubated in PBS at 37°C as a function of incubation time. Values reported are an average $n = 5$, ±standard deviation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

insulin/ConA/Dex hydrogels were changed in incubation, and the values increased up to 14 days during incubation. At Day 14, the SRs of insulin/Dex and insulin/ConA/Dex hydrogels significantly increased to 32.9 and 26.5, respectively.

For the design of a device which responds effectively to glucose, sufficient gel structure must be present to create the swelling differential required to respond. To achieve insulin release, glucose dependent swelling of gel is required when glucose concentration increases. Swelling kinetics of the insulin/Dex and insulin/ConA/Dex hydrogels were evaluated in response to step changes in glucose concentration.

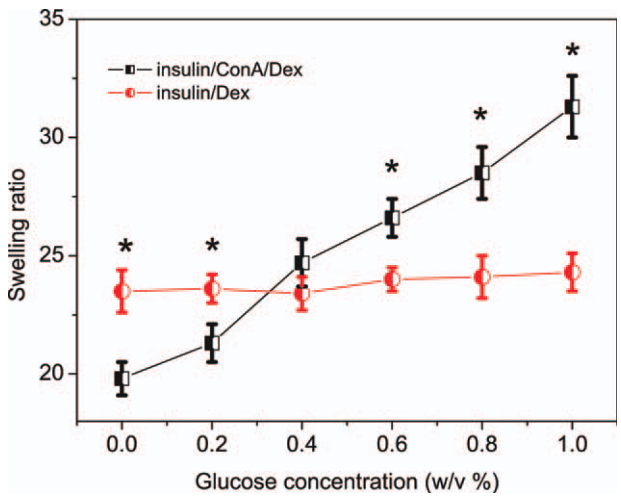


**Figure 9** Swelling ratio of insulin/Dex and insulin/ConA/Dex hydrogels in PBS at 37°C as a function of glucose concentration after 24 h incubation. Values reported are an average $n = 5$, ±standard deviation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 9 indicates the effects of immobilized ConA on the glucose dependent swelling of the gel. The swelling kinetics experiments took place in PBS, pH 7.4, after 2 h incubation with several glucose concentrations, showed higher SRs at higher glucose concentrations than at lower glucose concentrations. The SR of the insulin/ConA/Dex gel immobilized ConA linearly increased from 19.8 to 31.3, whereas no significant SR changed on the gel without ConA. The comparison of the swelling behavior of the glucose-responsive hydrogels with increasing glucose content shows that the SR was considerably greater for the ConA immobilized versions. Based on these results, the insulin/ConA/Dex system showed a highly glucose-responsive property with immobilized ConA.

The swelling seen with glucose addition must result solely from the dismantling of the three-dimensional dextran–lectin network due to the competitive displacement of dextran by free glucose from the lectin receptor sites. Two main types of interaction are present in the hydrogel with immobilized ConA, in addition to the polymer entanglements. These are the lectin–saccharide interactions (physical cross-linking) and interactions associated with the covalent bonding of Schiff-base (chemical cross-linking). Dismantling of the physical cross-linking caused by the competitive displacement would result in a partial gel–sol transformation and a rise in the SRs, which would be favorable for insulin release.

## Controlled insulin release

Figure 10 shows the glucose dependent release of insulin, using the glucose-sensitive insulin/ConA/Dex hydrogel described above. The *in vitro* insulin

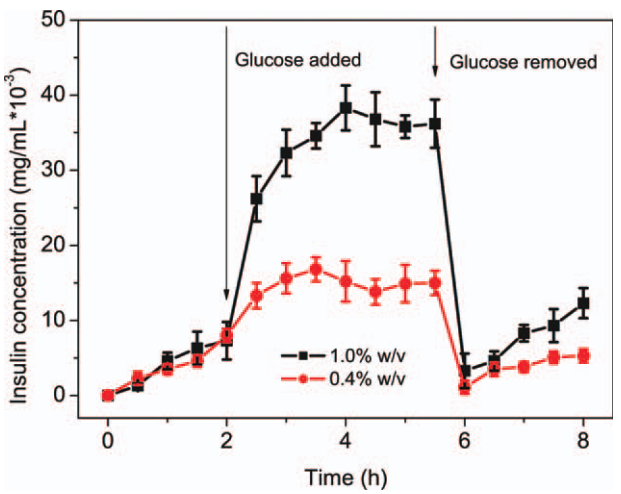


**Figure 10** Insulin release profiles in glucose dose response studies in PBS at 37°C. Values reported are an average $n = 5$, ±standard deviation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

delivery diffusion experiments demonstrated the delivery of insulin by using the insulin/ConA/Dex hydrogel at 37°C in response to physiologically relevant glucose levels. The result showed that the response of insulin/ConA/Dex hydrogel was affected by the trigger glucose concentration. It is apparent that in these repeated glucose-trigger experiments, comprising the glucose challenge and removal, glucose induced increased release of insulin with the flux reverting to a low level on removal of glucose from the receptor solution was observed on hydrogel challenged with 0.4 and 1.0% (w/v) glucose. The insulin/ConA/Dex hydrogel has maintained the activity of the glucose-responsive physical cross-links of the dextran and conA in terms of controlling the diffusion of insulin as a function of glucose content. Therefore, the ConA immobilized Schiff-base cross-linking dextran-based hydrogel can tune the release of insulin with response to external glucose.

## CONCLUSIONS

A biodegradable and glucose-responsive dextran hydrogel system immobilized with ConA has been designed via Schiff-base cross-linking reaction for insulin delivery. The morphologies and compressive modulus of the freeze-dried hydrogels demonstrated that the incorporated ConA results in the formation of a tighter network structure in hydrogels due to a physical lectin–saccharide interactions by free glucose of the dextran from the lectin receptor sites. The immobilized ConA as an additional cross-linker progressively dissociated from the gel on adding glucose, and results in the cross-linking density decreased. The preliminary results indicate that the insulin would be released from this hydrogel device into the local microenvironment in response to glucose by the swelling of hydrogel network. Different to nondegradable hydrogels which are appealing drug carriers due to the stable manners for drugs delivery, this biodegradable hydrogel could be utilized as cell carriers and scaffolds for tissue engineering and regenerative medicine. This biodegradable and glucose-responsive hydrogel has potential uses in ASC encapsulation and differentiation *in vitro* and *in vivo*, and thus might be applicable as promising scaffold for adipose tissue engineering.

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