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Dextran modified pH sensitive silica hydro-xerogels as promising drug delivery scaffolds

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ABSTRACT

Hybrid organically modified xerogels based on silica Si/Ca or Mg (90/10) content have been developed via a two step process with a pH sensitive dextran hydrogel. Doxorubicin hydrochloride (DOX) was coupled on the functionalized surface. The textural properties were optimized by *ex vitro* prediction of bioactivity and evaluation of drug release. The results indicated that the DOX-conjugated xerogels exhibited good apatite deposition properties after being soaked in Simulated Body Fluid (SBF) for 7 days. Furthermore, the DOX release study presented better behavior at pH = 4.5 in relation to neutral pH. The results of the present study are indicative of a promising scaffold for potential application as drug delivery vehicle for dual functionalities in bone cancer and bone repair.

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1. Introduction

Over the last decade bone regeneration has been applied as a novel technique of filling the periodontal pocket with neo-bone tissues [1]. In various experimental and clinical studies in relation to bone treatment, different non-resorbable and resorbable materials have been used. Among them expanded polytetrafluoroethylene (e-PTFE) has been mainly applied. The main disadvantage of non-degradable materials is the requirement for a second surgical intervention in order to be removed. Therefore, several biodegradable devices have been successfully used in bone and periodontal regeneration including collagen type I, polyurethane, polylactic acid and polyglycolic acid. However, the main disadvantage of biodegradable materials is that the barrier function duration is not strictly controlled and that the resorption process may possible interfere with the wound healing and bone regeneration process [2,3]. Among the resorbable polymers, dextran is a natural polysaccharide that has gained interest in biomedical applications owing to its cell biocompatibility, non-toxic and anti-bacterial properties [3,4]. The degradation products of polysaccharides are metabolized by the act of human enzymes, mainly lysozyme [5]. These properties make polysaccharides a suitable material for hybridization with silica xerogels and as a room temperature coating layer.

In the present study silica xerogels hybrid scaffolds have been modified with dextran hydrogel coating for use in biomedical applications. Dextrans are especially interesting for these applications due to their excellent biocompatibility, wide range of available molecular weight and their functionalization [6]. Two silica xerogels' composition will be potential materials as specific bone substitutes and drug delivering systems [7]. Thus, the bone bioactivity and drug-carrying possibility of the xerogel in relation to the flexibility of dextran should provide a scaffold with improved wound healing and bone-forming ability.

2. Experimental procedure

2.1. Materials and reagents

Tetraethoxysilane (TEOS, $Si(OC_2H_5)_4$ purity > 98%) was purchased from Aldrich; calcium nitrate tetrahydrate ($Ca(NO_3)_2 \cdot 4H_2O$) and magnesium nitrate tetrahydrate ($Mg(NO_3)_2 \cdot 4H_2O$) were used as received from Aldrich. CM-dextran was obtained from Sigma with a molecular weight of 500 kDa. Maleic anhydride, N,N-diisopropylcarbodiimide (DIC, <99%), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, triethylamine (Et_3N), and N,N,-dimethyl aminopyridine (DMAP), 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride(EDC.HCl) were supplied by Acros Organics. Dry tetrahydrofuran (THF) was purchased by Aldrich. Doxorubicin HCl (DOX) was provided by Pharmacia & Upjohn and used as received.

2.2. Surface functionalization of silica xerogels

The xerogels, with composition summarized in Table 1, were synthesized through the sol–gel process according to literature [12].

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Table 1
Composition of the xerogels (in mol%).

Sample composition	SiO_2 (mol%)	CaO (mol%)	MgO (mol%)
Si/Ca(90/10)	90	10	–
Si/Mg(90/10)	90	–	10

According to literature [13] it is well known that the dissolution of calcium ions under SBF treatment leads the apatite formation aiming at producing new, bone-like minerals on the xerogel surfaces. On the other hand Mg binds to the enzyme, alters its structure and occupies a catalytic role. Additionally, the Mg-ions enter in the apatite crystal lattice or are absorbed on the apatite surface leading to magnesium-substituted formation of β-tricalcium phosphate (β-TCP).

Carbodiimide chemistry was employed to cross-link carboxylic groups and hydroxylic groups in CM-dextran. According to the expected cross-linking mechanism, DIC was used aiming at formation of an esteric bond [8]. More detailed, dextran (0.45 g, 30% w/w related to respective xerogel) is coupled to the OH groups of the substrates (1.5 g) by mild shaking for 24 h at room temperature ($T=25$ °C) in a water solution (2 ml). After that, dextranized substrates are washed by being shaken for 48 h at room temperature ($T=25$ °C) and then centrifuged at 2000 rpm for 5 min in order to be collected. The carboxylated dextran substrates can be further functionalized by the similar chemistry. To make the dextran coating, 0.5 g of substrate was suspended in 3 ml THF with DMAP and the mixture was stirred for 30 min thoroughly under nitrogen. DIC (0.75 ml), maleic anhydride (0.75 g) and Et_3N (1 ml) were dissolved in 2 ml dry THF and stirred for 30 min. After this period, the second solution was added to the suspension and the reaction gradually was warmed up at 60 °C for 24 h. The resulting product was centrifuged three times for purification. A suspension of functionalized xerogel was treated

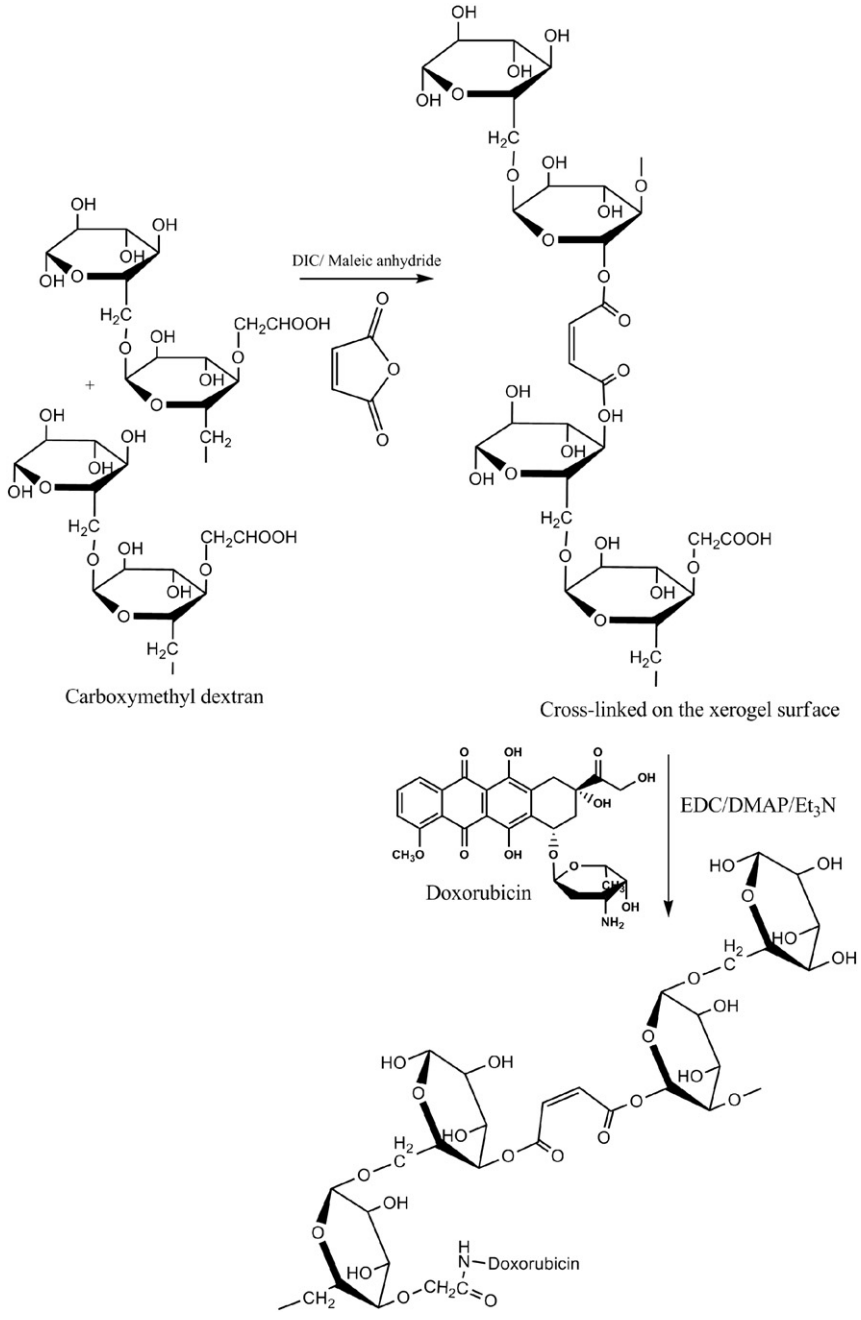

Fig. 1. Schematic presentation of modified pH sensitive dextran hydrogel.

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