Injectable, *in-situ* gelling, cyclodextrin-dextran based hydrogels for the release of a hydrophobic drug

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Introduction:

Hydrogels are one of the most investigated drug delivery platforms. These networks of cross-linked water soluble polymers display highly advantageous properties such as a high water content, low interfacial energy and mechanical and chemical similarities to native extracellular matrix. However, developing hydrogels for the delivery of hydrophobic drugs is considered a challenging endeavour. Subpar loading efficiencies and unpredictable release kinetics are consequences of hydrogel systems where drug loading is attempted following gel formation. Even if a sufficient degree of loading is achieved, the absence of interactions between the hydrophobic drug and the hydrophilic matrix results in a rapid release profile. Delivery vehicles can be designed for drugs with limited aqueous solubility by incorporating cyclodextrin, a molecule that exhibits both (external) hydrophilic and an (internal) hydrophobic character. Not only can CDs facilitate increased drug loading through an increase in drug solubilization, but they can also exert a finer level of control on the rate of drug release depending on whether they are physically or covalently attached to the hydrogel network. In this study, a dexamethasone-loaded hydrogel based on dextran and βCD (Dex-βCD) was synthesized. These materials were gelled *in situ* upon injection through the reaction of aldehyde-functionalized dextran with hydrazide-functionalized βCD. Different release profiles were generated by modifying the concentrations of the drug host and cross-linker, βCD, and a hydrazide-functionalized dextran polymer. The hydrazone cross-links between the aldehyde and hydrazide-functionalized precursors allow for rapid hydrogel formation as well as offering the advantage of being slowly hydrolyzed at normal physiological pH.

Materials and Methods:

βCD was functionalized with multiple hydrazide groups by reacting 5 g of carboxymethylated βCD (3.8 COOH/ βCD) with 12.6 g of ADH in 120 mL of water. The pH of the solution was adjusted to 4.75 with 1 M HCl and the reaction was started with the addition of 13.85 g of EDC. The pH was maintained at 4.75 until it stabilized. The solution was neutralized to a pH of 7.0 and water was removed from the product under an aspirator vacuum in a rotary evaporator at 60°C. The product was precipitated with a large excess of acetone and collected through vacuum filtration. The degree of substitution of the hydrazide-functionalized product was determined through potentiometric titration (3.1 Hzd/βCD). A hydrazide-functionalized dextran polymer (~600 hydrazide groups per polymer chain) was synthesized in a similar fashion, except the modified polymer was purified through dialysis against water and isolated through lyophilization. Aldehyde-functionalized dextran was synthesized as follows: 10 mL of an 80 mg/mL aqueous solution of sodium periodate was slowly added to 1.5 g of dextran [Mr- 500,000] in 150mL of water. The reaction was allowed to proceed for two hours and was stopped with the addition of 0.4 mL of ethylene glycol. The modified polymer was dialyzed and isolated through lyophilization. Drug loading was achieved by adding an excess of dexamethasone to 2 mL of a βCD-Hzd solution that was shaken for 3 days at ambient temperature. Drug uptake by βCD-Hzd was quantified using gravimetric methods. Dexamethasone loading in the control dextran hydrogel was achieved by suspending the hydrazide-functionalized dextran in a 90 μg/mL solution of dexamethasone in water. The hydrogel was formed using a double-barrel syringe. Each barrel contained the contents of the gel

precursor solutions, composed of either a hydrazide phase or an aldehyde phase. Equal amounts of both phases were extruded through the mixing device and injected into silicone rubber molds. Six hydrogels were used for each release study and were placed in cell culture inserts in a 12-well culture plate. The release study was carried out at 37°C over the course of 21 days. Quantitative determinations of dexamethasone in PBS release solutions were performed on a high-performance liquid chromatographic (HPLC) system using a reversed-phase Atlantis C_{18} column (100 mm x 4.6 mm, Waters Corporation), a mobile phase of 40% acetonitrile and 60% water, and a flow rate of 1.0 mL/min (retention time ~ 3.7 min). The absorbance of dexamethasone was measured at 263 nm.

Results

Figure 1 shows the release of dexamethasone from a Dex-βCD gel (11βCD/2Dex-Hzd, where both values indicate weight percent) compared to a dextran-only gel (2Dex-Hzd). Drug release from 2Dex-Hzd consisted of an initial burst, followed by first order release that was largely completed after 1 day. In comparison, when βCD was added to the hydrogel, only 5.4% of the total drug was released over the 20-day sampling period. By doubling the concentration of the Dex-Hzd polymer in the gel precursor solution to 4wt%, (11βCD/4Dex-Hzd), there was an 11-fold higher release rate relative to the gels prepared with 2wt% Dex-Hzd (11βCD/2Dex-Hzd, Figure 2).

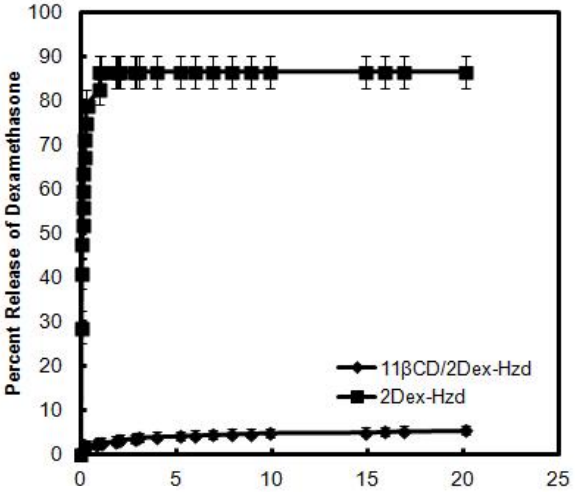

Figure 1

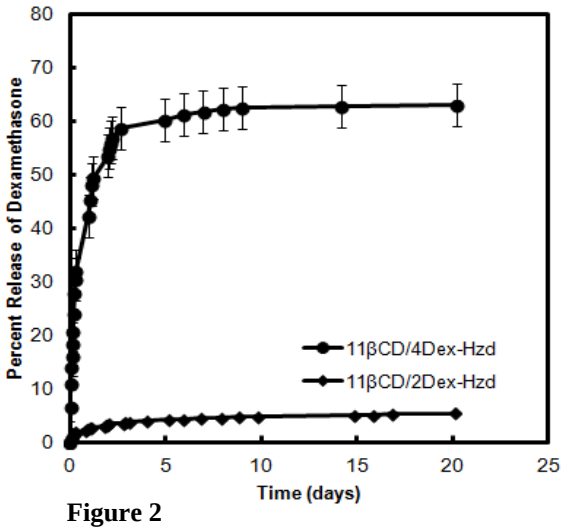

Figure 2

Discussion

The differences in release kinetics observed were attributed to the distinct patterns of distribution of CD in each hydrogel network. In the case of the 11βCD/2Dex-Hzd hydrogel, βCD was immobilized through crosslinking, preventing the diffusion of the soluble βCD-dexamethasone complex out of the hydrogel. The limited mobility of the βCD-drug complexes generates an extremely slow release profile from this hydrogel formulation driven entirely by partitioning. In contrast, the increased number of polymer-bound hydrazide groups in the 11βCD/4Dex-Hzd hydrogel compete with the hydrazide groups on the functionalized βCD, making βCD less likely to crosslink to the gel and thus more likely to become physically entrapped in the hydrogel network. Since the βCD-drug complexes are mobile, an increased level of drug release is observed. This result suggests that rate and mechanism of drug release from βCD-containing hydrogels can be adjusted by modifying the degree to which those βCD groups are covalently attached to the hydrogel network.

References

1. Bibby, D. C., N. M. Davies, et al. (2000). *International Journal of Pharmaceutics* 197(1-2)

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